1. 

Saliva

Of all the organs in the craniofacial-oral-dental complex, it is perhaps the salivary glands and their remarkable secretory product, saliva, that forge the strongest link between oral and systemic health. Salivary function is extremely sensitive to changes in our general well-being, ranging from subtle effects of over-the-counter cold medications to the devastation of life-threatening disease.

Even the ancients recognized an association between the human condition and saliva, which served as judge and jury in cases of wrong-doing. A suspect was given a mouthful of dry rice. If his anxiety reduced his saliva flow so that he could not swallow it, the verdict was guilty as charged. To this day, "cotton mouth" betrays all of us at some point in our lives, signaling to the world that our nerves have taken control.

Gatekeeper

With its vast antimicrobial arsenal, saliva represents a remarkable evolutionary selective advantage for the host against invading pathogens such as HIV, the fungus Candida albicans, and a host of bacteria associated with oral and systemic diseases. Secretory antibodies, for example, directed against viral pathogens such as poliovirus and cold viruses, as well as the anti-HIV agent SLPI, are found in saliva. Large salivary glycoproteins called mucins appear to have antiviral properties as do cystatins, a family of cysteine-rich proteins that are active against herpes viruses.

Saliva also contains histatins, antifungal proteins that are potent inhibitors of candida, which is normally kept in check at extremely low levels in the mouth. When the oral balance is upset, however, by HIV infection or other immunosuppressive and debilitating disorders, antifungal defenses are overwhelmed and candida flourishes uncontrolled. Reinforcing saliva’s antiviral and antifungal activity are salivary constituents that thwart bacterial attack. These enzymes destroy the opposition by various mechanisms, including degrading
bacterial membranes, inhibiting the growth and metabolism of certain bacteria, and disrupting vital bacterial enzyme systems.

Functioning in concert, these and other protective factors in saliva help to maintain the oral environment in optimal working order and restore it to more normal conditions when disturbed. But protection of the oral tissues reflects only one dimension of this versatile fluid and its constituents. Research has found a new role for saliva as an effective laboratory tool.

Familiarity with the composition, function and normal flow of saliva will give the practitioner a better understanding of the sequelae of hyposalivation. Saliva initiates the digestive process and contributes to the maintenance of healthy oral tissues. Whole saliva consists of secretions from the major and minor salivary glands. The parotid gland produces a pure serous secretion, while the submandibular and sublingual glands produce a mixed seromucous or mucous secretion, respectively. About 99 percent of saliva is water. The remaining one percent consists of large and small organic molecules, proteins, lipids and carbohydrates, and electrolytes. Some of these molecules are transported from the blood into salivary secretion; others are locally synthesized.

**New Diagnostics**

Long known primarily for its protective and lubricating properties, saliva is now meeting the demand for inexpensive, noninvasive, and easy-to-use diagnostic aids for oral and systemic diseases, and for assessing risk behaviors such as tobacco and alcohol use. Detection of HIV by the presence of virus-specific antibodies in saliva, for example, has led to the development of commercially available test kits. These offer the sensitivity of a blood test, but without the discomfort of a needle stick. The strong correlation between HIV antibodies in saliva and serum has spurred the use of saliva as a monitor for other viral antibodies and antigens. Experimental salivary assays have already been developed for detecting antibodies for measles, mumps and rubella. Saliva is also reliable in diagnosing viral hepatitis A, B and C in laboratory tests.

As an investigational diagnostic aid and potential monitor of disease progression, saliva has been used increasingly in systemic disorders that affect salivary composition and gland function, including Alzheimer's
disease, Sjgren's syndrome, cystic fibrosis, diabetes, and diseases of the adrenal cortex. Saliva is also proving to be an effective tool to monitor levels of hormones and therapeutic medications—as well as the presence of illicit drugs.

**Saliva**

**Table 1. Saliva Composition**

**Water**
- Large Organic Molecules
  - Proteins
  - Carbohydrates
  - Lipids

**Small Organic Molecules**
- Creatine
- Sialic acid
- Glucose
- Urea
- Nitrogen
- Uric Acid

**Electrolytes**
- Ammonia
- Magnesium
- Bicarbonate
- Phosphates
- Calcium
- Potassium
- Chloride
- Sodium
- Fluoride
- Sulphates
- Iodine
- Thiocyanate

**Major Proteins Produced by Acinar or Ductal Cells**
- Proline-rich proteins
Histatins
Cystatins
Statherin
Mucins (high and low molecular weight)
Amylases
Saliva peroxidases
Lysozyme
Lactoferrin
Secretory component of IgA
Epithelial growth factor

Compounds Transported from Blood into Saliva
Albumin
Immono-globulins IgA, IgG, IgM
Vitamins
Drugs
Hormones
Water

Research opportunities abound to develop more sensitive and specific assays to measure and understand changes in saliva beyond oral and systemic diseases to areas such as genetic defects, nutritional status, and age-specific changes.

Salivary Gland Dysfunction

Although viewed as champions of the oral cavity, the salivary glands are not spared insult or disease. The parotid, submandibular, and sublingual glands that comprise the major salivary glands are directly affected by a
variety of conditions, including infection (such as mumps), obstructions, developmental disorders, and tumors. Two major diseases, cystic fibrosis (CF) and Sjgren’s syndrome, can devastate these vital glands. In cystic fibrosis, a defect in chloride ion transport causes exocrine gland secretions, including saliva, to be thick and viscid and leads to chronic lung disease and pancreatic insufficiency. Studies of salivary acinar (salt and water secreting) cells, a convenient model for exploring mechanisms of chloride ion transport, have greatly expanded the understanding of exocrine gland transport systems in human salivary glands. The identification of the defective gene in cystic fibrosis has also led to clinical trials using gene therapy to treat this disorder.

**Sjgren’s Syndrome**

Eagerly awaiting clinical advances in salivary gene transfer are many thousands of people with Sjgren’s syndrome (SS), an autoimmune disorder that primarily affects women. Classic symptoms include dry mouth, eyes and other mucosal surfaces, accompanied in about half the cases by a connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus. The oral dryness interferes with normal functions of talking, chewing and swallowing and, deprived of the protective properties of saliva, puts SS patients at high risk for dental and oral infections. Investigators are looking closely at alterations in salivary gland function associated with Sjgren’s syndrome. Because salivary involvement in this disorder is highly variable, ranging from mild impairment to total loss of function, early diagnosis is difficult. Studies are aimed at defining criteria for early and unequivocal diagnosis and establishing clinically useful markers for salivary gland disease activity. The inflammatory cytokine interleukin-6 (IL-6), for example, has been found at elevated levels in the saliva of SS patients and may serve as a marker for this disorder. IL-6 and other elevated cytokines are thought to play a significant role in the pathogenesis of Sjgren’s syndrome; the mechanism, however, is unknown.

Research is also under way to develop a new noninvasive or minimally invasive means of diagnosing salivary gland involvement in SS using laser spectroscopy techniques. Currently, definitive diagnosis requires surgical removal of minor salivary glands. Laser spectroscopy to detect labeled cells specific to Sjgren’s syndrome would not only obviate the need for surgery, but would also permit repeated testing of the salivary glands to follow the course of the disease and effectiveness of therapy.
Xerostomia

Another major source of dry mouth—medication—affects most of us at some time in our lives. More than 400 prescription and over-the-counter drugs are known to have xerostomic effects. Many of these medications are taken daily, particularly by older Americans, to treat chronic conditions such as hypertension and depression. Although salivary gland function does not normally decline with age, the oral dryness experienced by many older persons from certain diseases and long-term medications heightens their risk for oral and dental infections. As the population ages—by 2010, 40 million Americans will be 65 or older—vulnerability to an array of chronic and disabling disorders and the oral effects of medications prescribed for their management will present significant challenges to health care providers. Elderly patients, in or out of the hospital, are more than twice as susceptible to adverse drug reactions than are younger patients. When one considers that the elderly fill 18 prescriptions annually and take three times as many drugs as does the general population, one can understand how xerostomia is a major concern. According to one survey, the three most frequently occurring oral side effects of prescription drugs are xerostomia (80.5%), taste disorders or dysgeusia (47.5%), and stomatitis (33.9%). By further examining only the xerostomia-producing drugs studied in the survey (Table 2), one can see the potential for a compounded xerogenic effect in the patient who takes more than one medication each day. The table shows drugs whose potential ranges from a slight xerogenic effect to those that have a potential of up to 54 percent. The survey covers a limited sampling of all drugs used by the elderly. The dentist is in a treatment dilemma: the cause of the xerostomia is known, but the solution could prove life-threatening to the patient if the medications causing the problem are discontinued. It is critical that the dentist consults with the patient’s physician(s) about replacing the problem drugs with substitutes to palliate the symptoms of xerostomia without creating further health risks.

The drugs with the highest potential for causing dry mouth side effects are tricyclic antidepressants, antihistamines, benzodiazepine sedatives, phenothiazine antipsychotics, and anti-Parkinson medications. Drugs having lower potential for causing dry mouth are antidepressants, such as Prozac and Zoloft, diuretics, antihypertensive and NSAID’s. The drugs most commonly prescribed for the elderly are diuretics, antiarthritics, antihypertensives, narcotic analgesics, coronary vasodilators,
corticosteroids, digitalis preparations, bronchodilators, psychotropics, antispasmodics, alpha/beta blockers and analgesics. Three groups of over-the-counter medications have great potential for causing xerostomia. These include laxatives and cold/allergy products, both of which have a dehydrating effect with long-term use, and weight control products, which may contain the xerogenic agents phenylpropanolamine hydrochloride and caffeine.

**Diagnosis of Xerostomia**

At the initial patient interview a thorough inquiry is made into the patient’s medical, dental, psychosocial, dietary and pharmacological histories, both past and present. The dentist may ask questions pertaining to subjective symptoms, such as, "Do you have increased thirst?" The objective symptoms listed in Table 3 can be a helpful reference in clinical evaluation. After clinical evaluation, a simple chairside salivary flow can be performed to determine stimulated and unstimulated flow rates. The tests involve collecting whole saliva through the following techniques: spitting, draining (drooling), suctioning and swabbing.

The spitting method is a preferred means, since it is an easy chairside procedure that can be performed by the dentist or a trained dental auxiliary. In this approach, the patient is told to swallow any saliva that may be present and then to allow the unstimulated saliva to gradually seep into the mouth. After two minutes, this is expectorated into a graduated collecting vessel. Two more two-minute samples are collected, for a six-minute total. The physical characteristics and volume of the saliva are then recorded. Flow rate is expressed in ml/minute.

**Table 3. Subjective and Objective Symptoms of Xerostomia**

- Increased thirst
- Mucositis
- Increased fluid intake while eating
- Tongue sticks to the palate/or
- Difficulties in speaking, eating cheeks or swallowing
- Dry eyes, dry skin or dry nose
- Oral burning sensation in mouth
- Angular chelitis and chapped lips
- Sensitivity to acidic (citrus) and spicy
- Recurrent decay or new gingival foods
- Taste disorders
- Parotid gland enlargement
- Depapillated, cracked, glossy
- Clicking of tongue fissured or erythematous tongue
- Bad breath
- Increased food debris in the oral
- Cancerophobia,
depression cavity (extreme cases) n Accentuated gingival recession
• Thin, atrophic, friable marginal gingiva n Increased plaque accumulation

Table 4. Saliva Composition and Flow Rates

Healthy individuals
• Whole saliva n 0.3-0.5 ml/min n 1.0-3.0 ml/min
• Parotid n 0.04 ml/min/gland n 0.7 ml/min/gland
• Submandibular/ sublingual n 0.15 ml/min n 0.6 ml/min/gland

Xerostomic Individuals
• Whole saliva n 0.01-0.01 ml/min n 0.5 ml/min
• Parotid n 0.02 ml/min/gland n 0.18 ml/min/gland

A standard piece of paraffin wax or sterile elastic bands are used to obtain a stimulated saliva flow sample. The patient is asked first to swallow any accumulated saliva. Next, he or she is instructed to continually chew the wax or bands at a normal rate. Three two-minute samples are obtained. Flow rate (ml/min) and physical appearance are recorded. When paraffin wax cannot be used, two percent citric acid may be administered as a stimulant. The citric acid solution is swabbed on the dorsum of the tongue every 15 seconds. The patient’s flow rates can be compared to those listed in Table 4. A less-than-normal salivary flow can readily suggest xerostomia.

2.

Oral Pilocarpine Hydrochloride for Radiation-Induced Dry Mouth

The FDA has granted marketing approval for an oral preparation of pilocarpine hydrochloride (Salagen/MGI Pharma) for treatment of radiation-induced xerostomia (dry mouth) in patients with cancer of the head and neck. The product is the first pharmacologic treatment for dry mouth. Pilocarpine, which has been used for over a century to treat glaucoma, was first isolated from the leaves of the South American plants *Pilocarpus jaborandi* and *Pilocarpus microphyllous* in 1875.

Salagen was developed as an Orphan Drug. An estimated 40,000 cancers of the head and neck are diagnosed each year in the United States, and
most of the patients undergo radiation therapy. The radiation can cause permanent damage to the salivary glands, with a major effect on the patient’s quality of life. Direct effects can include difficulty in talking, eating, and sleeping; rapid tooth decay; and increased risk of periodontal disease and oral infections. Indirect effects can include nutritional deficiencies, weight loss, and altered social habits. Pilocarpine is a cholinergic parasympathomimetic agent with a broad range of pharmacologic effects. It increases secretion by the exocrine glands and can affect the sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucosal cells of the respiratory tract. A 5-mg tablet produces a peak plasma drug concentration of about 15 mg/mL in 1.25 hours, with an elimination half-life of 0.76 hours. Although the mechanisms of metabolism and elimination are uncertain, pilocarpine is believed to be inactivated at the neuronal synapses and probably in the plasma. Pilocarpine and its metabolites are eliminated in the urine.

**Clinical Studies**

Two pivotal studies have demonstrated the efficacy of Salagen in improving salivary function in patients with radiation-induced xerostomia. The first [Johnson JT et al. N Engl J Med. 1993;329:390-395] was a prospective, randomized, double-blind trial involving 207 patients who had received radiation therapy for head and neck cancers. The patients received 5 or 10 mg pilocarpine or placebo by mouth three times a day for 12 weeks. Oral dryness improved in 44% of the 5-mg pilocarpine group, compared with 25% of the placebo group. Overall improvement occurred in 54% of the 5-mg group, compared with 25% in the placebo group. These differences were statistically significant (p<0.05). The 10-mg pilocarpine group also showed significantly greater improvement than the placebo group. The second study [LeVeque FG et al. J Clin Oncol. 1993;11:1124-1131] was a randomized, double-blind, placebo-controlled, multicenter trial. A total of 162 patients received placebo or 2.5-mg pilocarpine tablets for 4 weeks, followed by 5-mg tablets for 4 weeks and then 10-mg tablets for 4 weeks. Patients were permitted to adjust their individual doses for best effect (up to increase therapeutic effect, down to reduce side effects). Overall global assessments showed significantly greater improvement with pilocarpine than with placebo. Active treatment also produced less need for artificial saliva, hard candy, water, and other "oral comfort agents." All the drug dosages were found to be safe, and there were no serious treatment-related adverse events.
Severity of Xerostomia Reduced When Taking Salagen Tablets

A study presented at the annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) in Minnesota, Minn. in Oct. 1996 reported that taking Salagen tablets (pilocarpine hydrochloride) during radiation therapy is better at reducing the symptoms of xerostomia (severe dry mouth) than when taking the drug after radiation therapy is completed. According to lead investigator Robert P. Zimmerman, M.D., UCLA Department of Radiation Oncology, Los Angeles, the study compared the severity of xerostomia endured by head and neck cancer patients when Salagen was administered during therapy, after therapy, and not at all. The study involved a total of 29 cancer patients: 17 who received Salagen during radiation therapy and 12 who did not take the drug during therapy. After the radiation therapy was completed, the 12 non-treated patients were placed on Salagen for one month and then compared to the concurrently treated group again. The 17 patients who began taking Salagen tablets concurrently with radiation therapy suffered significantly less from dryness and discomfort and encountered markedly less difficulty sleeping, speaking and eating. The most severe xerostomia was seen in post-radiation patients that had not yet received Salagen tablets. The results of this study concur with those from another study presented in May 1996 at the annual meeting of the American Society of Clinical Oncology by Francis G. LeVeque, D.D.S., Chief of Oral Medicine and Oncology at DMC Harper Hospital, Detroit. Dr. Leveque’s study in 16 patients showed that using Salagen tablets concurrently with radiation therapy significantly reduced oral dryness and pain, as well as the incidence of oral mucositis (mouth ulcers) by 60 percent. Radiation therapy used to treat tumors of the head and neck damages the salivary glands, reducing their ability to produce saliva. Research shows that a decrease in salivary flow typically begins as early as the first week of radiation therapy. The resultant dry mouth predisposes patients to a multitude of oral complications, including mucositis, oral infections, and tooth decay. Additionally, patients who suffer from this condition can have difficulty speaking, eating and swallowing. Salagen is the only prescription pharmaceutical indicated in the United States for the treatment of symptoms of radiation-induced xerostomia. It works by stimulating the moisture producing glands throughout the body, including the salivary and tear glands. The most common side effect with Salagen treatment has been moderate sweating. Other side effects have included nausea, runny nose, chills, flushing, urinary frequency, dizziness, and
fatigue. Salagen use is contraindicated in uncontrolled asthma, known
hypersensitivity to pilocarpine, and when miosis (contraction of the pupil)
is undesirable, in acute iritis and narrow-angle glaucoma. Patients with
cardiovascular disease should receive pilocarpine only under close
supervision. Concomitant administration of beta-adrenergic antagonists
could result in conduction disturbances. Salagen is available as 5-mg film-
coated tablets. The recommended dosage is 5 mg three times a day,
titrated up to 10 mg three times a day if the lower dosage is not
effective. However, the lowest effective dosage should be used to avoid
or minimize side effects.

Salagen Indication Extended to Dry Mouth in Sjgren's Syndrome

The United States Food and Drug Administration has granted marketing
clearance to MGI Pharma, Inc.'s Salagen tablets (pilocarpine HCl) as a
treatment for the symptoms of dry mouth resulting from Sjgren's
syndrome, a chronic, autoimmune disease (Feb. 1998.)

The company conducted two Phase III human clinical studies, involving
629 patients, to determine the ability of Salagen tablets to provide relief
for the symptoms of dry mouth caused by Sjgren's syndrome. Study
results showed significant increases in salivary flow following the first
dose of Salagen tablets, which was maintained throughout the duration
(12 weeks) of the study.

The studies also showed an improvement in overall dry mouth conditions,
as well as specific symptoms, including: severity of dry mouth and mouth
discomfort; the ability to speak, sleep and swallow food without drinking;
and a decreased use of saliva substitutes. The most common side effects
related to the drug were sweating, urinary frequency, chills and
flushing. Sjgren's syndrome is a chronic, inflammatory, autoimmune
disease that gradually damages the moisture-producing glands, such as
the salivary glands, causing patients to suffer significantly from the
resulting dryness. Symptoms of the disease can vary depending upon
which moisture-producing glands are affected and to what degree the
glands are damaged. As a primary condition, Sjgren's syndrome affects
approximately 200,000 people in the U.S., most commonly women.
Sjgren's syndrome can also occur secondarily to other autoimmune
diseases, particularly rheumatoid arthritis, raising the number of people
in the U.S. who may suffer from some form of Sjgren's syndrome to
about one million.
The U.S. Public Health Service’s office on Women’s Health lists Sjogren’s syndrome, along with other autoimmune diseases, as an important and neglected health issue affecting American women. Taken together as a class of illnesses, autoimmune diseases are the fourth leading cause of disability in women, with an annual cost to the nation of an estimated $86 billion.

Source: Medical Sciences Bulletin Pharmaceutical Information Associates, Ltd.

Table 1. Incidence of Adverse Experiences With 5 mg.
Pilocarpine HCl

<table>
<thead>
<tr>
<th>Adverse experiences</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>29%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
</tr>
<tr>
<td>Chills</td>
<td>3%</td>
</tr>
<tr>
<td>Rhinitis (rhinorrhea)</td>
<td>5%</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6%</td>
</tr>
</tbody>
</table>

3.

Differentiation of Dry Mouth Etiology

Dry mouth is a frequently voiced complaint. In some older populations, persistent dry mouth is reported in as many as 25% of the individuals queried. Symptomatic dry mouth can have a marked impact on an individual’s quality of life. When oral dryness is the result of diminished or altered salivary function, there may be profound effects on oral functions and structures as well. Too often, the complaint of dry mouth is dismissed as being trivial or is ascribed to a vague cause such as aging.
What is required for the practitioner is a coherent, systematic diagnostic approach to the dry-mouth patient. This should establish (if possible) a definitive diagnosis, assess secretory capabilities and (in cases of salivary hypofunction) attempt treatment to augment salivary output and to protect and support oral functions. The subjective complaint of dry mouth is termed "xerostomia". Xerostomia may result from both salivary and non-salivary causes (Table 1). As can be seen from Table 1, all complaints of dry mouth are not indicative of salivary gland dysfunction. It is important to distinguish dry mouth that is related to true secretory hypofunction, since these individuals are at risk for disturbances of oral hard and soft tissues. They should be identified and placed on appropriate preventive and corrective regimens. Many non-salivary causes of xerostomia can be discerned readily by history. If a cause is not apparent, a full evaluation is warranted. Certain of these causes (such as oral sensory dysfunction) require specialized diagnostic procedures, while others are diagnoses of exclusion (such as psychogenic xerostomia). Critically, it must be recognized that the complaint of xerostomia is not sufficient for the diagnosis of salivary dysfunction. Conversely, the absence of a complaint of dry mouth is not a guarantee of adequacy of salivary function. It has been estimated that salivary output must decrease by approximately 50% before dryness is appreciated. It is therefore possible for a substantial decline in secretion to occur without symptomatic awareness. This argues for objective measurement of salivary function as a means of diagnosing secretory hypofunction. This is an important tool; however, the diagnostic value of a single measurement of salivary output is limited by the very wide variation in normal function. Of greatest utility are serial measurements of salivary function and a comprehensive evaluation approach. Such a scheme is shown in Table 2. The techniques are listed in the order of increasing invasiveness and are discussed below.

Table 1. Causes of Complaints of Xerostomia

<table>
<thead>
<tr>
<th>Nonsalivary</th>
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<tbody>
<tr>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Cognitive alteration</td>
<td></td>
</tr>
<tr>
<td>Oral sensory dysfunction</td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salivary</th>
<th></th>
</tr>
</thead>
</table>
• Diminished salivary output
• Altered salivary composition

Table 2. Methods of Evaluation of Salivary Function

• History
• Symptom questions
• Physical examination (signs of secretory hypofunction)
• Measurement of salivary output
• Sialochemical analyses
• Serum laboratory studies
• Salivary imaging
• Salivary biopsy

History

The cornerstone of medical diagnosis is a thorough history. In the dry-mouth patient, one should seek, in particular, a past history of conditions or treatments which might result in salivary alterations. These include radiation therapy to the head and neck region, usually by external beam. There are also many systemic disorders which may cause salivary gland dysfunction. Primary Sjögren’s syndrome and secondary Sjögren’s syndrome, in association with other connective tissue diseases, have profound effects on salivary glands. Other systemic conditions with salivary effects include cystic fibrosis, sarcoidosis, diabetes, alcoholic cirrhosis, and many additional examples. In each case, a full evaluation of salivary function is indicated to determine the extent of secretory involvement. Pharmaceuticals are the most frequent causes of xerostomia complaints. There are >400 medications which report dry mouth as a side-effect. Interestingly, there are only a small number which have been demonstrated to cause diminished salivary function. Even among the classes of drugs which are known to decrease salivary flow (such as antidepressants and antihypertensives), not all medications have measurable effects. Indeed, certain drugs have been shown to produce marked symptomatic dryness without alterations in the salivary flow.

Symptom Review

Although symptomatic xerostomia is not sufficient for a diagnosis of salivary dysfunction, detailed evaluation of more specific dryness complaints can help to identify individuals likely to have true secretory hypofunction. In a study of 100 consecutive individuals presenting for
evaluation at a "dry mouth" clinic, specific questions concerning oral dryness and other oral functions were asked in a structured interview. Salivary function was then determined from each major salivary gland in both resting and stimulated states. Certain complaints were found to correlate well with decreased salivary flow, while others were unrelated to salivary function. In general, the questions which concerned functions dependent on saliva (such as swallowing) were significantly associated with secretory capabilities. Specifically, four complaints were identified which correlated well with decreased glandular function: oral dryness when eating, a need to sip liquids to swallow dry foods, difficulty swallowing, and the perception of too little saliva in the mouth. These questions serve as a useful screening tool to determine those individuals with a great likelihood of being found to have diminished salivary flow.

Physical Examination

A number of findings on physical examination may indicate salivary dysfunction. The mucosa may have a desiccated or glossy appearance. The tongue may be fissured and red, with partial or complete papillary atrophy. Saliva pooling in the floor of the mouth will not be seen. Saliva should be expressed from the duct orifice and may appear viscous or opaque. Oral candidiasis of the pseudomembranous or erythematous type is frequent, and angular cheilitis may be seen. Dental caries, particularly involving the tooth at the gingival margin or on cusp tips, is characteristic. Recurrent caries may be severe. Finally, the major salivary glands should be inspected and palpated for signs of enlargement or tenderness.

Measurement of Salivary Output

There are many methods for measurement of salivary output. Whichever method is selected, the critical issues are to use a well-defined, reproducible technique and to control as many of the physiological variables as possible. Whole saliva, the combined fluid contents of the mouth, can be collected easily in an office setting with no specialized equipment. It provides a general assessment of salivary capabilities. Greater detail and a sample that can be used for further constitutive analysis are obtained by collection of individual gland secretions. Both parotid and submandibular secretions can be collected by means of individualized collectors. Salivary flow rates alone may be useful in the diagnosis of certain conditions such as autoimmune exocrinopathies. Determination of salivary flow also allows one to recognize severe cases of salivary hypofunction and to obtain information concerning progression
of systemic exocrinopathies. It is generally accepted that the normal resting flow rate (RFR) is about 0.3-0.4 mL/min, the stimulated flow rate (SFR) about 1-2 mL/min. Problems arise when attempts are made to define a specific cut-off point between normal and abnormal rates. Most clinicians use 0.1 mL/min as the cut-off point for resting whole saliva, and 0.5 mL/min for stimulated saliva.

The resting secretions play the principal role in protecting and maintaining the integrity of the oral tissues. Although RFRs vary widely from person to person, they are quite stable for each individual. Low RFRs indicate that the basal activity of the glands is depressed. Several studies have shown that the RFRs of whole saliva are low in SS patients. Stimulated saliva plays a major role in mastication and deglutition. Low SFRs indicate a decline in the capacity of the glands to respond to external stimuli. It is known that SFRs demonstrate greater variability than do resting rates. Like other organs, the salivary glands can compensate functionally for a modest loss of parenchyma. Thus, in the early stages of the disease, SFRs may be normal or only slightly reduced. In later stages, there is a much greater loss of tissue, and the SFRs decrease significantly. Female patients with low resting (± 0.1 mL/min) and stimulated (± 0.5 mL/min) whole saliva flow rates have Sjögren’s syndrome until proven otherwise.

Sialochemical Analyses

Saliva is a very complex fluid containing a mixture of many protein and non-protein constituents. Extensive work has been done describing alterations in salivary composition in a variety of salivary and systemic conditions. While changes in saliva are found frequently, a limiting factor in sialochemical analysis as a diagnostic tool is a lack of specificity. In general, alterations in saliva resulting from glandular inflammation or decreased output are similar, regardless of the specific etiology. Recent research suggests that, in autoimmune exocrinopathies, there may be specific salivary changes which will have diagnostic value. This may prove to be of value as a means of non-invasive diagnosis and monitoring of patients.

Laboratory Studies Clinical laboratory evaluation is an important aspect of diagnosis in suspected Sjögren’s syndrome. There are specific markers of autoimmunity which are found in a high percentage of patients. Determination of the presence of significant titers of anti-nuclear antibodies, antibodies to the extractable nuclear antigens SS-A (Ro) and
SS-B (La), and rheumatoid factors may be useful. Additional tests which have diagnostic significance include quantization of serum immunoglobulins, the erythrocyte sedimentation rate, and white blood cell number. More specialized studies (such as serum and urine immunoelectrophoresis) should be considered in the appropriate clinical setting.

**Salivary Imaging** Imaging of the salivary glands can provide valuable information in the diagnosis of cases of acute and chronic gland enlargement. Magnetic resonance imaging (MRI) is a useful technique due to the high water content of the salivary glands. MRI can distinguish between solid and cystic masses of the glands with excellent resolution and will also visualize regional lymphadenopathy. This may be important for evaluation of the chronically enlarged glands which may be found in patients with Sjögren's syndrome. Sialography, the instillation of a radiopaque fluid into the gland via retrograde infusion through the main duct, provides clear visualization of the anatomy of the ducts and integrity of the acini. It is valuable in identification of non-calcified sialolith and certain salivary tumors. Characteristic changes have been reported in Sjögren's syndrome, but the diagnostic specificity is questionable.

**Salivary Biopsy**

Salivary biopsy provides definitive tissue diagnosis of salivary pathology. In cases of suspected Sjögren's syndrome, a labial minor salivary gland biopsy with appropriate histomorphometric grading is the best single criterion for definitive diagnosis of the salivary component. Similar diagnostic information can be obtained with biopsy of the major salivary glands (parotid or submandibular) but with increased morbidity. Demonstration of a focal, peri- ductal mononuclear cell infiltrate is the most specific test available presently for the salivary component of Sjögren's syndrome. The increased risk of lymphoma in Sjögren's syndrome makes this examination essential in patients with chronically enlarged salivary glands.

**Summary**

A systematic approach to the dry-mouth patient allows one to recognize individuals with salivary gland dysfunction and to establish a diagnosis of the cause of salivary alteration. Identification of secretory hypofunction should trigger appropriate preventive measures and therapeutic
approaches. With early intervention, one may prevent or limit the effects on oral tissues and functions of salivary gland disease.

Source: Advances in Dental Research, Vol. 10, No. 1. April 1996.
International Association for Dental Research

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4.

Gene Transfer Triggers Saliva Production in Damaged Salivary Glands

Using gene transfer technology in animals, scientists at the NIDR have tricked non-fluid-producing cells into making saliva. Their work could one day lead to a new treatment for the thousands of Americans whose salivary glands are damaged by radiation therapy for head and neck cancer.

While head and neck radiation therapy kills cancerous cells, it also often destroys the acinar (fluid-producing) cells of salivary glands that lie within the field of radiation. When this occurs, patients are unable to produce adequate saliva, and as a result suffer a host of long-term problems including xerostomia (dry mouth), inflammation of the mucous membranes lining the mouth, dental caries, frequent infections of the mouth and pharynx, and difficulty with swallowing, speech, and taste. Although clinicians and researchers have recognized these side effects for nearly a century, they have had little to offer patients in the way of treatment.

Re-Engineering Cells

Now NIDR researchers may have found a way around the problem by coaxing cells into doing what doesn’t come naturally. Unlike acinar cells, ductal cells in salivary glands frequently are not destroyed by irradiation.
But ductal cells lack the ability to make or secrete saliva. The researchers sought to re-engineer ductal cells into fluid-producing cells by giving them the gene for an aquaporin protein. Aquaporins are a recently discovered family of proteins that form pores in cell membranes, through which fluid can pass. The scientists inserted an aquaporin gene into an adenovirus—similar to a cold virus—that had been genetically altered so it could not reproduce. After irradiating the salivary glands of rats to significantly diminish saliva production—mimicking what happens to head and neck cancer patients following radiation therapy—the researchers infected the animals' salivary glands with the adenovirus carrying the aquaporin gene. Remarkably, the rats' salivary glands produced fluid. Although the investigators caution that it may be several years before this technique can be tried in humans, they are optimistic about the potential use of the therapy for restoring salivary gland function. "It is an important first step to managing a condition for which no suitable and effective therapy is currently available," said Dr. Bruce Baum, chief of the NIDR Gene Therapy and Therapeutics Branch and principal investigator on the study.

Production of Fluid

In the first stage of their study, the researchers irradiated a group of rats with a single dose of radiation that, in rats, causes moderate salivary gland damage. A second group of rats served as controls and were sham irradiated—that is, they were placed in the irradiator, but it was not activated. Three months later, the irradiated rats experienced a 30 percent reduction in salivary flow. The investigators then infected the salivary glands of both irradiated and control rats with an adenovirus. Some animals received the adenovirus containing the aquaporin gene; others were given a control virus without the aquaporin gene. Several days later, the animals' salivary flow was measured. Irradiated rats who received the virus containing the aquaporin gene secreted nearly 2-3 times as much saliva as irradiated rats infected with the control virus. In the next stage of the study, one group of rats was exposed to an even higher level of radiation, and a control group was sham irradiated. Four months later, salivary secretion decreased by 64 percent in the irradiated rats, but not in the control animals. The researchers note that this level of salivary hypofunction is similar to what head and neck cancer patients can experience following radiation therapy. In addition, the salivary glands of the irradiated rats showed a significant loss of acinar cells. When the irradiated rats' salivary glands were infected with an
adenovirus containing the aquaporin gene, their salivary secretion increased two-fold, approaching a normal level.

**Issues to Resolve**

Findings from this study suggest the possibility of someday using gene therapy to correct the salivary gland defects that result from head and neck radiation therapy. The researchers point out, though, that the fluid-producing effect from the adenovirus infection is a transient one, since the viral infection does not last indefinitely. The next step, they say, will be to conduct similar studies in nonhuman primates. The investigators also will assess the composition of the fluid produced by aquaporin-infected glands to see if it functions like normal saliva.

Source: National Institute of Dental Research

5.

**Dry Mouth or Xerostomia: Patient Information**

Do you feel like you have less saliva than you used to? Does your mouth feel dry especially at mealtime? Do you have trouble eating dry foods? Is swallowing difficult? Do you need to moisten your mouth often or sip liquids often?

If you answer yes, you are one of many people who suffer from xerostomia ("zero-stoh'-me-a.") Xerostomia can cause health problems by affecting nutrition as well as psychological health. It can contribute to and increase the chances of contracting tooth decay and mouth infections. With the aging of America the number of older Americans is increasing. It is normal for the gums to recede as we age and the incidence of root surface decay is increasing especially in people who are taking certain medications.
What is dry mouth?

Many people who suffer from dry mouth, or xerostomia exhibit one or more of the following symptoms:

- The need to moisten their mouth frequently
- Mouth is dry at bedtime
- Less saliva is present than before
- Difficulty swallowing
- Trouble eating foods such as crackers or toast

Most cases of dry mouth are caused by the failure of the salivary glands to function normally. However, in some people dry mouth occurs even though their salivary glands are normal. Although dry mouth is not a disease itself, it can be a symptom of certain diseases. Dry mouth is also a common side effect of some prescription and over-the-counter medications and medical treatments.

Saliva

Saliva has important functions which include:

- Wash away food debris and plaque from the teeth to help prevent decay.
- Limit the growth of bacteria that cause tooth decay and other mouth infections.
- Bathe the teeth and supply minerals that allow remineralization of early cavities.
- Lubricate foods so they may be swallowed more easily.
- Provide enzymes that aid in digestion.
- Help us enjoy foods by aiding in the "tasting" process.
- Moisten the skin inside the mouth to make chewing and speaking easier.

What happens when you have dry mouth?

Patients with dry mouth have a range of discomfort and symptoms. Some people feel a dry or burning sensation in their mouths or an inability to chew, taste, swallow and speak. Changes in saliva can also affect oral and dental health. Severe cases of dry mouth can include symptoms such as splitting or cracking of the lips and/or corners of the mouth, changes in
the surface of the tongue, rampant tooth decay, ulceration of the mouth’s linings, and infection.

**What causes dry mouth?**

*Medications*

Over 400 commonly used drugs can cause the sensation of dry mouth. The main culprits are antihypertensives (for high blood pressure) and antidepressants. Pain killers, tranquilizers, diuretics and over-the-counter antihistamines can also decrease saliva.

*Cancer Treatment*

Radiation therapy can permanently damage salivary glands if they are in the field of radiation. Chemotherapy can change the composition of saliva, creating a sensation of dry mouth.

*Nerve Damage*

Trauma to the head and neck area from surgery or wounds can damage the nerves that supply sensation to the mouth. While the salivary glands may be left intact, they cannot function normally without the nerves that signal them to produce saliva.

*Diseases*

Sjgren’s Syndrome is an autoimmune disorder whose symptoms include dry mouth and dry eyes.

*Other*

Bone marrow transplants, endocrine disorders, nutritional deficiencies such as vitamin A, vitamin B12, iron or zinc, anemia, anxiety, mental stress, and depression can all be causes of dry mouth.

*Is relief available?*

Although there is no single way to treat dry mouth, there are a number of steps you can follow to keep teeth in good health and relieve the sense of dryness. These suggestions will not correct the underlying cause of xerostomia, but may help you feel more comfortable.
To preserve your teeth:

- Brush your teeth at least twice a day.
- Use dental floss daily.
- Use a toothpaste that contains fluoride. Ask your dentist about using a topical fluoride.
- Avoid sticky, sugary foods or brush immediately after eating them.
- See your dentist at least three times a year for cleanings and early treatment of cavities.
- Ask your dentist if you should use a remineralizing solution or prescription strength fluoride.

To relieve dryness and preserve the soft tissue:

- Take frequent sips of water or drinks without sugar.
- Pause often while speaking to sip some liquid. Avoid caffeine-containing coffee, tea, and soft drinks.
- Drink frequently while eating. This will make chewing and swallowing easier and may increase the taste of foods.
- Keep a glass of water by your bed for dryness during the night or upon awakening.
- Chew sugarless gum. The chewing may produce more saliva.
- Eat sugarless mints or hard sugarless candies, but let them dissolve in your mouth. Cinnamon and mint are often most effective.
- Place a small piece of lemon rind or a cherry pit in your mouth. The sucking action helps stimulate saliva.
- Avoid tobacco and alcohol.
- Avoid spicy, salty, and highly acidic foods that may irritate the mouth.
- Ask your dentist about using artificial salivas to help lubricate the mouth.
- Use a humidifier, particularly at night.

**What is being done about dry mouth?**

At the National Institute of Dental Research (NIDR), one of the National Institutes of Health in Bethesda, MD, scientists study the causes of dry mouth and possible treatments for this condition. In 1983, they opened a Dry Mouth Clinic to evaluate, diagnose, and treat patients with salivary gland dysfunction.
Researchers at the NIDR Dry Mouth Clinic have developed better methods of diagnosing salivary gland dysfunction. A complete evaluation of a patient with dry mouth includes measurement of both "stimulated" salivary flow—found when a person actively chews, sips, or tastes sour substances—and "unstimulated" flow—found when a person is at rest or sleeping. Researchers also analyze saliva composition and look at other aspects of saliva secretion to distinguish between salivary gland dysfunction and other causes of dry mouth.

The investigators are now testing a drug—pilocarpine—to treat dry mouth in patients with minimally functioning salivary glands. Their studies show that pilocarpine can stimulate saliva production and relieve a patient’s sense of oral dryness without causing untoward side effects. The increased output of saliva might also help prevent tooth decay, ulcerations, and infections. Further studies are needed, however, before the drug will be available to the public. NIDR investigators are also looking into other possible treatments for dry mouth. Several research studies focus on the cause of Sjögren’s syndrome and treatment for the dry mouth associated with this condition.

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