Sook-Bin Woo
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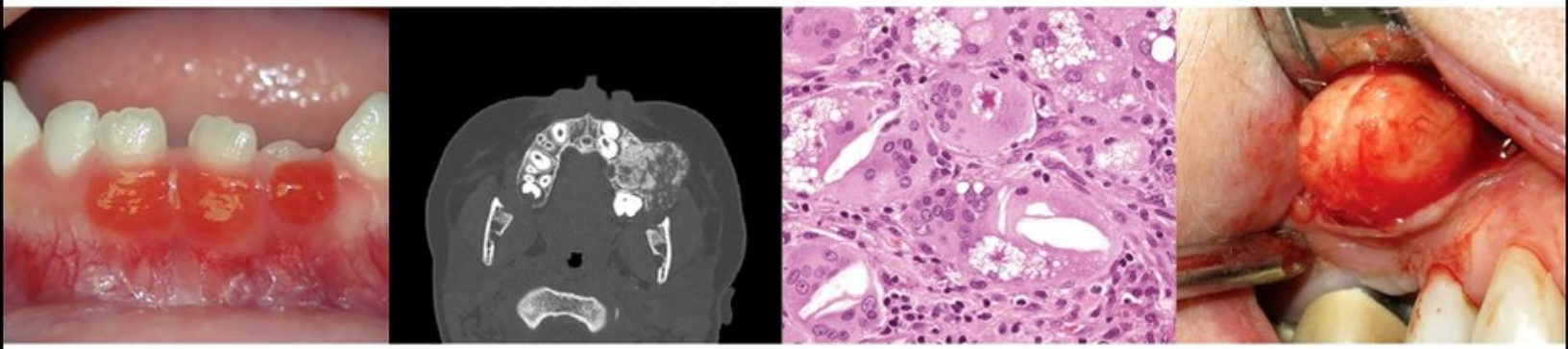
ORAL PATHOLOGY



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ORAL PATHOLOGY

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PREFACE

This atlas was written to serve pathologists in training, dermatopathologists, general pathologists, as well as dental and medical specialists interested in diseases of the oral mucosa, minor salivary gland, and jawbones. Specific and detailed diagnostic criteria are provided for the diagnosis of pathology in the oral cavity. For the clinician, medications used in the treatment of inflammatory oral disease and viral and fungal infections are provided in Appendices A and B, which have been expanded in this edition.

Advances in molecular pathology in soft tissue and bone tumors, as well as salivary gland tumors, have occurred in leaps and bounds and brought new understanding to diagnosis, tumor biology, etiopathogenesis, and treatment. The chapter on salivary gland tumors has been expanded and now includes molecular findings in salivary gland tumors as are known at the time of writing. Similar molecular findings are now included for soft tissue tumors often encountered in the oral cavity, primary bone tumors, and some odontogenic tumors.

However, it is inflammatory diseases of the mucosa, salivary glands, and jawbones that constitute the bulk of oral and maxillofacial pathology. Diagnosis of these conditions requires a deep understanding of the "lives of lesions," as they evolve, resolve, and recur. Knowing the clinical presentation of oral mucosal disease is often essential for accurate diagnosis, especially for leukoplakia, the most common precancerous condition in the mouth. In this era of the ubiquitous smartphone, obtaining a photograph of a clinical lesion is simple and takes only seconds, and all clinicians should be encouraged to send in photographs of such lesions to the pathologist with whom they collaborate. Similarly, clinicians should be encouraged to send oral radiographs, including computerized tomograms for accurate diagnosis of intra-bony lesions.

Practicing and teaching pathology teaches me humility on a regular basis. I continue to enjoy being challenged by my trainees and dental students, revisiting old concepts and hopefully, debunking myths, or at least trying to view lesions in light of new concepts of etiopathogenesis and new diagnostic technologies. Pathology is a specialty that has much to offer the lifelong learner and the curious mind. I hope that you will find this atlas to be informative and useful in your daily clinical or pathology practice.

ACKNOWLEDGMENTS

I am indebted to my colleagues and friends who contributed slides and images for this atlas and to clinician colleagues who contribute cases to our biopsy service and have steadfastly supported the oral and maxillofacial pathology training program at Harvard School of Dental Medicine. Some cases were retrieved from the files of the American Board of Oral and Maxillofacial Pathology and the now defunct Armed Forces Institute of Pathology. Grateful thanks are due to my colleagues at the Ohio State University, Columbus, Ohio; Oral Pathology Laboratories, Queens, New York; University of Florida, Gainesville, Florida; and in Guatemala for their study sets. This endeavor would be less than what it is without the patients who have shared their stories and insights about their diseases with me, and whose images appear within these pages; it is an honor to care for them.

Sook-Bin Woo, DMD, MMSc, FDSRCS (Edin)

CONTENTS

1 INTRODUCTION

CHAPTER CONTENTS

Pathology of the oral cavity affects the following structures: (1) the mucosa, (2) the salivary glands, and (3) the jaw bones. Lesions may extend into the oropharynx, sinuses, and the skin. As such, the scope of practice of oral and maxillofacial pathology overlaps with otorhinolaryngologic pathology, dermatopathology, and bone pathology. The oral cavity is also the primary site for the development of lymphomas and many soft tissue tumors, and is also sometimes the location of metastatic tumors. This atlas focuses on pathology that is either frequently or specifically seen in the oral cavity.

Unlike the skin, papular-macular mucosal lesions in the oral cavity may manifest only in a limited number of ways clinically:

- erythematous/erosive lesions from epithelial atrophy, erosion, vascular ectasia, inflammation, and dysplasia;
- white lesions from keratosis or underlying fibrosis;
- yellow/ulcerative lesions from fibrinous exudate:
- vesiculobullous lesions which rarely present with intact blisters but rather as erosions from blister rupture:
- pigmented lesions: and
- space-occupying lesions.

The last may present as papillary lesions, solitary nodules, diffuse swellings, and masses.

It is important for the pathologist to be familiar with clinical presentations of mucosal disease for accurate diagnosis. Clinical images (even those taken with a smartphone) or radiographic images are often indispensable for the diagnosis of mucosal lesions and osseous pathology, respectively.

ANATOMY

The oral mucosa varies histologically from site to site, and is divided into keratinized and nonkeratinized mucosa (Fig. 1.1). Most oral mucosa is nonkeratinized except for the tongue dorsum, hard palatal mucosa, and attached gingiva and this is of importance when evaluating whether a lesion is hyperkeratotic or not. Specific oral conditions correlate with oral anatomy: for example, recurrent aphthous ulcers occur almost exclusively on the nonkeratinized mucosa, whereas recrudescent herpes simplex virus infections occur almost exclusively on the keratinized mucosa (such as the hard palatal mucosa and keratinized gingiva) in immune-competent patients. The tongue dorsum (with the thickest epithelium in the oral cavity) but not ventrum (with thin epithelium) is specialized for gustatory, masticatory, and deglutition functions. Filiform papillae cover the entire surface of the dorsum and consists of spires of parakeratin with bacterial colonies; this is the only oral epithelium which is normally parakeratinized (Fig. 1.2A). Taste buds are present within fungiform (on dorsum), circumvallate (8–14 on the posterior dorsum), and foliate (posterior lateral tongue) papillae but not within filiform papillae (Fig. 1.2). The lingual tonsil extends across the base of the tongue and may extend into the foliate papillae.

The oral mucosa contains no submucosa per se because there is no muscularis mucosa or any other consistently recognizable histologic landmark that separates mucosa from submucosa. As such, the terms *papillary* (between rete ridges), *superficial*, and *deep lamina propria* are preferable to *submucosa*. In general, the epithelium of the oral cavity is much thicker than that of the skin (Table 1.1; Figs. 1.3–1.9). This has important diagnostic significance because normal thickness of epithelium on the ventral tongue (10–15 cells) would represent epithelial atrophy on the buccal and lip mucosa, gingiva, and tongue dorsum. Keratinocytes are generally well glycogenated and may exhibit perinuclear halos from processing; these should not be misdiagnosed as koilocytes. Muscle is present fairly superficially on the tongue and slightly deeper on the buccal and lip mucosa. Minor salivary glands are predominantly mucous, although serous acini and demilunes are frequently seen (Fig. 1.10); they are present everywhere in the mouth except on the keratinized gingiva (also known as "attached" gingiva because of its "attachment" to the periosteum and bone). Serous salivary glands are frequently encountered on the anterior ventral tongue (glands of Blandin-Nuhn) and posterior lateral and dorsal tongue (glands of von Ebner), sometimes invested in muscle.

The subgemmal (gemma = Greek for bud) neurogenous plaque (also known as "subepithelial nerve plexus")

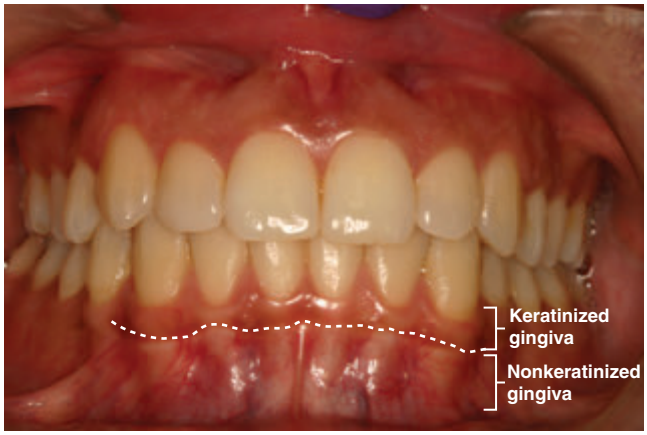


FIG. 1.1 Gingival mucosa showing marginal and attached (keratinized) gingiva and nonattached (nonkeratinized) gingiva.

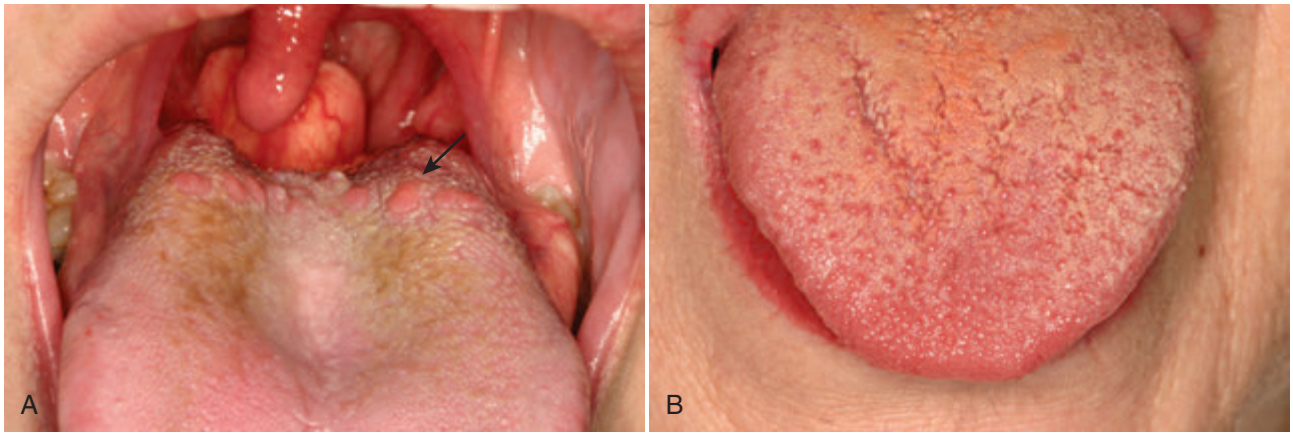


FIG. 1.2 (A) Tongue dorsum showing filiform papillae (generalized "fur") and circumvallate papillae *(arrow)*, as well as epiglottis behind the uvula. (B) Tongue dorsum with inflamed fungiform papillae in the anterior *(small red papules)*.

TABLE 1.1 Histology of Oral Mucosa at Different Sites

Site	Appearance
Nonkeratinized mucosa (thick epithelium) Buccal mucosa Lip (labial) mucosa	Buccal and lip (labial) mucosa are contiguous and similar (see Fig. 1.3) Epithelium 15–20 cells thick Broad, tapered rete ridges Loose fibrovascular tissue in the lamina propria or corium; muscle at the base
Nonkeratinized mucosa (thin epithelium) Floor of mouth Ventral tongue Soft palate/fauces	Floor of mouth and ventral tongue are contiguous and similar to soft palate (see Fig. 1.4) Epithelium 10–15 cells thick Poorly formed rete ridges Ventral tongue in the anterior and posterior often contains serous salivary glands (glands of Blandin-Nuhn and von Ebner, respectively) (see Fig. 1.5)
Keratinized mucosa Hard palatal mucosa Attached gingiva	Hard palatal mucosa and attached gingiva are similar (see Fig. 1.6) Thin layer of orthokeratin with thin granular layer Epithelium 15–20 cells thick Dense fibrous tissue and periosteum at the base Hard palatal mucosa often has fatty tissue investing neurovascular bundles and minor salivary glands Gingiva has more tapered, slender rete ridges; may see odontogenic rests of Serres (see Fig. 1.7) ; crevicular epithelium is usually inflamed
Keratinized and specialized mucosa Tongue dorsum	Moderate-to-thick layer of parakeratin Epithelium 20–30 cells thick Filiform papillae are parakeratin spires surrounded by bacterial colonies (see Fig. 1.8) Fungiform, circumvallate, and foliate papillae are fibrovascular polypoid structures containing taste buds (see Fig. 1.9); subgemmal neurogenous plaque are usually present in the lamina propria Posterior dorsum and lateral tongue contain lingual tonsils composed of mature lymphoid tissue Skeletal muscle is superficial

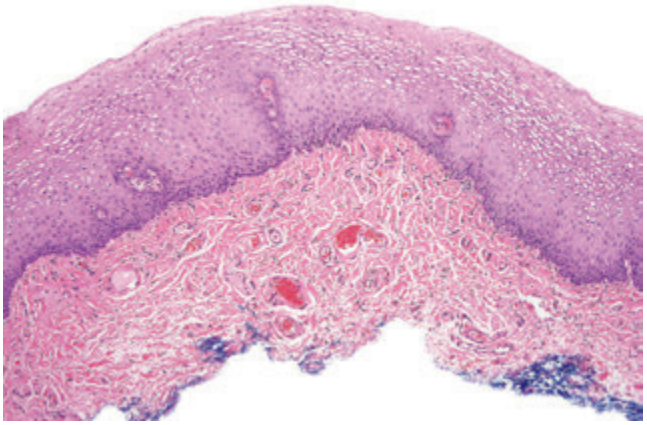


FIG. 1.3 Normal buccal mucosa: nonkeratinized stratified squamous epithelium 15 to 20 cells thick; perinuclear halos are present because of glycogen and do not represent koilocytes.

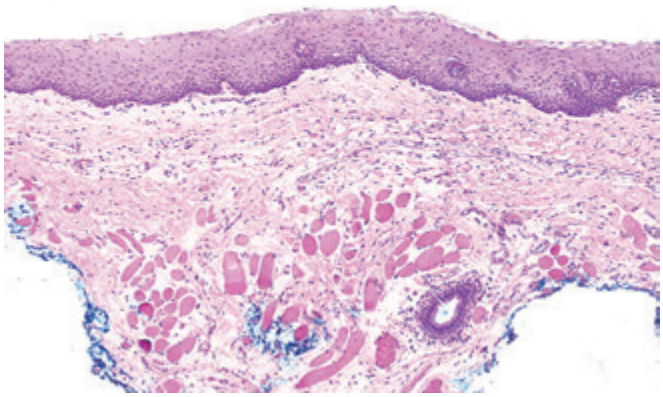


FIG. 1.4 Normal floor of mouth and soft palate: thin, nonkeratinized stratified squamous epithelium with poorly formed rete ridges and delicate lamina propria.

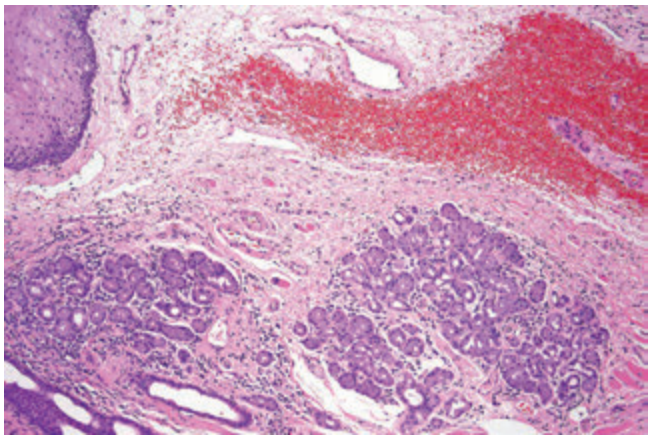


FIG. 1.5 Serous glands of von Ebner in the posterior tongue.

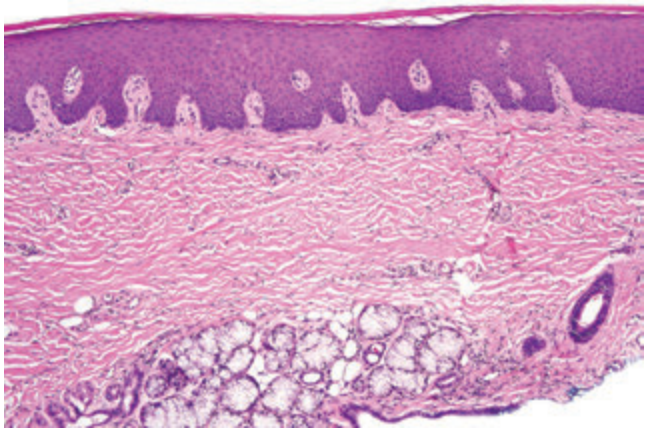
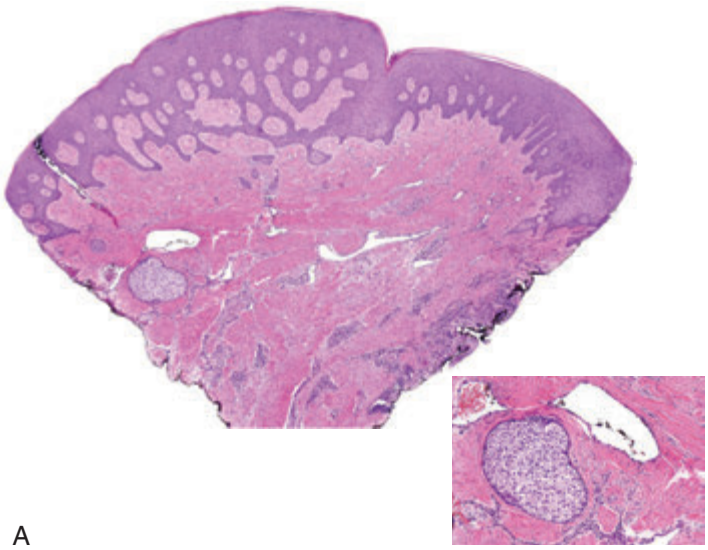
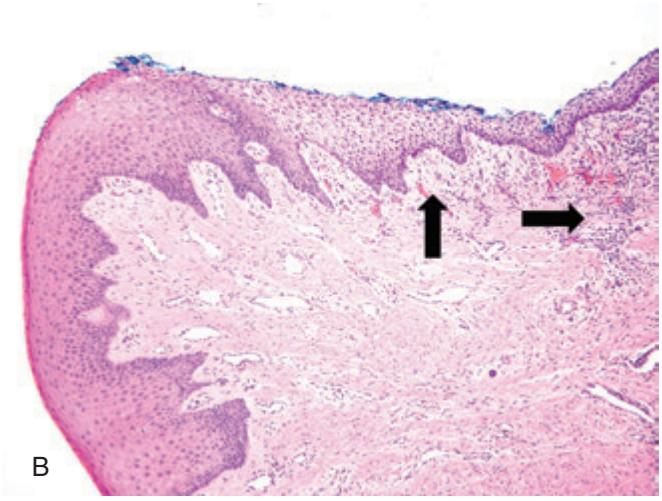


FIG. 1.6 Normal hard palatal mucosa: thin layer of orthokeratin, epithelium 15 to 20 cells thick, dense lamina propria, and mucous salivary glands.



A



B

FIG. 1.7 (A) Gingiva is thinly orthokeratinized and 15 to 20 cells thick with tapered rete ridges and dense lamina propria. Odontogenic rest of Serres contains many clear cells *(inset)*. (B) The crevicular epithelium is nonkeratinized and 5 to 10 cells thick, often associated with spongiosis and underlying inflammation of varying severity *(arrows)*.

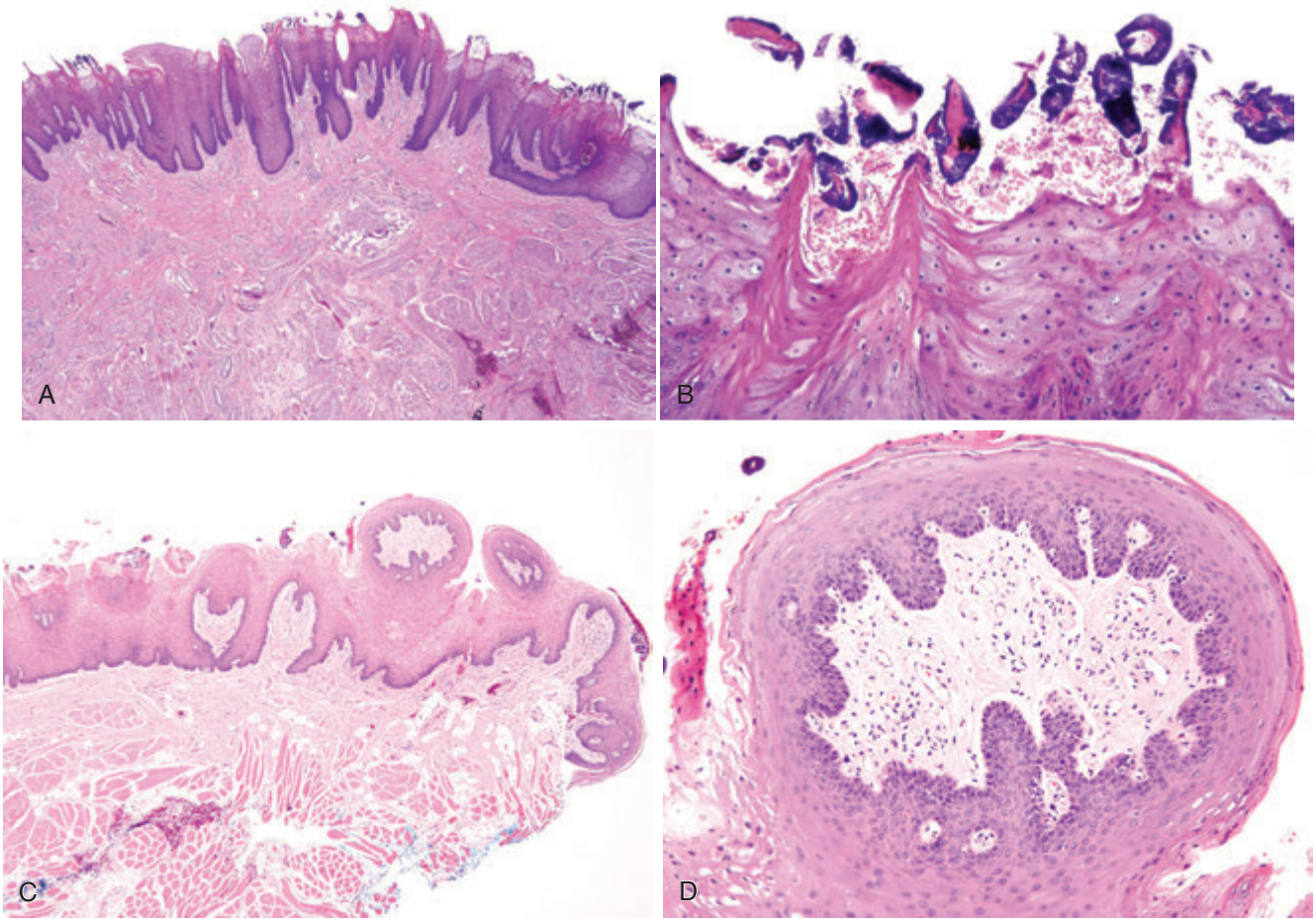


FIG. 1.8 (A) Tongue dorsum: thick epithelium with superficial skeletal muscle. (B) Tongue dorsum: filiform papillae composed of parakeratin spires with bacterial colonies. (C) Fungiform papillae. (D) Fungiform papilla with many neurovascular bundles.

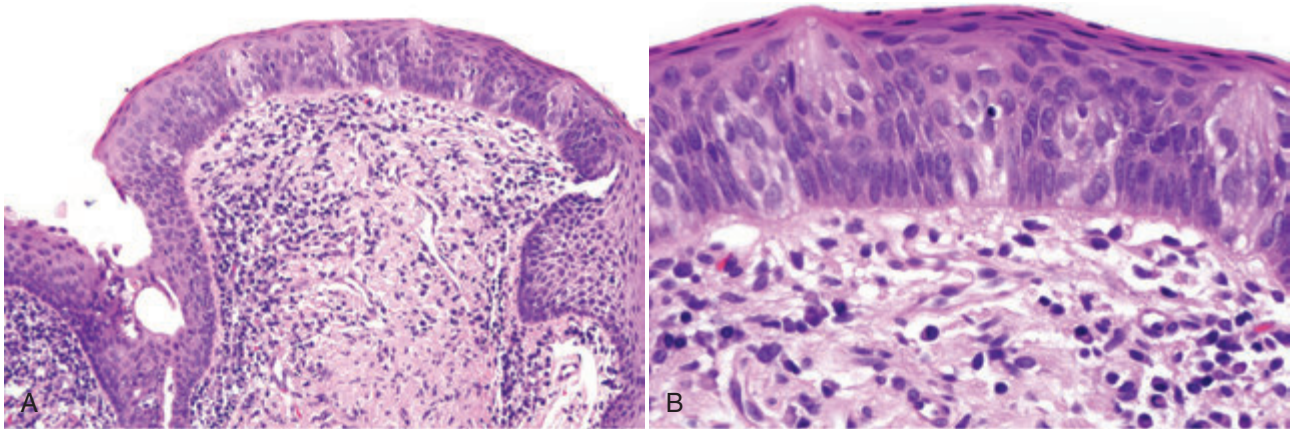


FIG. 1.9 (A) Fungiform papilla with taste buds in the epithelium and subgemmal neurogenous plaque in the lamina propria. (B) Taste buds: lens-shaped clusters of sustentacular and gustatory sensory cells that open to the surface via a gustatory pore.

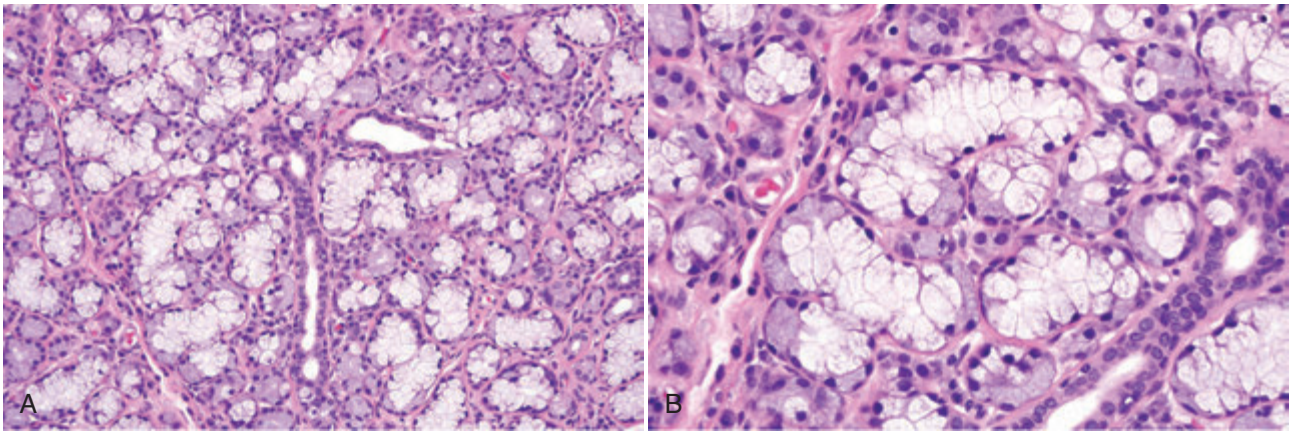


FIG. 1.10 (A) Mucous glands of the lower lip with some serous acini. (B) Serous acinar cells in caplike demilune arrangement over mucous acini.

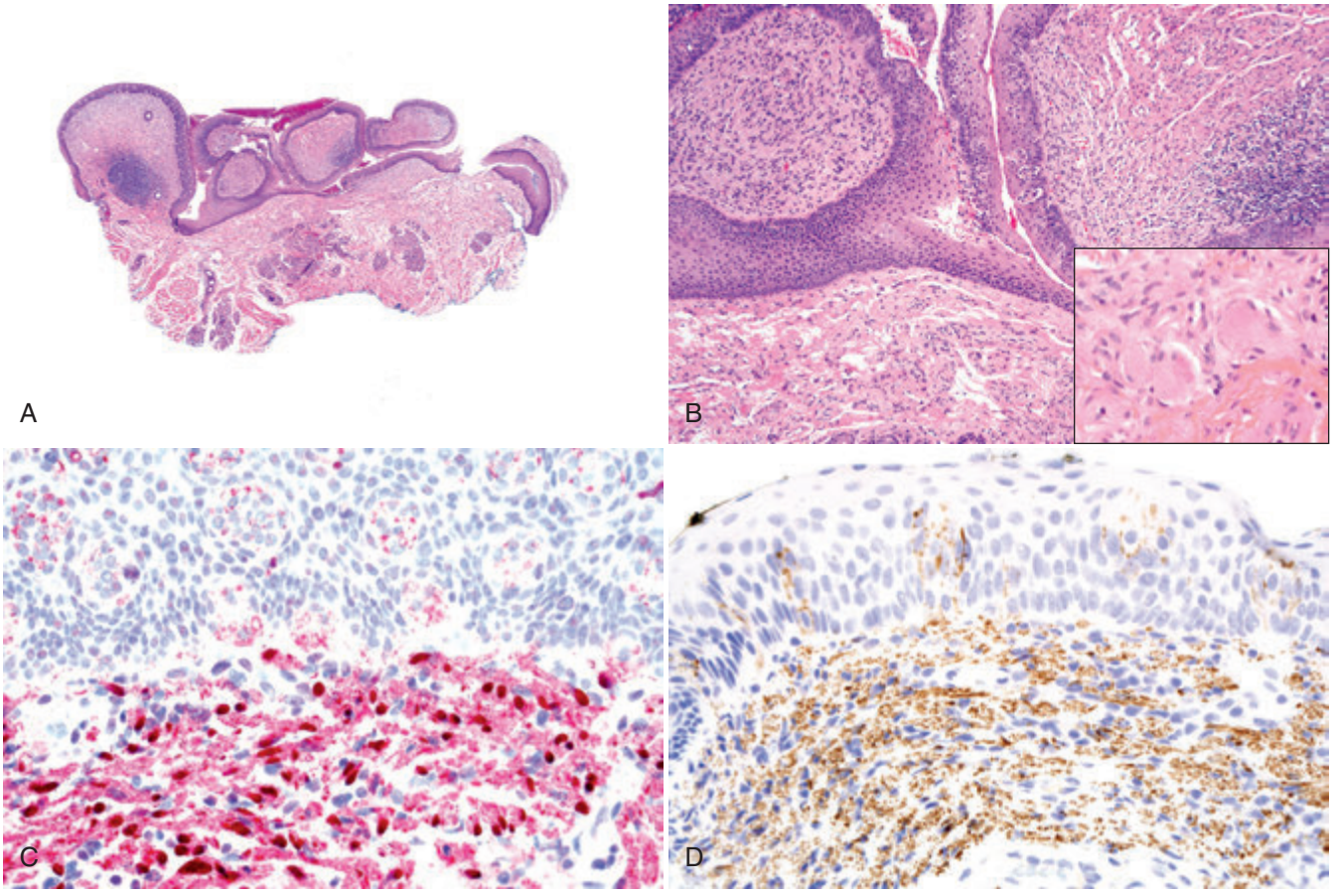


FIG. 1.11 Subgemmal neurogenous plaque, hyperplastic. (A) Foliate papillae of tongue with serous glands. (B) Numerous taste buds in the epithelium and subepithelial neural plexus with ganglion cells *(inset)*. (C) Spindle cells and taste buds are positive for S100 protein. (D) Spindle cells and taste buds are positive for neurofilament protein.

is a normal nerve plexus located in the superficial lamina propria beneath epithelium rich in taste buds, and should not be mistaken for neurofibroma or traumatic neuroma especially when hyperplastic; ganglion cells are sometimes present (Fig. 1.11A–B). This neural plaque is positive for S100 protein, neurofilament protein, and PGP9.5 (Fig. 1.11C–D). It is often noted in biopsies from the posterior lateral tongue in the area of the foliate papillae but is not exclusive to that site. Infrequently, neuroepithelial islands similar to the organ of Chievitz may be seen within this neurogenous plaque.

The juxtacortical organ of Chievitz is a remnant from embryogenesis and consists of small islands of benign epithelium with peripheral basal cells closely apposed to, or

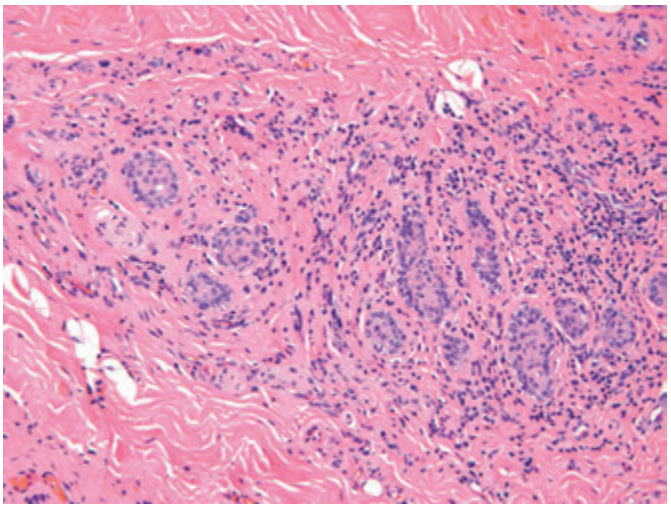


FIG. 1.12 Juxtacortical organ of Chievitz composed of nests of benign squamous epithelium with closely associated nerve fibers.

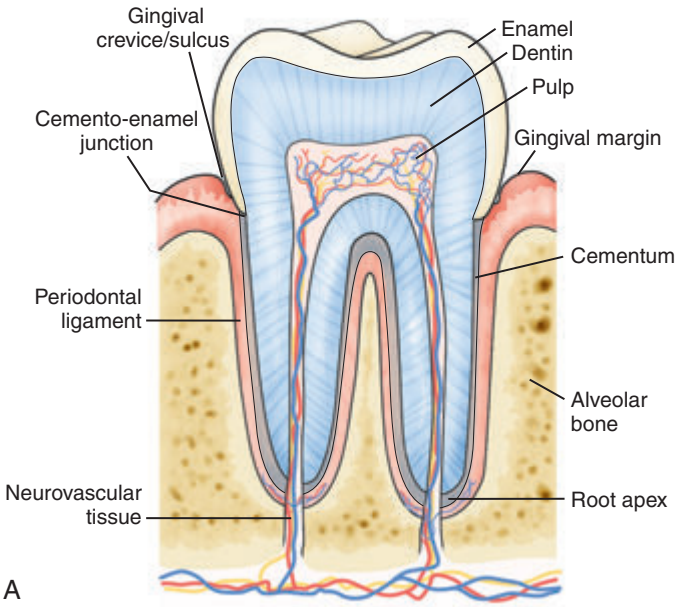
within nerve fibers (often the buccal nerve) (Fig. 1.12). This organ may be located in the area of the pterygomandibular raphe, medial or buccal to the mandible, and may extend toward the opening of the parotid duct. These structures must not be misinterpreted as perineural invasion by carcinomas in the vicinity.

TEETH

Teeth are made up mostly of tubular dentin that is capped by a thin shell of very hard enamel overlying the crown of the tooth. The root of the tooth is surrounded by a thin layer of cementum (Fig. 1.13). The periodontal membrane attaches to the cementum on one side and the alveolar bone on the other, allowing for slight movement of teeth within the bone. This fibrocollagenous membrane contains Sharpey ("perforating") fibers rich in types I, III (argyrophilic reticular fibers), and VI collagen. Although the term Sharpey fibers has been used to refer almost exclusively to these fibers of the periodontal membrane in the dental literature, they are also present in muscle-bone and periosteum-bone interface elsewhere in the body.

Enamel (ectodermal in nature) is 96% mineral (carbonate apatite crystals with a parallel crystalline rod structure) and 4% organic material and water; it is acellular and avascular. The organic material consists of noncollagenous proteins called amelogenins (90%), enamelin, and ameloblastin. Mature tubular dentin is composed of 70% inorganic material (hydroxyapatite also organized into rods), 20% organic material, and 10% water. The organic base is composed of 90% collagen (mainly type I), noncollagenous proteins such as dentin phosphoprotein, dentin sialoprotein, and dentin matrix protein-1, as well as bone matrix proteins such as osteocalcin, osteopontin, and bone sialoprotein. Dentin is produced by the odontoblast which is of ectomesenchymal/neural crest derivation; it wraps around an odontoblastic process that traverses the entire thickness of the dentin from the pulp where the odontoblast resides, to the enamel or cementum. Hence, dentin is a vital structure and damage to this tissue and pulp leads to devitalization of the tooth. Cementum is closest to bone in composition, with 45% to 50% hydroxyapatite and 50% collagen and noncollagenous matrix proteins. Type I collagen constitutes 90% of the nonmineral portion of cementum; noncollagenous proteins include bone sialoprotein, osteocalcin, dentin sialoprotein, and dentin matrix protein-1.

The dental pulp contains fibrous and neurovascular tissue and supplies the tooth with nutrients and sensation. Recently, retained ectomesenchymal stem cells have been identified mostly within the dental pulp in



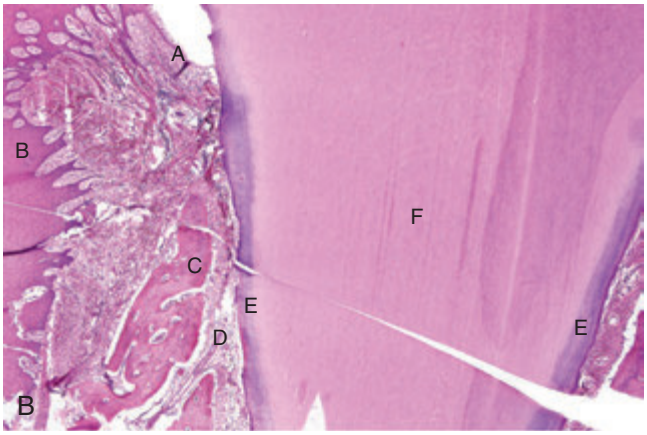


FIG. 1.13 (A) Diagram of a tooth in bone. (B) Tooth showing crevicular/sulcular epithelium *(A)*, surface epithelium *(B)*, alveolar bone *(C)*, collagenous periodontal ligament *(D)*, cementum *(E)*, and dentin *(F)*.

permanent and deciduous teeth, in the dental follicle of developing teeth (see Chapter 14 on odontogenesis) as well as in the periodontal soft tissues. These cells express neural progenitor protein markers because of their original from the neural crest, and are a potential source of stem cells for neural regeneration.

Tooth Numbering System and Nomenclature

There are three commonly used nomenclatures for tooth identification. There are 20 deciduous or primary teeth and 32 permanent teeth although many individuals are missing four third molars.

In the American Dental Association (ADA) system, each permanent tooth is identified by a unique number, #1 to #32 starting from the right maxillary third molar moving clockwise when facing the patient (Fig. 1.14A). Palmer notation used in Britain and the system adopted by the Fédération Dentaire Internationale (FDI) use a single number for each of the eight distinct permanent teeth in a quadrant, starting from the central incisor (#1) moving posteriorly to the third molar (#8). In the FDI system, a qualifier is added for the specific quadrant in which the tooth is located also in a clockwise fashion; quadrant 1 is right maxilla, 2 is left maxilla, 3 is left mandible, and 4 is right mandible. For example, tooth #12 by the ADA system is the left maxillary first premolar or bicuspid. By Palmer notation, this is designated left upper 4 or ⌊4, and by the FDI system it is tooth 24 (quadrant 2, tooth #4). For supernumerary teeth, the ADA adds 50 to the number of the tooth to which the supernumerary is closest. For example, tooth 76 is a supernumerary in the vicinity of tooth #26 (76–50 = 26). Supernumerary teeth are designated "S" after the number for the closest tooth, in the Palmer and FDI systems, and also sometimes in the United States.

For the deciduous or primary dentition, the ADA nomenclature names the teeth clockwise when facing the patient, starting from the right upper second molar which is A, to T which is the left lower second molar (Fig. 1.14B). The Palmer notation uses a single letter for each of the five teeth in each quadrant with A being the central incisor and E being the second molar, and quadrants designated with symbols. In the FDI system, deciduous teeth are numbered 1 to 5 for the five teeth in each quadrant and a qualifier is used for each quadrant to indicate these are deciduous arches, namely 5 for the right maxilla, 6 for the left maxilla, 7 for the left mandible, and 8 for the right mandible. For example, in the ADA notation, the right mandibular deciduous canine is tooth "R" while in the Palmer notation it is C⌋ and in the FDI nomenclature, it is 83 (quadrant 8 tooth #3). For supernumerary teeth in the deciduous dentition using the ADA notation, the letter "S" is added to the closest tooth, for example, CS is a supernumerary

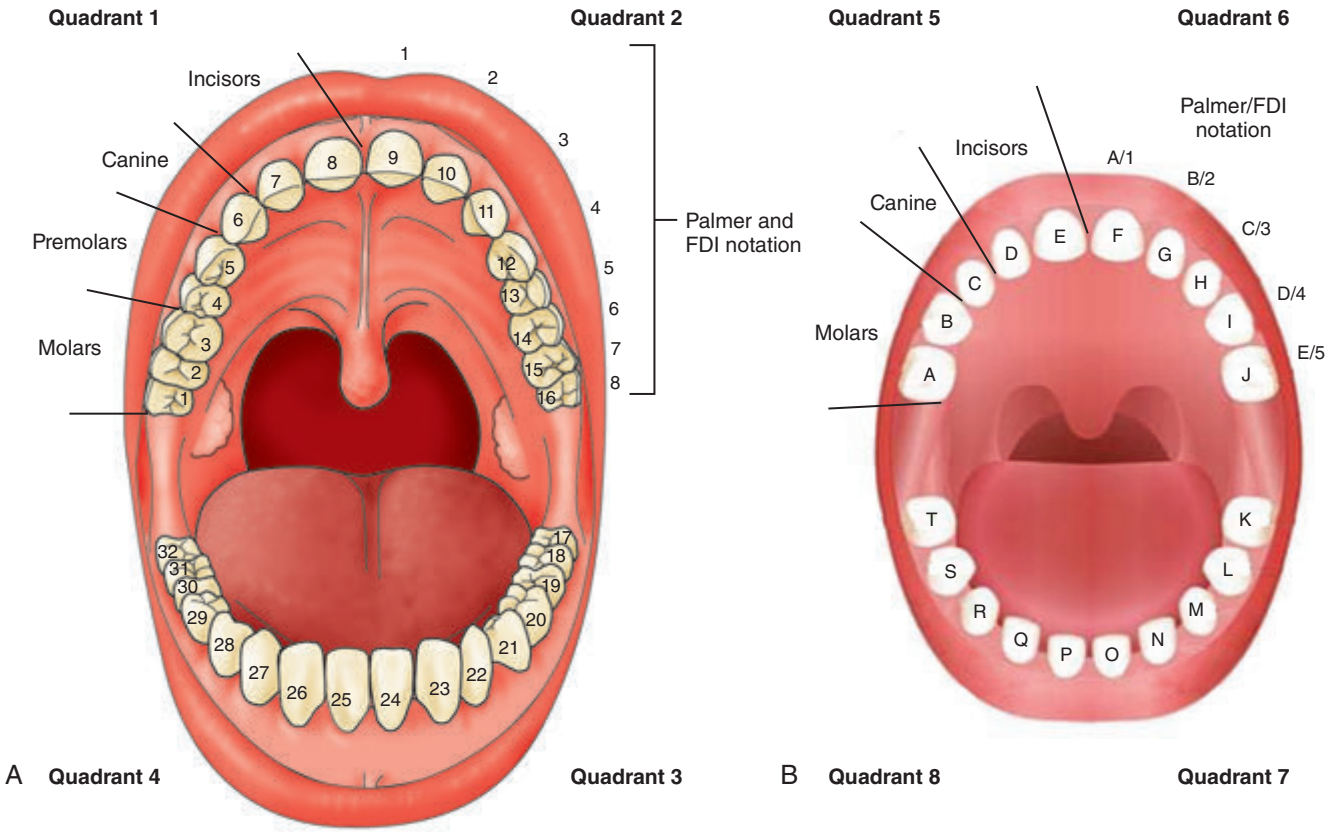


FIG. 1.14 Tooth numbering system: *(Left, A)* For permanent teeth: #1 to #32 (American Dental Association); #1 to #8 (British Palmer notation and European Fédération Dentaire Internationale *[FDI]* system). *(Right, B)* For deciduous teeth: A–T (American Dental Association), A–E (British Palmer notation), and 1–5 (FDI notation)

near tooth C, the right maxillary canine. The same is true for Palmer and FDI notations.

DIAGNOSIS AND MANAGEMENT

For macules or larger lesions, biopsies using a 3- to 5-mm skin punch provide tissue that is easy to orient for processing; primary closure with one to two sutures is readily achieved (Fig. 1.15A–B). Small papules or nodules should be excised with a shave biopsy or a lenticular wedge excision (Fig. 1.15C). The hard palatal mucosa/gingiva abuts the periosteum and as such, is not amenable to primary closure after biopsy; the use of silver nitrate or aluminum chloride to control hemostasis is preferable (Fig. 1.15D). Laser removal of lesions for evaluation of dysplasia is not recommended because of the difficulty of evaluating margins with laser cautery artifact. For the purposes of the clinician, Appendices A and B at the end of the book provide the most commonly used medications for definitive treatment of mucosal diseases and common infections, and agents for topical pain control.

SOME BASIC GUIDELINES

The histopathologic features of inflammatory mucosal disorders depend on the stage at which the lesion is biopsied (evolving or resolving) and whether it has been treated. The "typical" or "classic" histology for many inflammatory conditions is seen in untreated, fully evolved lesions, an infrequent occurrence. As such, a range of histopathologic features is presented for inflammatory lesions in this atlas.

Dysplastic conditions are probably the most challenging for the pathologist, because the clinical appearance of the lesion plays an important if not crucial role in the accurate diagnosis of dysplasia. To this end, clinicians are encouraged to send a photograph (such as a smartphone image) of the lesion with the biopsy. Many dysplastic oral lesions show architectural rather than cytologic evidence of dysplasia and these concepts are covered in depth in Chapter 11.

The teeth and salivary glands are adnexa of the oral cavity in the same way that hair and sweat glands are skin adnexa. As such, there are histopathologic similarities among odontogenic, salivary gland and skin adnexal neoplasms. Ameloblastoma, for example, resembles a basal cell carcinoma. Teeth and salivary glands are derived from the same primordium and it is therefore not surprising that salivary gland tumors may occur as primary tumors within the jawbones. The diagnosis of odontogenic cysts and tumors and primary intraosseous lesions can be rendered accurately only if radiographic images are provided.

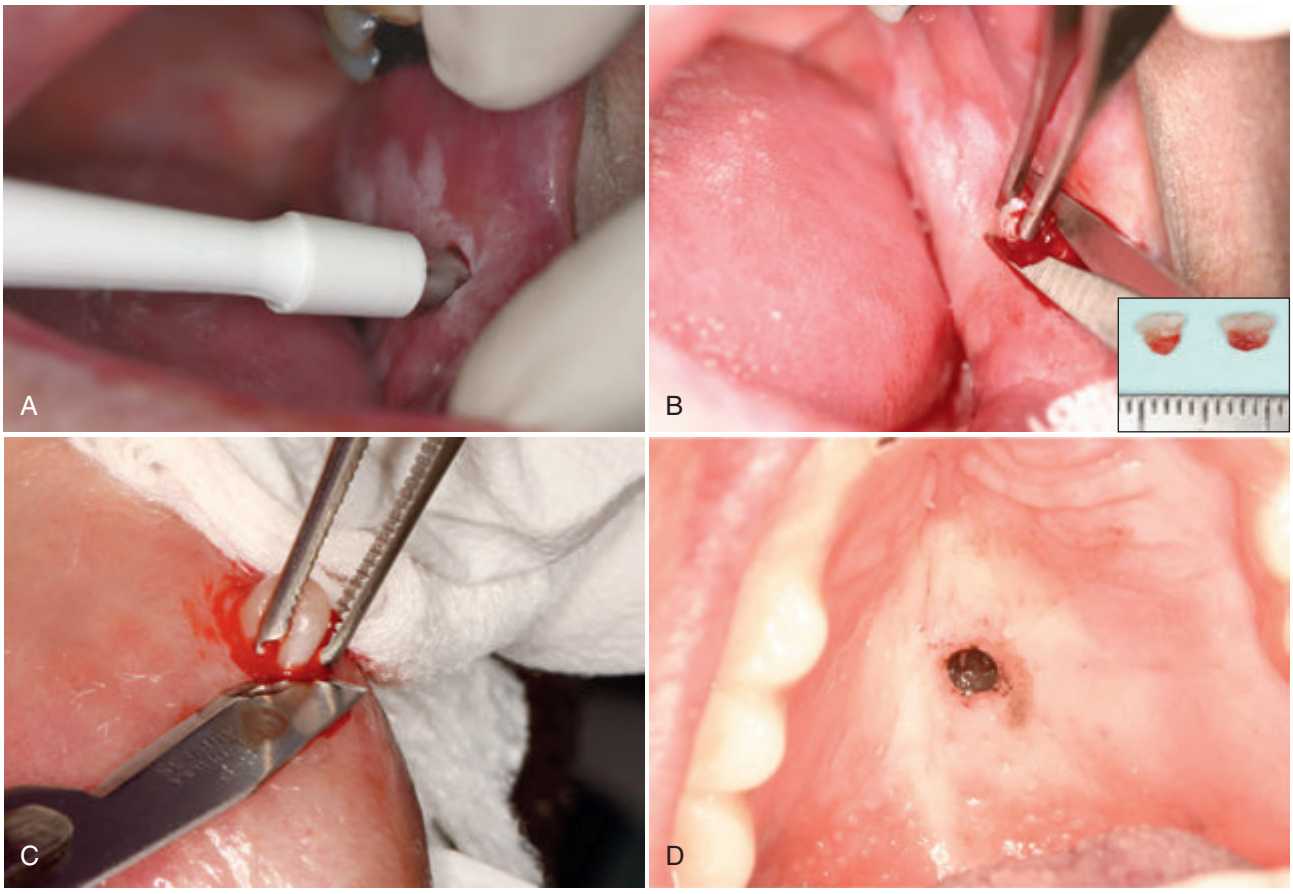


FIG. 1.15 (A) Punch biopsy: inserting the skin punch. (B) Punch biopsy: cutting the tissue at the base; bisected punch biopsy specimen *(inset)*. (C) Shave biopsy of a fibroma with scalpel blade parallel to the mucosal surface. (D) Silver nitrate to seal punch biopsy site on the palatal mucosa.

Finally, a few words on terminology. The oral mucosa has no submucosa per se as mentioned previously, because it lacks a muscularis mucosae. There is only lamina propria, superficial and deep, and even then, the demarcation between the two is somewhat arbitrary. The term *hard palatal mucosa* is preferable to hard palate, because the hard palate is the bony plate to which mucosa is attached. Similarly, *mandibular* and *maxillary mucosa* are preferable to mandible and maxilla (implying bone) if one is referring to the mucosa overlying the bone. The terms *facial*, *buccal*, and *labial* refer to the aspect of the gingiva or teeth that is in contact with the labial/lip or buccal mucosa and oriented outwards. Conversely, the terms *palatal* and *lingual* are used for aspects that are oriented inwards toward the palate or the tongue.

The term *parakeratosis* is used without the modifying "hyper" because all parakeratin is abnormal in the oral cavity, except on the tongue dorsum, which contains parakeratotic filiform papillae, so that hyperparakeratosis would be appropriate only for tongue dorsum lesions. The term *hyperkeratosis* is preferred over *hyperorthokeratosis* in keeping with usage by general pathologists and dermatopathologists.

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2 DEVELOPMENTAL AND CONGENITAL CONDITIONS

CHAPTER CONTENTS

Definitions

Choristoma: An overgrowth of tissues that is mature and found in an area where such tissue is not usually present, such as an osseous or cartilaginous choristoma of the tongue.

Hamartoma: An overgrowth of tissue that is mature and normally found in that area, such as a leiomyomatous hamartoma.

Nevus: An overgrowth of tissue that is normally found in the skin or oral mucosa, such as melanocytic, epidermal, or vascular nevus.

Terminology will likely evolve over the next few years. Lesions previously considered hamartomas or nevi may be found to harbor mutations (such as melanocytic nevi) and be more appropriately classified as neoplasms,

although for historical reasons, the nomenclature may be retained.

While the disorders here have been classified into macular lesions, nodules, and cystic lesions, there is overlap between nodular or mass-like lesions and cystic lesions since some mass-like heterotopias such as gastrointestinal heterotopias are often cystic

Epithelial Lesions

Developmental macular epithelial conditions fall into three categories: diffuse white lesions, diffuse red lesions, and nevi that may be mucosa-colored or pigmented. Diffuse white lesions are often dyskeratotic and represent oral manifestations of genodermatoses, of which the most well-known is Cannon white sponge nevus that involves mucosal sites only. Patients with dyskeratosis congenita develop reticulate skin pigmentation, nail dystrophy, bone marrow failure over time, and oral dysplastic leukoplakias at a young age. Oral lesions of pachyonychia congenita are rarely biopsied, because the diagnosis is established via skin biopsies. Oral lesions of hereditary mucoepithelial dysplasia, a condition of defective expression of cytoskeleton junctional elements, presents as erythematous plaques.

Macular Epithelial Lesions

WHITE SPONGE NEVUS (CANNON WHITE SPONGE NEVUS)

Clinical Findings

- Lesions are noted in the first two decades of life and persist throughout life. The skin is not involved, although there may be esophageal, upper airway, and genital involvement.
- The buccal mucosa (the most commonly affected site) appears diffusely white to gray, thickened, nontender, edematous, and spongy. The tongue, lip mucosa, and floor of the mouth may also be involved (Fig. 2.1).

Etiopathogenesis and Histopathologic Features

White sponge nevus is a rare, autosomal dominant condition resulting from a mutation of the helical domain of keratins K4 (chromosome 12q) and K13 (chromosome 17q), leading to keratin instability and abnormal tonofilament aggregation. There may be abnormal degradation of K13 protein and abnormal ubiquitination.

- Variable parakeratosis and acanthosis with cytoplasmic vacuolation are partly due to glycogen but mostly from abnormal aggregation of keratin and not spongiosis. There is minimal to no inflammation (Fig. 2.2A–C).
- Perinuclear eosinophilic condensations of keratin and dyskeratotic cells are the sine qua non for diagnosis (Fig. 2.2D).
- High Ki-67 index has been reported.

Differential Diagnosis

- Chronic frictional/factitial keratosis of the buccal mucosa, a very common condition, exhibits shaggy parakeratosis often with bacterial colonization, acanthosis, and keratinocytic edema but not perinuclear keratin condensations (see Chapter 10).
- Hereditary benign intraepithelial dyskeratosis exhibits dyskeratosis and "cell-within-a-cell" structures and sometimes perinuclear condensations. Patients have gelatinous conjunctival lesions.
- Keratosis follicularis exhibits dyskeratosis as well as acantholysis.
- Other genodermatoses such as *pachyonychia congenita* exhibit similar histology, tends to affect the tongue more than the buccal mucosa, but extensively involves the nails and skin; 55% of cases show oral involvement but diagnosis is generally with a skin biopsy. Depending on the type, mutations occur in one of five keratin genes, *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17* resulting in tonofilament misaggregation.

Management and Prognosis

- There is no effective treatment. Patients who purportedly respond to antibiotic or chlorhexidine therapy are likely to have some other entity, such as frictional keratoses, which typically wax and wane.

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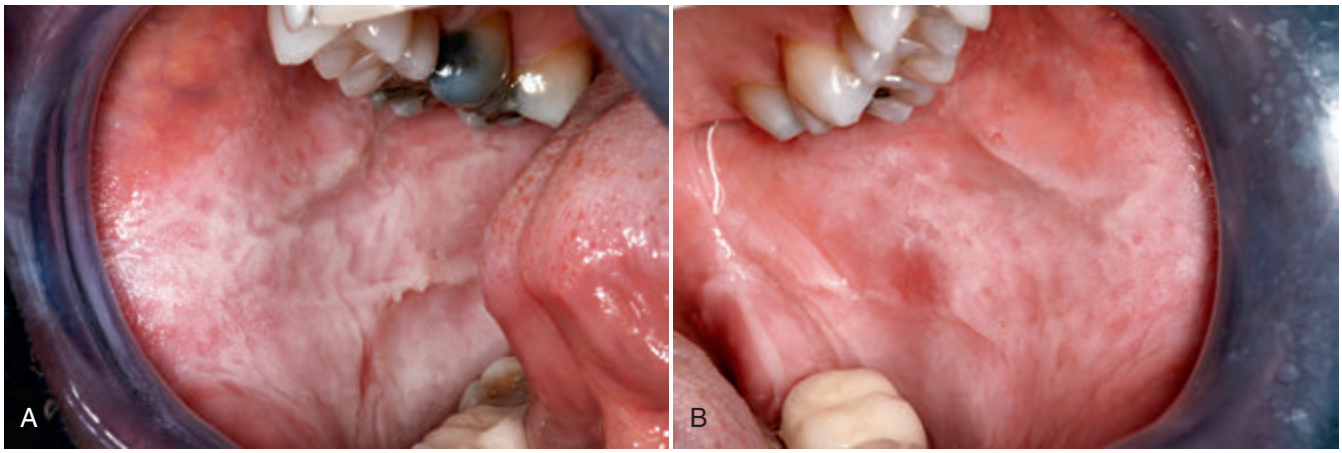

FIG. 2.1 (A) and (B) White sponge nevus: diffuse, boggy white plaques of the buccal mucosa present bilaterally. *(Courtesy Dr. Carl Allen, The Ohio State University, Columbus, OH.)*

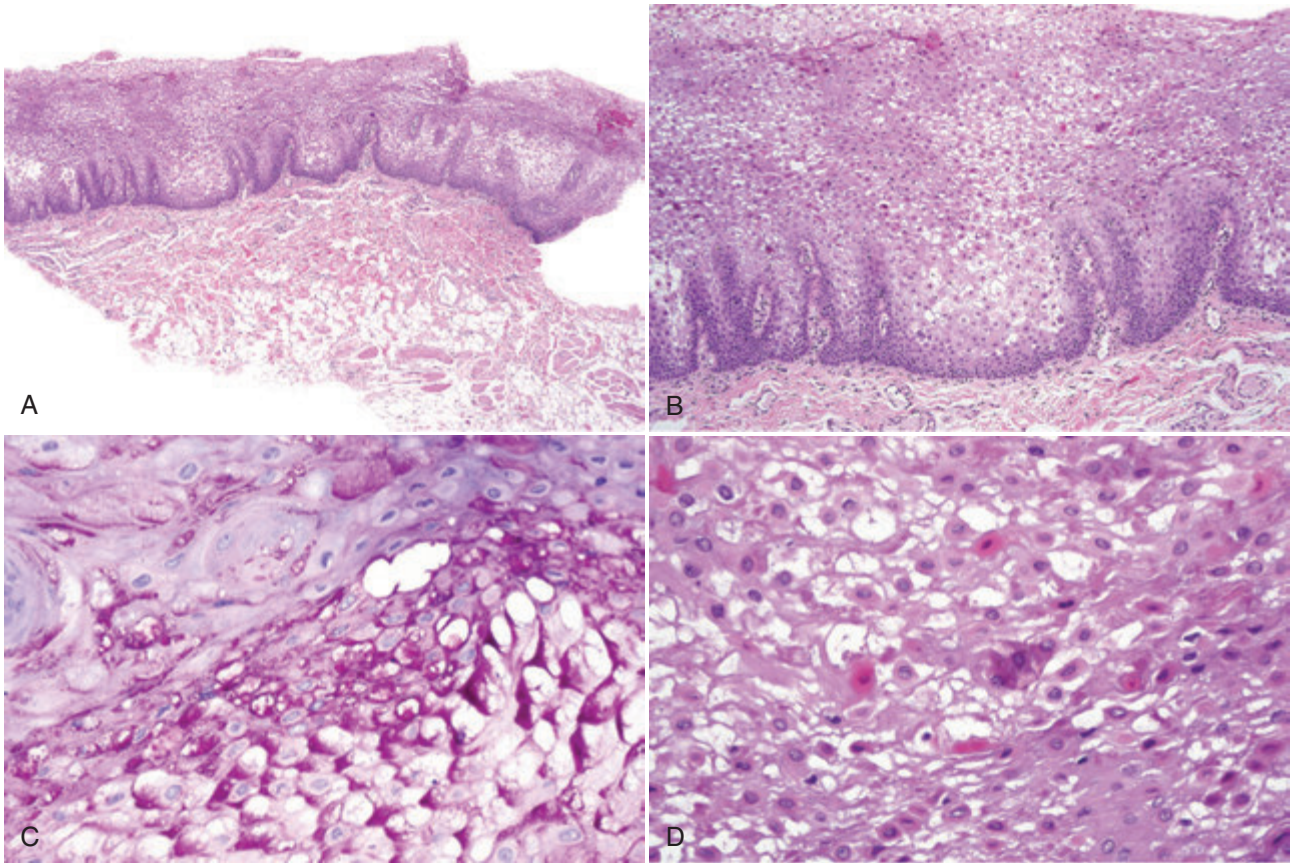

FIG. 2.2 White sponge nevus. (A) The epithelium exhibits acanthosis with a pale "spongy" appearance. (B) The pale epithelium is caused by intracellular vacuolation and dyskeratosis that spares the basal cells. (C) There is positive periodic acid–Schiff staining of intracytoplasmic granules typical for glycogen. (D) There are perinuclear eosinophilic condensations and intracytoplasmic vacuolation (not spongiosis).

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HEREDITARY BENIGN INTRAEPITHELIAL DYSKERATOSIS

Clinical Findings

- This is diagnosed in the first two decades of life and affects Haliwa-Saponi Native Americans in North Carolina and their descendants (usually on the east coast of the United States), although sporadic cases exist. The skin is not affected.
- The oral mucosa exhibits diffuse, thickened, nontender, spongy white plaques similar to white sponge nevus (Fig. 2.3A–B).
- Eye lesions are present as gelatinous plaques on bulbar conjunctiva in a perilimbic location (see Fig. 2.3C).

Etiopathogenesis and Histopathologic Features

Hereditary benign intraepithelial dyskeratosis is an autosomal dominant condition resulting from a duplication (without coding regions) on chromosome 4q35. There is a corneal dyskeratotic condition that does not also affect the oral mucosa but does affect the laryngeal mucosa that exhibits a missense mutation of the *NLRP1* on chromosome 17p13.

- Parakeratosis, acanthosis, and many dyskeratotic "tobacco" cells (so called because of their brown color seen in Papanicolaou stains) are located in the upper epithelium. Sometimes these dyskeratotic cells are surrounded by epithelial cells, resulting in a cell-within-a-cell appearance (see Fig. 2.3D–F). Perinuclear condensations may be present.

Differential Diagnosis

- White sponge nevus shows perinuclear keratin condensations.
- Keratosis follicularis and warty dyskeratoma are acantholytic and dyskeratotic.

Management and Prognosis

- There is no effective treatment.

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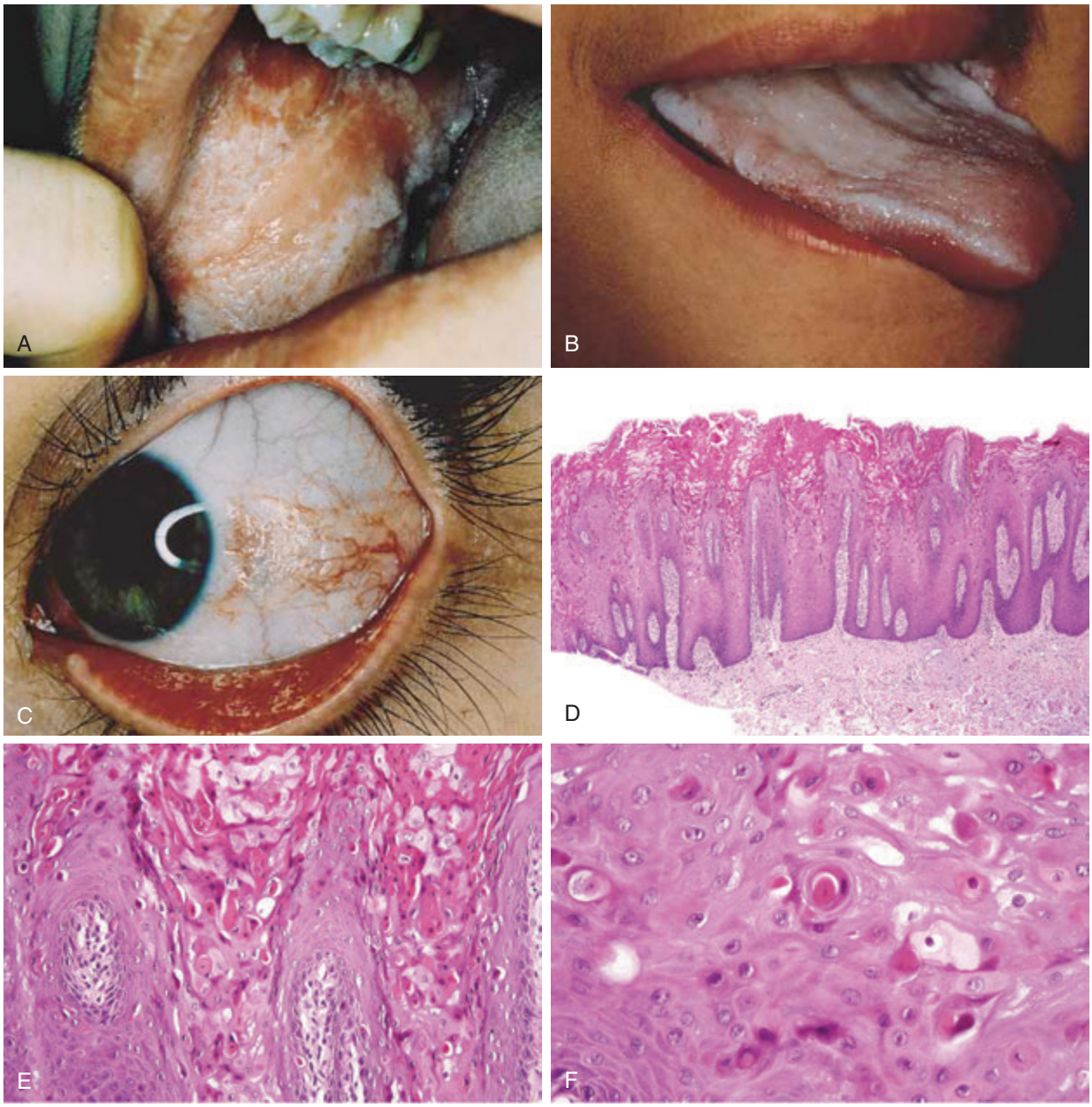

FIG. 2.3 Hereditary benign intraepithelial dyskeratosis. (A) and (B) Dense white plaques of the buccal mucosa and tongue. (C) Gelatinous plaque of the lateral bulbar conjunctiva. (D) Parakeratosis and acanthosis with dyskeratosis. (E) Prominent dyskeratosis within the superficial keratinocytes. (F) Dyskeratotic cells with "cell-within-a-cell" morphology. *(A–C, From Haisley-Royster CA, Allingham RR, Klintworth GK, Prose NS. Hereditary benign intraepithelial dyskeratosis: report of two cases with prominent oral lesions. J Am Acad Dermatol. 2001;45:634-636.)*

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KERATOSIS FOLLICULARIS (DARIER DISEASE, DARIER-WHITE DISEASE)

Darier disease in the mouth does not occur in the absence of skin lesions. A localized papule or nodule with similar histopathology is known as *warty dyskeratoma* or *focal acantholytic dyskeratosis* and is discussed in Chapter 3.