1 The Extraoral and Intraoral Soft Tissue Head and Neck Screening Examination

It is paramount that the dental clinician establishes a repeatable, logical, sequentially organized, and systematic approach to screening the soft tissues of the head and neck region. It should be understood that this is not an "oral cancer screening," since all abnormal conditions should be detected. Performing an oral cancer screening means looking for a single condition, cancer, at a single point in time; the dental clinician performs a complete exam, looking for all soft tissue abnormalities at a single point in time. There is no universally acknowledged step-by-step approach; therefore, the following is the one we adhere to and it can be modified as desired. The important point is that, whatever sequence is established, it should be strictly adhered to each time to ensure that no step is omitted. A suggested ideal sequence of steps for a complete oral mucosal screening procedure of a new patient includes the following:

- Introduction to the patient
- Patient's chief complaint
- History of the present illness
- Medical (including social) and dental histories
- Physical examination (to detect the site, morphology, and color of abnormalities)
- Review of data and formulation of a clinical differential diagnosis
- Additional clinical and laboratory tests ordered, as indicated
- Final definitive diagnosis with a treatment/management plan formulated

Certainly, the clinician should establish a pleasant rapport with the patient so that excellent communication and trust are established. Often, the most critical or important piece of information a patient possesses does not get transmitted to

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the many forms filled out at the initial dental appointment. Once the patient's trust, confidence, and respect have been secured, the patient's chief complaint must be established. This can be a specific dental problem or a more generic goal such as "I need a checkup exam."

If the patient voices a specific reason for the dental appointment, it is very important to gather as much subjective information from him or her as possible. The collective sets of subjective information are the patient's symptoms. Symptoms include descriptions such as pain, burning, dry mouth, soreness, swelling, roughness, and paresthesia. Whatever the symptom, its specific nature should be questioned, such as onset, duration, periodicity, nature or character, severity, and triggering factors or association. This information helps establish the history of the present illness. The clinician gathers a pocketful of diagnostic clues provided by the patient and combines them with the clinician's pathology knowledge to guide him or her to ask appropriate and insightful follow-up questions. Thus, the clinician acts as a detective and must possess foundational knowledge of head and neck disease and pathology in order to learn more about the patient and gather more clues for the formulation of a well-honed clinical differential diagnosis. Subsequent chapters of this book provide foundational knowledge – both general and specific – of the most common soft tissue head and neck pathology.

Following determination of the history of the patient's present illness, the medical history is reviewed with the patient. Typically, the patient has previously completed a detailed form providing the clinician with basic information about childhood diseases, vaccinations, hospitalizations and prior surgeries, any current medical care, date of the last physical examination, and medications (i.e. prescription and over-the-counter, including herbs) being taken or previously used, especially in the past 6 months. Details about the medications, including name, dosage, and duration of use, are recorded. A complete review of systems (e.g. cardiovascular, pulmonary, renal, endocrine, nervous system) is performed to gather more details than the initial "yes" or "no" responses. In addition, the medical history also includes the patient's psychological and socioeconomic profiles as well as social habits (e.g. tobacco and alcohol abuse).

Next, the dental history, including details of any oral habits, is gathered. It is important to note decayed, missing, and restored teeth as well as any active caries; periodontal disease; history of extractions and other oral surgery procedures; tooth vitality status; and any need for patient premedication. Any previous problems during dental care are discovered and discussed. Oral habits include the patient's technique and frequency of flossing, brushing, use of mouthrinse, and occlusal disharmonies.

Physical Examination

It is popular to compare the left and right side for bilateral symmetry while understanding that perfect symmetry is often not present within the range of normal. This is particularly important in order to visualize enlarged lymph nodes or parotid glands.

Extraoral Sites

Specific sites include the following:

- Hair and facial skin
- External eyes
- External ears
- Temporomandibular joints
- Facial muscles
- Nasal vestibule
- Thyroid gland (anterior neck)
- Lymph nodes (lateral and posterior neck, supraclavicular notch)
- Parotid gland

Assess the hair for thickness and loss; carefully examine the sun-exposed facial skin for ultraviolet damage and lesion development, as well as the neck, ears, forehead, nasal bridge and alae, malar region, eyebrows/eyelids/eyelashes, vermilion of the lips, and the chin. Next, perform careful palpation of each of these sites to rule out the presence of deeper, connective tissue and other types of tissue swellings.

Palpate all lymph nodes and note any enlargement for additional testing since normal lymph nodes are soft and not palpable (Fig. 1.1). Specifically, the subcutaneous tissue is digitally kneaded with a rotating motion in the areas of lymph nodes based on the clinician's knowledge of anatomy. This process can begin in the submental area, below and lingual to the chin, against the mylohyoid muscles. Next, palpate the submandibular nodes by pressing the tissue below the jaw against the medial side of the mandible or by bimanual palpation with one finger in the mouth and the other externally pushing up. Next, palpate the parotid gland and its associated lymph nodes – look and feel anterior and posterior to the ear. Next, palpate the cervical lymph node chain. The posterior cervical chain is along the back of the neck, and the anterior and deep cervical chain is along the

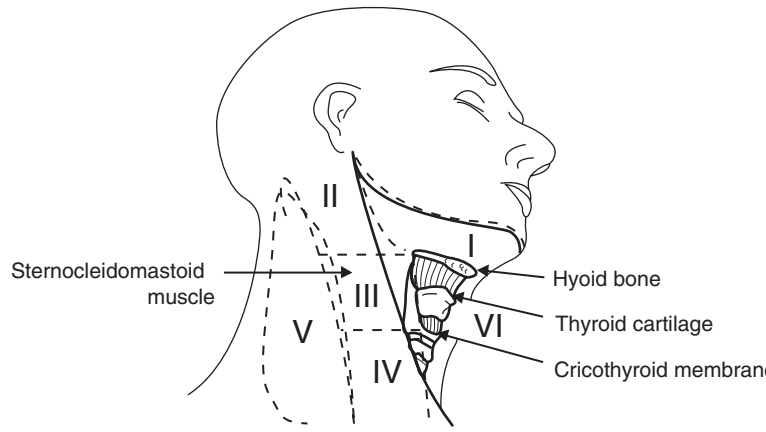

Figure 1.1 Cervical lymph node levels.

front. An anatomical landmark for the latter nodes is the sternocleidomastoid muscle – trace from behind the ear to the clavicle, kneading deep and medial to it. The postauricular and retrosternomastoid region should also be palpated along with the back of the neck. Lastly, palpate the thyroid gland by placing fingers gently over it and have the patient swallow. Sometimes, in order to discover an enlargement, the grouped fingers are placed on one side of the larynx and pushed laterally while palpating the opposite side.

Intraoral Sites

Specific mucosal covered sites include the following:

Oral cavity (Fig. 1.2a,b)
- Tuberosity/hamular notch
- Attached gingiva
- Retromolar pad/trigone area
- Vestibule (also called the mucobuccal fold)
- Buccal mucosa
- Labial mucosa
- Tongue (dorsal, ventral, and lateral surfaces)
- Floor of the mouth
- Hard palate
- Submandibular and sublingual glands

Oropharynx (Fig. 1.3a,b)
- Soft palate
- Tonsillar pillars and fossa
- Tongue (base)
- Pharynx (lateral and posterior walls)

It is recommended that the same examination sequence be followed each time, first by visual examination and then by palpation. As mentioned previously, any sequence can be used as long as it is organized and there is understanding of the findings and the significance of deviations from normal. Palpation should be bimanual or bidigital and, whenever possible, by direct vision. The following is a detailed suggested descriptive narrative:

1. *Lips* – Have the patient slightly part his or her lips to examine the upper and lower vermilion borders and the left and right commissures. Then, with the patient's teeth occluded, evert both the upper and lower lips to expose the labial mucosa. Observe the maxillary frenum, which at times may exhibit a mucosal tag, a variation of normal. As the upper and lower labial mucosa become dry, observe the minor salivary glands and attempt to express mucin from them. While the lips are everted, the anterior maxillary and mandibular vestibules can be observed.
2. *Labial and buccal mucosa/alveolar mucosa and attached gingiva/trigone* – Slide your fingers posterior on the left and right buccal mucosa as well as the posterior portion of the vestibules. The parotid papilla overlying Stensen's duct should be of normal coloration. To verify function, dry it, and then have

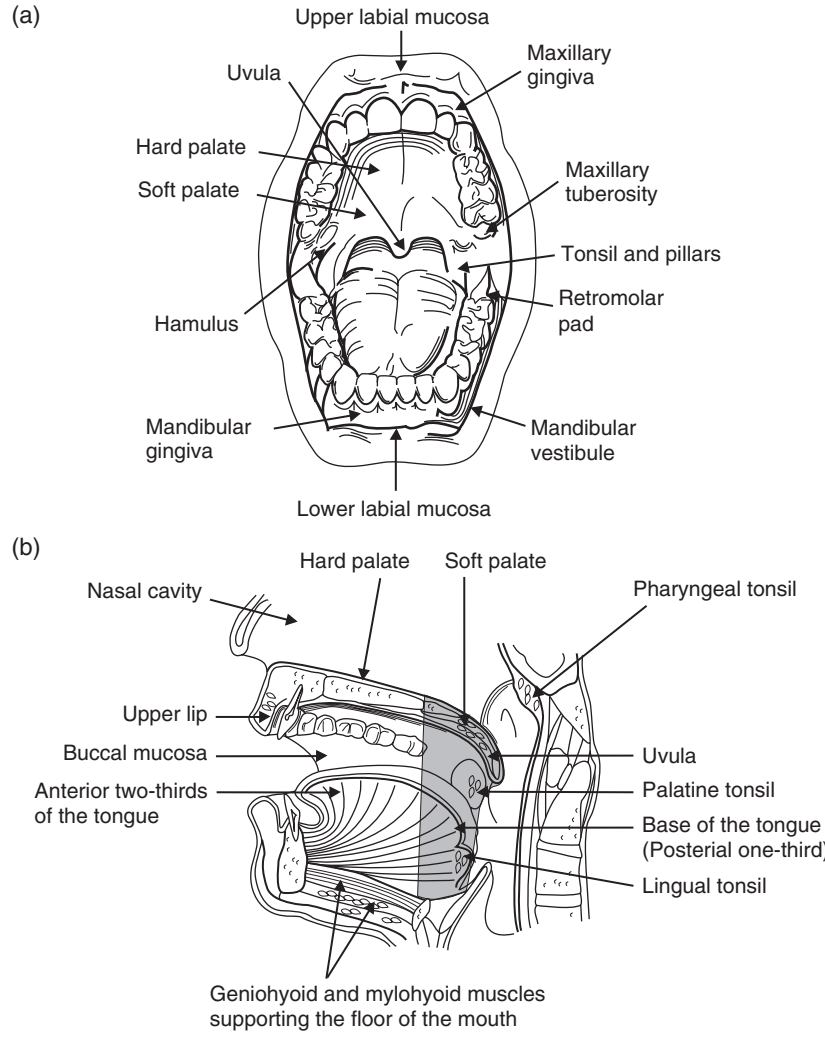

Figure 1.2 (a) Oral cavity proper, frontal view. (b) Major components forming the boundaries of the oral cavity proper, sagittal view. The oral cavity (unshaded area) is divided from the oropharynx (shaded area) anteriorly/posteriorly at the posterior extent of the anterior two-thirds of the tongue; the superior/inferior extent of the oral cavity is the hard palate and floor of the mouth; the superior/inferior extent of the oropharynx is the nasopharynx and hypopharynx.

the patient's mouth wide open so that the cheek is stretched taut. Place four fingers flat on the face over the parotid gland in the preauricular area and milk the gland by using digital pressure to compress it against the masseter muscle or ramus area. Most patients exhibit a subtle white line at the occlusal plane of the buccal mucosa (i.e. linea alba), which is considered a variation of normal. While retracting the cheeks, use mirror-assisted indirect vision to examine the tuberosity/hamular notch area and then, with direct vision, use the fingers and a mirror face to retract the buccal and labial mucosa, and observe the facial alveolar mucosa, mucogingival junction, attached gingiva, and free

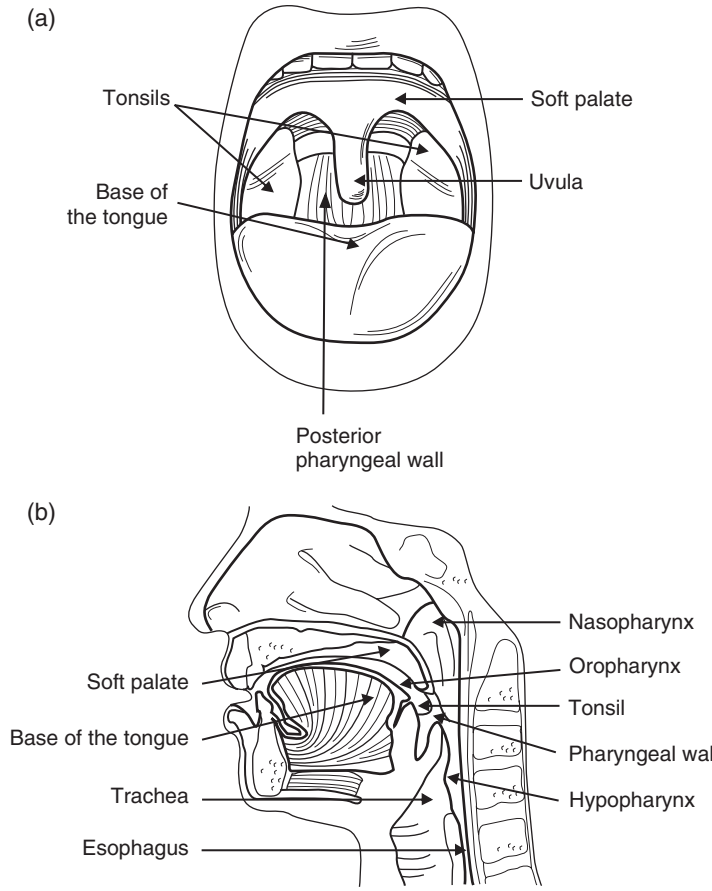

Figure 1.3 Oropharynx. (a) Frontal view and (b) sagittal view.

marginal gingiva on the maxilla and mandible as well as on the lingual mandible. Lastly, inspect and then palpate the retromolar pads and trigone area.

3. *Hard palate* – Examine its anterior portion, the rugae (firm folds), and then the posterior, which at times exhibits a subtle pink-white change due to slight amounts of extra keratin on the surface. Laterally, in the posterior hard palate area, many minor salivary glands (mucinous) are present and thus the palate can have a subtle pink-blue appearance. Often, the most posterior extent of the hard palate's midline has two small paired depressions, the fovea palatine.
4. *Tongue* – Gently hold the anterior tip with gauze and pull forward and to the left and right. While the tongue is in this position, examine the lateral and ventral surfaces of the tongue, including the most posterior lateral extent, which is occupied by foliate papillae. The anterior two-thirds of the dorsum should demonstrate filiform papillae, and often there is a mild white coating caused by slough of the keratin from the filiform papillae; in dark-skinned patients scattered physiologic pigmentation of the filiform papillae is frequently noted. Among the filiform papillae, the larger and fewer dome-shaped fungiform papillae are noted. At the junction with the posterior one-third, the dorsal

surface exhibits an upside-down "V" linear series of circumvallate papillae. After freeing the tongue, instruct the patient to protrude the tongue, move it left and right, and touch the hard palate with its tip. In this way, the tongue's full mobility is confirmed, and the latter movement enables further inspection of the tongue's ventral surface.

5. *Floor of the mouth* – Examine the anterior portion with its left and right sublingual plicae (V-shaped caruncula with its vertex toward the face), which contain the opening of the sublingual glands. At the most anterior extent of the plicae, there are raised areas that possess the opening of the submandibular glands (i.e. Wharton's duct). The posterior portion of the floor is also examined. Palpate both the sublingual and submandibular glands by supporting the external chin with one hand and extending a finger downward in the floor of the mouth. To test salivary flow, dry the lingual carunculae, and then place one or two outstretched fingers under the chin and alongside the inferior mandible. Upward pressure directed to the submandibular gland area should produce saliva from Wharton's duct orifice.
6. *Oropharynx* – With the patient's mouth wide open, and using a tongue depressor, ask the patient to say "ah"; at this point the vibrating line (i.e. where the palatal bone ends) at the beginning of the soft palate moves, and, centrally and posteriorly, the pendulous uvula should be present. In this area, a circular distribution of lymphoid tissue is present, Waldeyer's ring, which includes the palatine tonsils, lingual tonsils (intermixed with the foliate papillae), and scattered focal collections of lymphoid tissue on the pharyngeal wall, as well as on the posterior soft palate and floor of the mouth. Visualize all aspects of the oropharynx, especially the posterior pharyngeal wall. The latter is particularly difficult to visualize in some patients, and the adenoids and base of the tongue cannot be seen by direct or indirect vision with standard dental equipment. Particular attention should be paid to the tonsillar pillars (i.e. palatoglossal and palatopharyngeal folds) and tonsillar tissue fossa area. Lastly, examine the posterior wall of the oropharynx, taking note of any normal aggregates of lymphoid tissue.

Note: In patients who have undergone a tonsillectomy, there is some residual tonsillar tissue as well as a whitish scar tissue at the site of the surgery.

Adjunctive Diagnostic Examination Methods and Devices

There has been a renewed interest in a more consistent and thorough head and neck soft tissue examination, particularly in an effort to detect potentially malignant lesions at an earlier stage of development. Unfortunately, this has led to the misnomer of performing an "oral cancer screening examination," and many dental manufacturers have developed and marketed various devices in order to provide the clinician a purported "enhanced" screening method in addition to the conventional white-light and palpation method just described. No scientific studies to date have proven that these methods or devices improve detection of any type of oral mucosal disease [1–5]. Four categories of devices have been marketed: cytology, enhanced reflectance, narrowband imaging (autofluorescence), and saliva sampling.

Exfoliative Cytology

In the early 1950s the Pap smear was introduced in order to screen the cervical mucosa for earlier detection of cervical cancer. The technique was soon investigated by dental researchers for a possible similar use with oral mucosa; however, it was soon discovered that physically scraping the oral mucosa's upper-level epithelial cells and subsequently transferring them to a glass slide, stained and cover-slipped, resulted in an unacceptable number of false positives and false negatives. The crux of the matter is that, within the oral cavity, an inflammatory component often resides in the epithelium (i.e. inflammatory exocytosis) that causes keratinocytes to appear atypical due to a reactive change induced by the omnipresent inflammation; these atypical cells are then incorrectly interpreted as representing potentially malignant dysplasia – an abnormal maturation pattern of the stratified squamous epithelium.

Transepithelial (Full-Thickness Sampling) Cytology

In 1999, a new version of oral cytology, OralCDx's "brush biopsy" (currently marketed in dentistry as the BrushTest), was marketed in the United States by Oral Scan Laboratories (Suffern, NY) [6]. It subsequently received the American Dental Association's Seal of Acceptance. The dentist, a generalist or specialist, purchases the company's cytology kit, which contains bar-coded patient information forms, a pre-bar-coded slide, a slide holder, two fixative pouches, two patented nylon bristle brushes designed to harvest an oral transepithelial specimen of disaggregated cells, and a solution vial with stand (Fig. 1.4, Fig. 1.5). Chairside, the clinician brushes the lesion until pinpoint bleeding is obtained and then subsequently spreads these cells on the microscope slide. The cytology slide specimen is then immediately fixed with alcohol and set aside to dry, and the brush is inserted into the vial and capped. Then, with the second brush, the lesion

Figure 1.4 A brush biopsy (cytology) kit as supplied by OralCDx (Oral Scan Laboratories, Suffern, NY).

Figure 1.5 A close-up view of the OralCDx proprietary brush biopsy nylon cellular collection device.

is brushed again, and without the preparation of a slide, the brush is inserted into the vial and capped (i.e. two brushes are in the vial). Once the test forms have been completed, the samples are packed in the box kit and sent, in a prepaid mailer, to the company's laboratory. A neural-net software program optically screens the slide specimen for atypical or malignant-appearing cells. Atypical cells are captured as digital images and reviewed by a cytopathologist who then issues a pathology report in one of three categories – normal, atypical, or malignant cells. If atypical or malignant cells are reported, then a mandatory gold-standard diagnostic tissue biopsy is recommended to obtain a definitive diagnosis. According to the company's information, lesions to be sampled include innocuous (i.e. unsuspicious) looking red or white "spots" within the oral cavity; in other words, lesions of the surface oral mucosa a clinician does not feel could be squamous cell carcinoma or potentially malignant (premalignant) lesions. Clinically suspicious lesions (e.g. erythroplakia in a high-risk site) are not an indication for the brush biopsy; rather, if that type of lesion has persisted for more than 14 days, then an incisional surgical tissue biopsy must be performed. Since it was introduced, the validity and positive predictive value of this cytology procedure have been challenged by some investigators and promoted by others [7–10]. In addition, other companies in other countries (Second Step Laboratory Services – Perceptronix Medical, Inc., Laboratories, Vancouver, British Columbia, Canada) have offered similar morphological cytology tests with a different nylon bristle cytology brush (Rovers Medical Devices, the Netherlands; Fig. 1.6), and they also include DNA ploidy results.

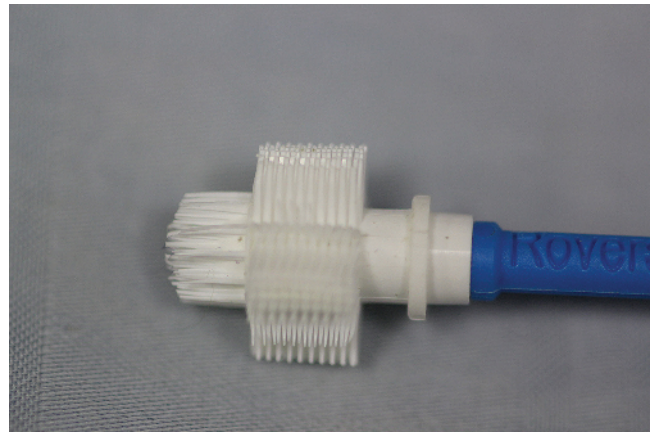

Figure 1.6 A close-up view of the Rovers cellular collection device (Rovers Medical Devices, the Netherlands).

Figure 1.7 A liquid cytology kit composed of an alcohol-based fixative transport medium and gynecological-type nylon cellular collection device.

More recently, a cytobrush technique involving liquid fixative has been introduced not only in hospitals and physician offices but also in some oral pathology laboratories. In this cytology technique, a nylon bristle cytology brush developed for gynecological ectocervical and endocervical scrapings is used to obtain a full-thickness epithelium specimen from the oral or oropharyngeal mucosal surface (clinically indicated by pinpoint bleeding spots as seen with the BrushTest), but instead of the clinician then smearing the harvested cells (i.e. keratinocytes) directly onto a glass slide (frosted or clear type), the bristle end of the brush is immersed directly into an alcohol-based fixative for transport to the oral pathology laboratory (Fig. 1.7). At the laboratory, the harvested cells in the fixative and retained on the brush's bristles are collected

and then segregated from the debris and inflammatory cells in the fixative by being placed in one of several competing manufacturers' processing machines. The harvested cells are affixed in a monolayer to the slide in a confined area, are stained and cover-slipped, and then are examined by the pathologist for cellular atypia, fungal hyphae (i.e. superficial candidiasis), or herpes-family cytopathogenic change.

One of the aforementioned companies (e.g. Forward Sciences Technologies, Inc., Houston, TX) has marketed combined use of their narrowband imaging detection device with its subsequent liquid brush cytology lesion sampling test.

Tissue Reflectance

In the early 2000s, Zila Pharmaceuticals (Division of Tolmar Corporation, Phoenix, AZ) introduced a single-use, disposable chemiluminescent screening device, ViziLite®, for early detection of leukoplakia. This FDA-cleared 501(k) medical device is based on a similar device (i.e. Speculite®) used by physicians for uterine cervical screening (Pap smear) to rule out early potentially malignant microscopic change (i.e. cervical dysplasia). Subsequently, two other companies marketed similar devices, Microlux/DL (AdDent, Inc., Danbury, CT; Fig. 1.8) and Orascoptic DK (Kerr Corporation, Middleton, WI) [11]. After undergoing a conventional exam and agreeing to this additional test, the patient rinses his or her mouth for 30 s with, and then expectorates, a raspberry-flavored 2% acetic acid solution, which acts as a drying (desiccant) agent. Then a light stick is chemically activated that produces a diffuse blue-white light (wavelength range 430–455 nm). As in the uterine cervix, the light is intended to highlight any subtle oral leukoplakias that may have been missed by the clinician during the previous conventional white-light soft tissue examination. A positive lesion is termed "acetowhite" and may indicate the need for invasive tissue biopsy. As with oral cytology screening, some investigators have found that the specificity and sensitivity, as well as the positive predictive value, of this test is not sufficient enough for clinical use. False positives are due to increased DNA seen in reactive atypical cells secondary to the concomitant and ubiquitous inflammation of the oral cavity.

Figure 1.8 Microlux DL (AdDent, Inc., Danbury, CT) oral mucosa reflectance adjunctive light-emitting diagnostic device.

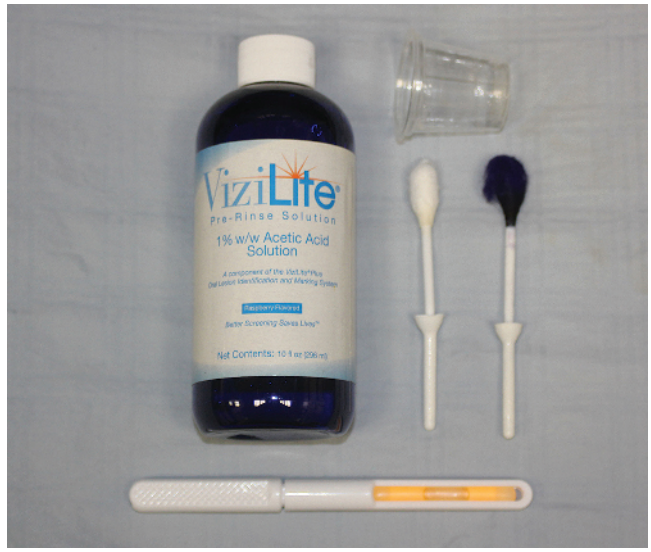

Figure 1.9 ViziLite Plus (Zila Pharmaceuticals, Division of Tolmar Corporation, Phoenix, AZ) oral mucosa reflectance adjunctive light-emitting diagnostic device with second-step marker system of trademarked toluidine blue.

A few years after the advent of ViziLite, Zila Pharmaceuticals gained FDA clearance to market ViziLite Plus® (Fig. 1.9). With this system, following a conventional light examination and the use of the ViziLite reflectance device, an additional marking step can be performed; it is not a stand-alone step. The marker is a large cotton swab of pharmaceutical-grade tolonium chloride (toluidine blue), marketed as TBlue630 (the numerical portion of the dye's trademark name represents the nanometer wavelength of the chemiluminescent blue-white light). Toluidine blue is a metachromatic dye with an affinity for DNA and can be used by the clinician to stain and subsequently photodocument a previously identified acetowhite lesion [12, 13]. Currently, ViziLite Plus and TBlue630 are manufactured by DenMat Holdings, LLC (Lompoc, CA).

Narrowband Imaging (Autofluorescence)

Late in the first decade of the 2000s, a new type of adjunctive screening device began to be marketed, predicated on the FDA 501(k) medical device clearance granted ViziLite. Current examples include the VELscope Vx® (LED Dental, Inc., White Rock, British Columbia, Canada; Fig. 1.10), Sapphire Plus® LD (DenMat Holdings, LLC), Oral ID 2.0 (Forward Science Technologies, Inc.), ViziLite PRO Oral Lesion Screening System (DenMat Holdings, LLC), Bio/Screen Oral Exam Light (AdDent, Inc.), Identafi Oral Cancer Screening System (StarDental, DentalEZ Group, Inc., Malvern, PA; Fig. 1.11), and DentLight DOE™ Oral Exam System (DentLight, Inc., Richardson, TX; Fig. 1.12). Each uses the principle of tissue fluorescence as opposed to tissue reflectance [14–18].

Normal oral mucosa, both surface epithelium and the underlying lamina propria's connective tissue, contain cellular structures – chromophores – that are

Figure 1.10 Narrowband emission autofluorescence VELscope Vx (L.E.D. Dental, Inc., White Rock, British Columbia, Canada).

Figure 1.11 Narrowband emission (autofluorescence and vascular evaluation) and white-light emission Identafi (StarDental, DentalEZ Group, Inc., Malvern, PA).

Figure 1.12 Narrowband emission DentLight DOE autofluorescence oral exam system (DentLight, Inc., Richardson, TX).

involved in normal biochemical reduction–oxidation reactions (e.g. NADH and FADH). These chemical reactions cause a pale green wavelength emission that cannot be seen with the naked eye under normal lighting conditions since it is extremely faint and overwhelmed by the absorbance, reflectance, and scattering of white light within the oral cavity. The VELscope and the similar devices just mentioned use light-emitting diodes (LEDs) to produce a narrow band of blue or violet (Identafi) wavelength light that stimulates the chromophore-related green autofluorescence. Through a series of filters either contained within the machine or worn by the clinician, all other wavelengths of white light are eliminated so that normal oral mucosal tissue appears green and an area of mucosa with loss of fluorescence indicates a loss of chromophores. The latter could indicate mucosal pathology including the presence of epithelial dysplasia. Thus, narrowband emitting lights can be used in formulating a clinical differential diagnosis of mucosal pathology that has already been examined by white light. It is very important to understand that these devices are not diagnostic but, at best, adjunctive clinical information that can be used by the knowledgeable clinician. A prerequisite for the adjunctive use of narrowband reflectance is the knowledge of oral mucosal conditions that can provide a false positive or a false negative result. Once a mucosal lesion is detected by white light and loss of fluorescence is demonstrated by one of these devices, the patient should return in 2 weeks to confirm the lesion's persistence. If the lesion persists, then an incisional biopsy should be performed in order to provide the patient with an accurate definitive diagnosis and subsequent treatment based on that diagnosis.

Saliva Samples

There are several commercially tests available or in development that claim to be helpful to the clinician in deciding whether to assign a patient over the age of 18 into a low-risk or high-risk group with respect to the development of oral and oropharyngeal cancer and, although unstated, specifically squamous cell carcinoma. It is very important to understand that, as of 2017, these tests have a paucity of research study results in peer-reviewed publications that confirm their reliability and validity [19, 20].

The OraMark Test (Vigilant Biosciences, Ft. Lauderdale, FL) measures the soluble CD44 and total protein levels in an oral saliva sample with the assumption that the patients with squamous cell carcinoma have an increased level of soluble CD44 and total salivary protein. As of May 2017 the company had begun clinical studies in the hopes of obtaining FDA clearance. The most pertinent patient study population is those at higher risk. Confounding variables with respect to the test's specificity and sensitivity include periodontal patients having elevated salivary CD44 and elevated crevicular and salivary protein levels, cigarette smokers having elevated CD44 levels, and the expression of CD44 by not all oral squamous cell carcinomas [21, 22].

The SaliMark OSCC salivary DNA test (PeriRx LLC, Broomall, PA) became commercially available in late 2015. It is purported to be an oral cancer risk stratification text recommended for use by the clinician when suspicious lesions are observed and additional testing is warranted. Six salivary mRNA biomarkers (i.e. ILIB, IL8, OAZI, SAT, S100P, and SUSP1) were validated in a multiple large

trial study by Elashoff et al. [23] and Martin et al. [24]. Two cc's of saliva is collected chairside with the manufacturer's sample collection kit. Subsequently, the specimen is sent to a laboratory for a specific assay polymerase chain reaction (PCR) with the results received by the clinician several days later. The results are stratified as low-, moderate-, and high-risk test scores. The clinician is advised to have their patient return for a follow-up appointment within 1 month if the result is low risk, to refer to a specialist for a second opinion if the result is moderate risk, and to refer for a biopsy if the result is high risk. As of 2017, FDA clearance for this test is still pending.

The OraRisk HPV Complete Genotype (originally marketed as OraRisk HPV) (OralDNA Labs, Inc., Eden Prairie, MN) analyzes a resting saliva sample, a site-directed swab, or tissue from paraffin-embedded tissue following biopsy. A PCR assay is performed to determine the presence of one or more of the 51 low- and high-risk types of human papillomavirus (HPV) known to involve the orores-piratory tract. The manufacturer states on their website that the test is useful for infections of the skin, lips, oral cavity, pharynx, and lower airway and asserts that the results mean patients can be followed over time to see if HPV persists. The test is stated to be useful in at-risk patients, such as those who are immuno-compromised. More recently, the company has produced another molecular saliva (rinse, swab, tissue) sample test, OraRisk HPV 16/18/HR. This FDA off-label test (FDA approved only for the anogenital tract) is designed to detect only the 14 high-risk HPV genotypes, which have been reported to be involved in a variety of transformative cellular events, including dysplasia and squamous cell carcinoma formation, on surface mucosa from a variety of anatomic sites including the oropharynx and, to a much lesser degree, the oral cavity proper [25–27]. The most common high-risk HPV type is 16, to a much lesser degree type 18, and extremely rarely one of the remaining 12 types. HPV16 is also well known to cause uterine cervix squamous cell carcinoma (as well as vaginal and anal) as well as some cases of male anal and penile squamous cell carcinoma. It is a sexually transmitted DNA virus that persists within the mucosa's surface epithelium for years and may eventually invade the basal layer cells with possible integration into the host cell's DNA. If this sequence of cellular events occurs, the rate-controlling genes of the normal cell cycle undergo mutation, and this results in cancerous growth. Following a positive OraRisk HPV 16/18/HR result, the definitive diagnosis of dysplasia or squamous cell carcinoma would involve the tissue biopsy of a suspicious lesion or, if lacking, other signs and symptoms that would prompt a PET scan screening. The company has more recently expanded its oral rinse testing to include detection of herpes simplex virus types 1 and 2, *Candida* spp., *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*.

The OraRisk manufacturer has established a proposed follow-up protocol for a patient who initially tests positive for HPV16, 18, or other oncogenic high-risk types in their saliva. Unfortunately, too little is known about the association of HPV and oropharyngeal cancer of the base of tongue and tonsils as well as its life cycle in the oropharynx to know what a positive HPV16 saliva sample means. The presence of HPV in a person's saliva does not necessarily indicate infection much less cellular invasion or DNA integration, and in cervical mucosa over 90% of HPV16 infections subsequently clear on their own. Additionally, it is very important to know that none of the preceding has

been proven to be a cause–effect relationship for oral cavity squamous cell carcinoma, which includes the known high-risk sites of lateral and ventral tongue as well as floor of the mouth. Epidemiological studies to date indicate HPV16-related squamous cell carcinomas are overwhelmingly located in the oropharynx, much of which is not visible during the course of a general dentistry examination [27, 28]. Most recently, metabolomics analysis results of saliva have been published in peer-reviewed journals [29, 30]. It is known that among the more than 100 biomarkers present that could indicate oral squamous cell carcinoma, many are also present in oral inflammatory diseases including periodontal disease. Therefore, this novel saliva testing hopes to achieve a higher specificity than current saliva analysis by studying metabolites with small molecular weights rather than the current marketed tests that rely on proteins or mRNAs.

Conclusion

The adjunctive oral mucosa pathology screening aids described in this chapter could possibly provide some additional information on the diagnostic and decision-making process, but they do not provide a diagnosis and are only to be performed after a routine conventional head and neck extraoral and intraoral examination has been completed. The latter examination under bright white light, with palpation, remains the highest standard in patient care.

The following chapters of this book are intended not only to aid the dentist in proper examination and documentation of detected oral and oropharyngeal (and possible facial skin) pathology but also to enhance differential diagnosis skills and aid in the decision of whether to observe, refer, or biopsy the lesion.

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Self-Assessment Multiple-Choice Questions and Answers/Explanations

1. Clinical examination reveals bilaterally paired small depressions near the midline of the posterior hard palate. The patient is unaware of their presence and palpation results in negative findings. There is no change at the 6-month recall. What is their likely cause?
   a. Fovea palatinae
   b. Minor salivary gland ducts
   c. Early necrotizing sialometaplasia
   d. Incomplete clefting
2. Where do secretions from the sublingual gland enter the oral cavity?
   a. Lingual caruncles
   b. Stensen's duct
   c. Sublingual plica
   d. Wharton's duct
3. Recently developed adjunctive diagnostic devices have claimed to enhance the earlier detection of dysplasia and oral cancer within the general population when used in conjunction with an intraoral examination. Which adjunct has been proven to enhance earlier detection?
   a. Analysis of salivary biomarkers
   b. Tissue reflectance (chemiluminescence)
   c. Narrowband imaging (autofluorescence)
   d. None of the adjuncts

4. Which examination technique provides a definitive diagnosis of oral squamous cell carcinoma?
   a. Transepithelial cytology
   b. Tissue reflectance
   c. HPV detection within saliva
   d. Tissue biopsy
5. The posterior wall of a patient's oropharynx reveals scattered, smooth, yellow papules. What is the next most appropriate clinical step to perform?
   a. Tissue biopsy
   b. Reevaluation within 2 weeks
   c. Transepithelial cytology
   d. Narrowband imaging
6. What causes the pale green fluorescence of the oral mucosa during the use of narrowband imaging?
   a. Chromophores
   b. Latent HPV
   c. Squamous cell carcinoma
   d. Inflammation