ELSEVIER

# *Oral Mucosal Embryology and Histology*

TRACEY A. WINNING, BDSc, GradDipHEd, PhD
GRANT C. TOWNSEND, BDS, BScDent(Hons), PhD, DDSc

The mucous membrane that lines the oral cavity consists of two layers: an outer layer of stratified squamous epithelium and an underlying layer of dense connective tissue (lamina propria). In those regions where there is looser connective tissue, beneath the lamina propria a submucosa exists containing blood vessels, fat and glands (eg, cheek, soft palate). The oral mucosa has both epithelial and connective tissue structural modifications in the different regions of the oral cavity, providing three recognizable histological types. These types of epithelia correspond to the function of the tissues: *masticatory* (tough) mucosa in the gingivae and hard palate; *lining* (flexible) mucosa in the lips, cheeks, vestibule, alveolar mucosa, soft palate, floor of mouth, and inferior surface of the tongue; and *specialized* (mix of masticatory and lining) mucosa on the dorsum of the tongue (Fig 1).

There are common features of the various tissues and cell products in the oral mucosa; however, features associated with the different types of oral mucosa lead to a range in histology and differentiation. This variation is, in turn, reflected in a variable clinical appearance. This review will present initially an overview of the development of the oral mucosa, followed by a summary of its histology and discussion of the different types of oral mucosa, relating the histological structure to the clinical appearance. Where applicable, comparison with skin will be made; we will also note aspects of the oral mucosal structure and features that relate to conditions discussed in other articles in this issue.

## Oral Mucosal Development

The beginning of an oral cavity (stomatodeum), albeit primitive, occurs with the folding of the embryo in the head–tail line at approximately 4 weeks.[1–4] This results in the formation of an opening lined by ectoderm above the level of the buccopharyngeal membrane and endoderm below this membrane. Soon after folding of the embryo, the buccopharyngeal membrane breaks down, resulting in direct communication between the oral cavity with the foregut and hence continuity between ectoderm and endoderm. Therefore, the oral mucosal epithelium develops mainly from ectoderm (lips, cheeks, vestibule, palate, gingivae, floor of mouth) and also from endoderm (tongue).

The connective tissue of the oral mucosa is derived from ectomesenchyme—in particular, neural crest cells that migrate from the midbrain and anterior rhombomeres to the developing facial region and relevant branchial arches.[4] Once these cells have migrated, they disperse within the mesenchymal tissues already present, proliferate extensively, and make essential contributions to the development of oral cavity structures, including the oral mucosa. Epithelial–mesenchymal interactions are important in development of craniofacial structures (eg, teeth)[5] and the maintenance of oral mucosa;[6] however, further elucidations of these interactions during oral mucosal development have not been published. The ectomesenchyme also contributes to the muscles associated with the lips, cheeks, and soft palate, while the tongue muscles are derived from the occipital somites.

Initially, a single layer of epithelial cells lines the oral cavity, followed by development of two cells layers at approximately 5 to 6 weeks. Soon after, the sparsely populated ectomesenchyme begins to secrete extracellular fibers. By 10 weeks, a multilayered epithelium is present.[3] At this time, surface features of the oral mucosa also commence development—namely the incisive papilla, palatal rugae, and the papillae of the anterior two-thirds of the tongue. In the connective tissues, capillary buds and collagen also begin to appear, and some differences between the lining and masticatory mucosae are recognizable, such that the latter has more cells and fibers.

Both epithelial proliferation and differentiation continue over several weeks, such that by approximately 23 weeks in utero, an oral epithelium with adult characteristics, including cytokeratin expression, has developed—that is, stratified ortho/parakeratinized palatal and gingival epithelium and stratified nonkeratinizing epithelium of the lips, cheeks, soft palate, ventral surface of tongue, and floor of mouth. During this process of development, separation of the lips and cheeks from the mucosa of the developing maxilla and mandible

*From the Dental School, The University of Adelaide, Adelaide, South Australia, Australia.*
*Address correspondence to T.A. Winning, PhD, Dental School, The University of Adelaide, Adelaide, South Australia 5005, Australia.*


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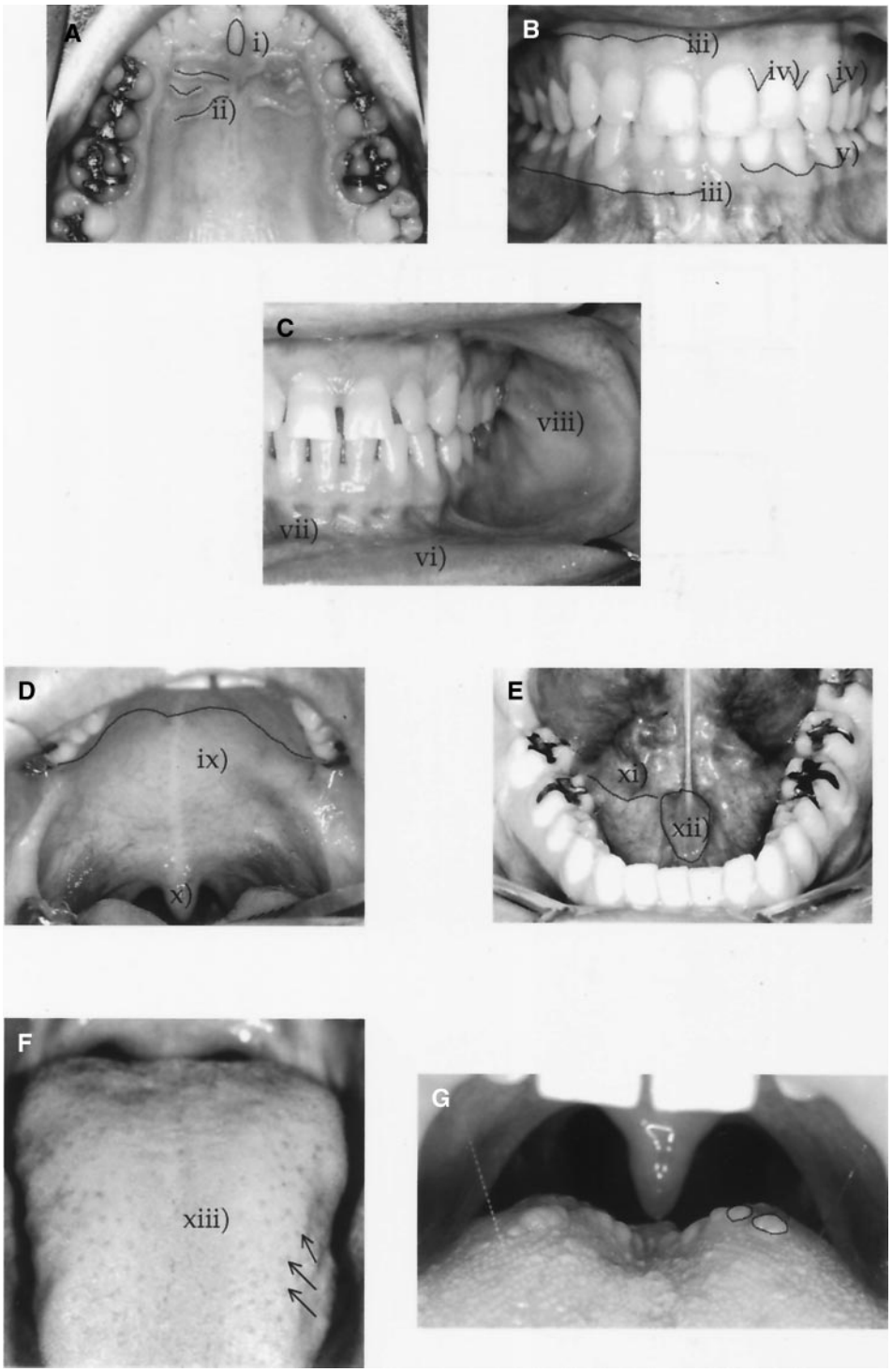


***Figure 1.*** *Intraoral views of the various types of oral mucosa. Masticatory* (keratinizing) *mucosa*: **(a)** *Hard palatal mucosa covering the bony palate; (i) incisive papilla; (ii) palatal rugae.* **(b)** *Gingiva, i.e., oral mucosa surrounding the teeth; (iii) junction (transition) between the gingiva and alveolar (nonkeratinized) mucosa (see Fig 3b); (iv) interdental papillae; (v) free gingiva, i.e., tissues not attached to tooth or bone. Lining (nonkeratinized) mucosa:* **(c)** *Vestibule showing various lining mucosae: (vi) labial mucosa; (vii) alveolar mucosa; (viii) cheek mucosa,* **(d)** *Soft palate; (ix) Line indicates junction between hard and soft palate; (x) uvula.* **(e)** *Floor of mouth and ventral surface of tongue; (xi) sublingual gland ducts; (xii) submandibular gland ducts. Specialized mucosa:* **(f)** *Anterior two-thirds of dorsal surface of tongue; (xiii) filiform papillae, which cover the majority of the anterior part of the tongue; fungiform papillae (arrows), which are dotted between the filiform papillae.* **(g)** *Posterior aspect of anterior two-thirds of tongue where a line of circumvallate papillae (circled) are located.*

occurs between 11 and 14 weeks, with the ingrowth of oral mucosal epithelial cells to form vestibular laminae, located laterally to the band of dentally related epithelium. The superficial cells of these laminae break down with the separation of the lips and cheeks from the mucosa overlying the developing jaws. This program of development is similar to that of fetal (interfollicular) skin, which shows development from a simple epithelium at the beginning of the second month to a multilayered epithelium, with expression of cytokeratins and other keratinocyte differentiation markers (eg, filaggrin) after approximately 6 months.[7]

### *Development of the Dentogingival Junction*

Development of the oral mucosal attachment around teeth is specific to the oral cavity. Simply, it involves the movement of a structure (tooth) embedded in connective tissues, through these tissues and epithelium, without causing an epithelial breach and so exposing the underlying tissues. The tissues involved in this dentogingival complex or junction are specific to gingiva and include the junctional epithelium (JE), sulcular epithelium, and underlying connective tissue (Fig 2).

When a tooth approaches the epithelial lining of the oral cavity, changes are evident in the reduced enamel epithelium (REE; ie, remaining cells of the enamel-producing dental organ). Associated with these REE changes is breakdown of the connective tissues intervening between the tooth and oral cavity, and proliferation in the basal layer of oral epithelium. Fusion between the oral epithelium and REE follows, with breakdown of the central area of the epithelium. This allows the emergence of the tip of a tooth into the oral cavity through an epithelial-lined channel, thus ensuring no loss of epithelial continuity. Following the emergence of the tooth into the oral cavity, the cells of the REE change into flattened and elongated (squamous) JE cells. These JE cells are responsible for ensuring maintenance of the junction between the enamel and epithelium (Fig 2). This is achieved via hemidesmosomal attachment to the basal lamina covering enamel, throughout the process of emergence of teeth into the oral cavity.

## Basic Histological Features of the Oral Mucosa

As in all tissues of the body, functional demands and tissue features are reflected by the structure and biology of tissues and cell products that make up the oral mucosa. The general histological features of oral mucosa include a surface epithelium, overlying and attached to connective tissue at the basement membrane region. Immediately deep to the epithelium, the superficial dense connective tissue (lamina propria) overlies the deeper submucosa.

### *Epithelium*

The surface epithelium of the oral mucosa is a stratified squamous epithelium that is either keratinized (masticatory) or nonkeratinized (lining) and provides protection against mechanical, microbial, and chemical damage. The epithelium, similar to skin, consists of tightly packed epithelial cells with varying degrees of differentiation, beginning with the deepest/basal layer of undifferentiated cells that divide continuously, through layers of suprabasal cells undergoing various morphological and biochemical changes dependent on the region/type of mucosa.[8,9] Various layers can be identified in the oral epithelium, especially keratinized oral mucosa—that is, the basal layer, spinous layer, granular (keratinized epithelium) or intermediate layer (nonkeratinized epithelium), and the keratinized (keratinized epithelium) or superfical layer (nonkeratinized epithelium) (Figs 3 and 4).

### *Keratinized Epithelium of Masticatory Mucosa*

The basal layer of the mechanically tough epithelial covering of the masticatory mucosa consists of the least-differentiated cells arranged in two to three layers and is responsible for cell division and production (Fig 3c, d). These cells are the smallest, being cuboidal or columnar in shape, with organelles characteristic of protein-producing cells involved in making the characteristic intermediate filaments of keratinocytes, in particular cytokeratins 5 and 14, in this layer. In the adjacent spinous layer, there are more desmosomes, increased cell volume, and more keratin filaments associated with an increase in cell size and change to a polyhedral shape,[10] with the expression of major differentiation-specific cytokeratins of 1 and 10, and 6 and 16.[9,11,12] In the more superficial aspects of this layer, membrane-coating granules (MCG), which have a similar ultrastructural appearance to epidermal MCG, begin to appear.

The granular layer, so-called because of the presence of basophilic keratohyalin granules, consists of flattened cells with a decreased nuclear size and densely packed keratin filaments. The MCG increase in number in this layer and contribute to the permeability barrier found in the adjacent superficial layer, the keratinized layer. At the transition of the granular and keratinized layers, the MCG fuse with the cell membrane, and their contents are released into the intercellular spaces. Thickening of the cell membrane and aggregation of the keratin filaments also begin at the transition between these layers, resulting in the keratinized cells having thickened plasma membranes, densely packed keratin filaments, few desmosomes, and no organelles. The cells at the surface of the epithelium are shed into the

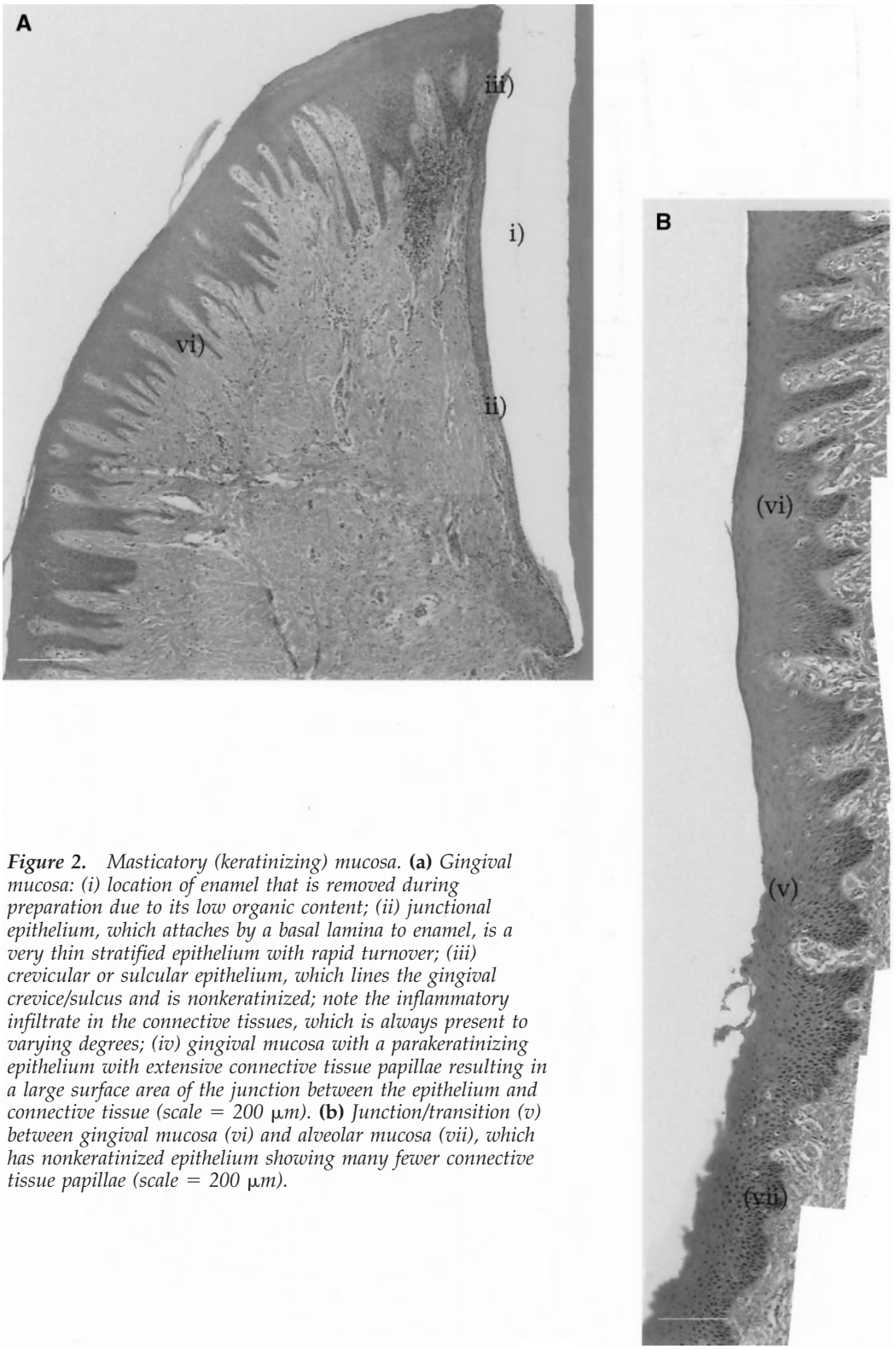


***Figure 2.*** *Masticatory (keratinizing) mucosa.* **(a)** *Gingival mucosa: (i) location of enamel that is removed during preparation due to its low organic content; (ii) junctional epithelium, which attaches by a basal lamina to enamel, is a very thin stratified epithelium with rapid turnover; (iii) crevicular or sulcular epithelium, which lines the gingival crevice/sulcus and is nonkeratinized; note the inflammatory infiltrate in the connective tissues, which is always present to varying degrees; (iv) gingival mucosa with a parakeratinizing epithelium with extensive connective tissue papillae resulting in a large surface area of the junction between the epithelium and connective tissue (scale = 200 μm).* **(b)** *Junction/transition (v) between gingival mucosa (vi) and alveolar mucosa (vii), which has nonkeratinized epithelium showing many fewer connective tissue papillae (scale = 200 μm).*

oral cavity. When no nuclei are present, the epithelium is described as *orthokeratinized*. If pyknotic nuclei are retained, the epithelium is referred to as *parakeratinized*. This latter type of keratinized layer is common in gingival epithelium. Like epidermis, the keratinized layer reduces the permeability of the oral mucosa, although palatal mucosa is approximately 10 times more permeable than skin.[13]

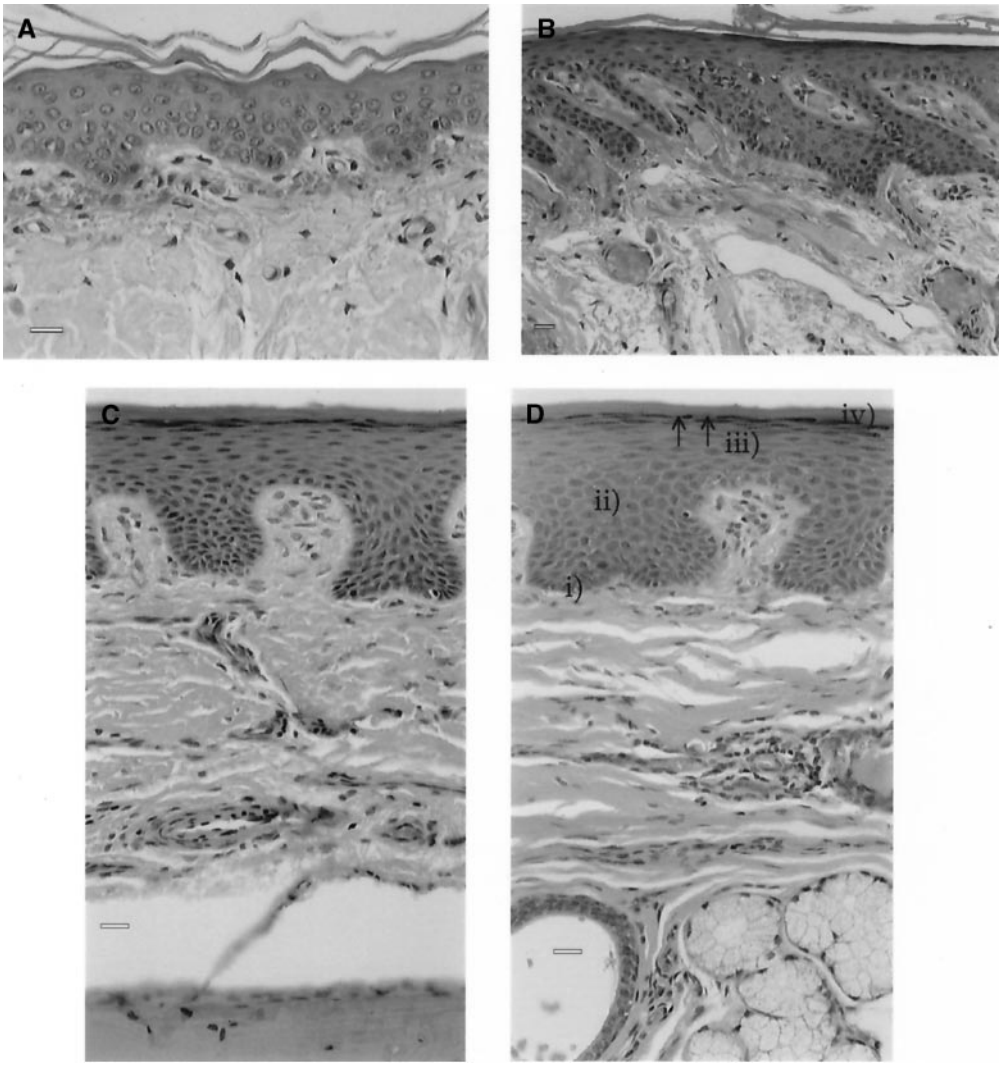


***Figure 3.*** *Keratinizing epithelia and underlying connective tissues (scale = 20 μm).* **(a)** *Interfollicular skin from the lip; note the thin epidermis and relatively flat junction between the epidermis and underlying dermis.* **(b)** *Vermilion zone of the lip; note the long connective tissue papillae containing numerous superficially located capillaries, which contribute to the clinical red appearance of this structure.* **(c)** *Hard palatal mucosa; note the thicker epithelium and more extensive connective papillae and dense connective tissue which is firmly bound to periosteum.* **(d)** *Hard palatal mucosa from the postero-lateral aspect of the hard palate where the lamina propria is bound to a fibrous submucosa containing salivary glands and fat (not visible); (i) basal layer; (ii) spinous layer; (iii) granular layer (arrows); (iv) keratinized layer.*

### *Nonkeratinized Epithelium of Lining Mucosa*

The nonkeratinized epithelium of lining mucosa, which is less able to resist damage but is capable of distension, has a basal layer similar to masticatory mucosa, with the additional expression of cytokeratin 19.[11,14] Similar changes occur in these cells as they move and differentiate into the spinous layer, including an increase in size, change in shape, and increased prominence of desmosomes and keratin filaments (Fig 4), with the expression of major differentiation-associated cytokeratins 4 and 13. The next layer is the intermediate layer, in which the cells become flattened with an increasing percentage of keratin filaments as they move through this and the superficial layer. Cells in this latter layer demonstrate membrane thickening, with a permeability barrier developing with the release of MCG contents, although the permeability of nonkeratinized mucosa is greater than keratinized oral mucosa and skin.[13] While the nuclei persist in this layer, there is a gradual decrease in volume of organelles and decreased desmosomes, followed by desquamation of the cells.

### *Epithelium of Specialized Mucosa*

Specialized oral mucosa is found on the dorsal surface of the tongue and consists of structures that are keratinized (filiform, and dorsal surface of fungiform and circumvallate papillae), as well as interpapillary regions that are nonkeratinized (Figs 1 and 5). (Refer below for further discussion of the structure of these papillae.)

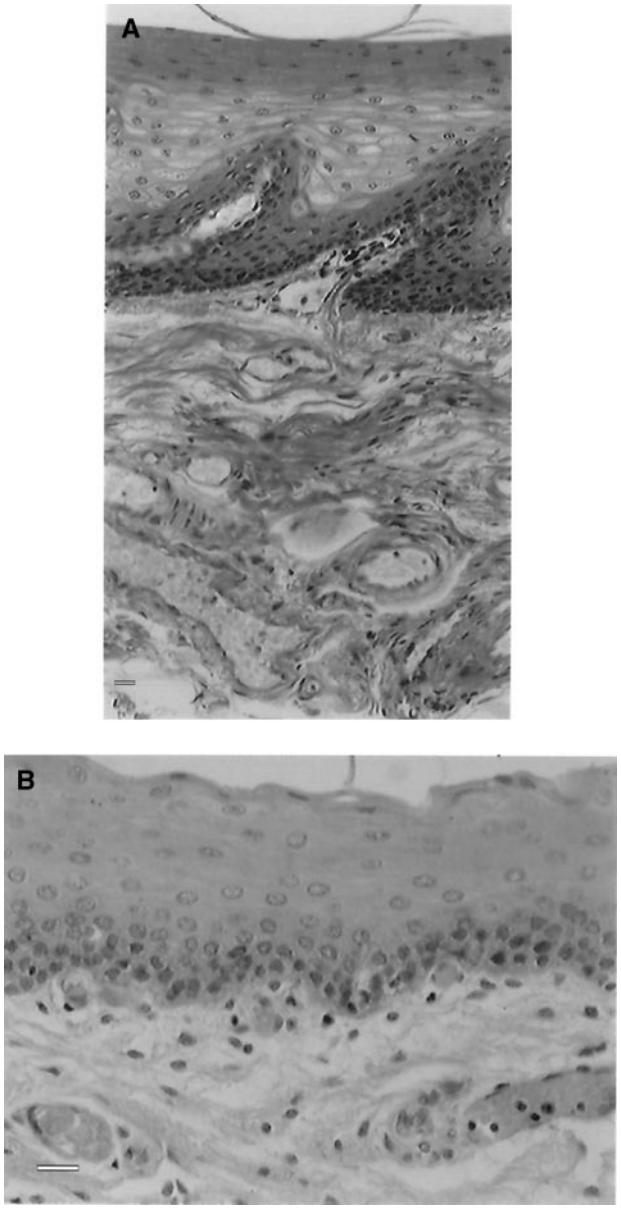


***Figure 4.*** *Lining (nonkeratinized) mucosa (scale = 20 μm).* **(a)** *Labial mucosa showing nonkeratinizing epithelium with a relatively flatter function between the epithelium and connective tissue, which is attached to a submucosa containing fat and salivary glands (not visible).* **(b)** *Ventral surface of tongue showing nonkeratinizing epithelium with a relatively flat junction between the epithelium and connective tissues.*

## *Epithelial Turnover*

Various studies have demonstrated a heterogeneous keratinocyte population in the basal layer, consisting of stem cells, probably slow cycling cells,[15,16] transient amplifying cells, and a group of nonproliferating maturing cells, referred to as *postmitotic cells*, that remain in the basal layer for a variable length of time before differentiating into cells in the spinous layer.[17] Just as there are regional differences in tissue kinetics of epidermis, the proliferation rate and turnover of the various anatomical sites of oral mucosa has been found to vary. This variation in epithelial turnover rate exists partly to different methods of detection.[18] Generally, however, there is a higher cell production rate in oral epithelium (buccal epithelium: approximately two to three times that of epidermis), with reduced turnover time in both keratinized and nonkeratinized epithelium (buccal epithelium: 1 to 3 weeks) compared with the epidermis (range of 4 to 10 weeks depending on site).[18]

## *Characteristics of Oral Mucosal Epithelial Differentiation*

A similar range of markers of differentiation of keratinocytes, as well as cell-cell and cell-matrix adhesion, has been identified in epidermis and oral mucosal epithelium (Table 1). Epidermal keratinocytes and keratinocytes in keratinizing oral epithelium follow similar differentiation pathways. Keratinocytes in nonkeratinizing oral epithelium follow a different differentiation pathway. In addition, the presence of inflammation in some regions of the oral mucosa (eg, JE) affects keratinocyte differentiation.[9] Although comprehensive studies of the oral mucosal components of cell-cell adhesion (desmosomal proteins) have not been reported, there appear to be few differences between the oral mucosal desmosomal structure and that of epidermis. The functional importance of the components of these cell-cell attachments is similar, as evidenced in pemphigus by the deposition of autoantibodies and the development of epithelial splits in the suprabasal layers of oral epithelium (see other articles in this issue).[46] More extensive investigations of cell–matrix adhesion in the oral mucosa indicate many similarities with epidermis.

The controls of differentiation of the surface epithelium in oral mucosa have been reported to be derived from the developmental origins of the epithelium, indicating an "intrinsic" characteristic of the epithelium.[47] The underlying connective tissue has also been shown to be important in the maintenance of epithelial differentiation.[6] More recent evidence has indicated that both inherent and extrinsic factors are likely to play a role in the determination of the differentiation pathway of oral epithelium—for example, expression of keratin 19 may be determined intrinsically by the epithelium, while expression of keratin 1, 13, and profilaggrin is determined extrinsically by factors derived from the underlying connective tissue.[48] Along with similarities in the development and maintenance of the epidermis and its oral counterpart, changes associated with epidermal disorders are also reflected in the oral cavity—for example, mutations in the basal or suprabasal keratins reported in palmoplantar keratoderma and pachyonychia congenita[49,50] and changes in expression of cytokeratins in oral squamous cell carcinoma.[14,51] Other epithelial components found to be altered in skin disorders have also been reported for oral mucosal disorders—for ex-

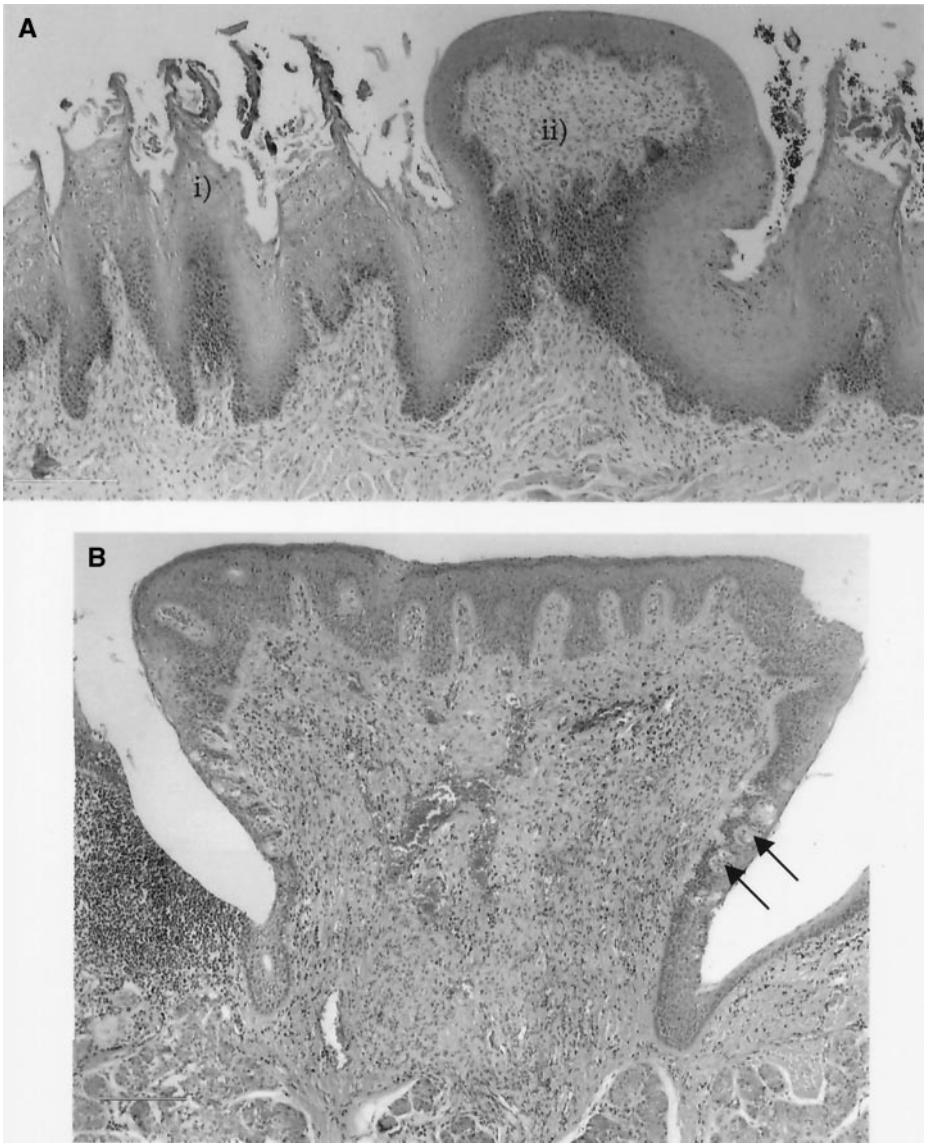


***Figure 5.*** *Specialized mucosa of the dorsal surface of tongue showing a mix of keratinizing and nonkeratinizing epithelium overlying the dense connective tissue of lamina propria, which is attached to tongue muscles (scale = 200 μm).* **(a)** *Filiform papillae (i) showing thread-like projections of keratinizing epithelium; fungiform papilla (ii), which has a keratinized dorsal surface and nonkeratinized lateral surfaces containing taste buds (not visible) overlying a richly vascularised connective tissue core.* **(b)** *Circumvallate papilla is surrounded by a trough into which salivary glands open and are covered on the dorsal surface with keratinizing epithelium and the lateral surfaces with nonkeratinizing epithelium containing taste buds (arrows).*

ample, altered expression of integrin subunits in squamous cell carcinoma (see other articles in this issue for further discussion).[35,40,41,52]

### *Nonepithelial Cells*

Like epidermis, other cells besides epithelial cells are found in the oral epithelium: melanocytes, Langerhan cells, Merkel cells, and lymphocytes. These cells may be recognized at the light microscope level with routine stains as small rounded cells with a clear halo around their nuclei, but accurate identification requires special techniques. Regional variations in the distribution and density of these cells (and their products) have been reported.[53–55] As the oral mucosa also has the ability to interact with the environment, there are also other structures within the epithelium that contribute to the senses of taste, touch, temperature, and pain; however, discussion of these is beyond the scope of this review.

### *Junction Between the Epithelium and Lamina Propria*

The epithelium is attached to underlying connective tissues via a basement membrane region. The morphology of this junction varies depending on the type of oral mucosa and is related to the functional demands of the tissue (see below; Figs 2, 3, and 4). The relative height of the connective tissue papillae to the thickness of the epithelium is generally similar for the different regions of oral mucosa (approximately 0.6 to 0.74 mm, with the exception of floor of the mouth at 0.3 mm); however, the number of connective tissue papillae varies with resultant differences in the surface area of this junction.[10] In matiscatory (gingiva and hard palate) mucosa, which is subjected to compressive and frictional forces, approximately 1.5 to 2.5 times more connective tissue papillae/mm$^2$ of mucosal surface can be found compared to lining mucosa (cheek, labial, and alveolar mucosa) (Fig

*Table 1. Summary of Comparison of Expression of Differentiation Markers and Adhesion Molecules Between Skin and Oral Mucosa*

| *Similarities* | *Differences from Epidermis* |
|---|---|
| ***Differentiation markers and related function*** | |
| • Intermediate filament-associated proteins and cornified envelope proteins, eg, filaggrin, involucrin, loricrin, cornifin-α/small proline-rich proteins (keratinized oral mucosa)[9,19–22] | • Cornifin-β/small proline-rich protein (keratinized and nonkeratinized oral mucosa[22] |
| • Keratinocyte transglutaminase (keratinized oral mucosa)[20] | • Filaggrin (patchy), involucrin, cornifin-α/small proline-rich proteins, transglutaminase (nonkeratinized oral mucosa)[9,19,20,22] |
| • Cytokeratins 5, 14, 1, 10 (keratinized oral mucosa, mRNA only for 1 and 10 in nonkeratinized buccal mucosa)[9,23] | • Cytokeratins 8, 18, 19 (junctional epithelium)[9] |
| • Cytokine production under various conditions,[24] eg, interleukins, tumor necrosis factors, colony stimulating factors,[25] chemokines,[26], growth factors,[27] interferons, and associated receptors[28,29] | • Cytokeratins 19, 4, 13 (nonkeratinized oral mucosa)[9] |
| • Stratum corneum chymotryptic enzyme (keratinized oral mucosa)[30] | • Cytokeratins 2, 6, 16 (keratinized oral mucosa, eg, palate, gingiva, tongue)[9,31,32] |
| | • Different form and constituents of membrane coating granules in nonkeratinizing epithelium[33,34] |
| | • Permeability of oral mucosa increased between 10 times (palate) to 20 times (floor of mouth)[13] |
| *Cell-Cell and Cell-Matrix Adhesion Molecules* | |
| • Integrin expression in basal cells[35] | • Integrin α2, α3 and β1 in suprabasal cells of floor of mouth and lateral border of tongue, which may relate to a high turnover rate[40] |
| • Cell-cell adhesion: CD44[36] | • Reduced expression of desmoglien-1[42] |
| • Desmosomal associated proteins: desmoplakin, desmoglein-3 and desmocollin[37,38] | • Connexin-26 expression in spinous layer of buccal epithelium[38] |
| • Connexin-43 expression in spinous layers of epidermis and buccal epithelium[39] | • Cell surface carbohydrates (ABO and Lewis blood group antigens and their precursors): differential expression related to tissue differentiation and status, eg, keratinized and nonkeratinized epithelium, epithelial wounds, or malignant epithelium[43–45] |
| • BP230, ladinin, BP180, laminin-5, collagen IV, and other lamina densa proteins and collagen VII[37,38,40,41] | |

2) and up to seven times more connective tissue papillae/mm$^2$ than the floor of the mouth.[10] These latter lining mucosae are not subjected to as much frictional force and need to be more flexible.

Differences in the basic structure and components of this attachment between oral mucosa and skin have not been reported. In summary, this attachment involves hemidesmosomal attachment of basal epithelial cells to a basal lamina, involving BP230, BP180, alpha-6 beta-4 integrin, laminin-5, and uncein in the lamina lucida, plus heparin sulphate, collagen IV, laminins, nidogen, and other proteins in the lamina densa. The basal lamina is in turn attached via anchoring fibrils (collagen VII) to collagen fibers of the underlying lamina propria.[10,38,40,41] The functional importance of components of this attachment zone in wound healing and disease is similar for oral mucosa and skin—for example, changes in expression of integrins in keratinocytes in healing wounds,[56] alterations in integrin expression in squamous cell carcinoma,[40] and deposition of autoantibodies against BP180 or laminin-5 in mucosal (cicatricial) pemphigoid.[37,38]

## *Lamina Propria*

The lamina propria, a dense connective tissue, provides support for the overlying epithelium.[2] The superficial region of the lamina propria, referred to as the *papillary layer*, consists of connective tissue papillae that interdigitate with the rete ridges of the overlying epithelium (Fig 2). Deep to this layer of interdigitating connective tissue papillae is the reticular layer, so-called because of its fiber network. There is little regional variation in the connective tissue of the oral mucosa, although there are elastic fibers in the connective tissues of the lining mucosa, and the collagen fibers are less regularly organized. Expected connective tissue components are present in the lamina propria, namely cells and fibers embedded in ground substance. Fibroblasts are the predominant cell involved in producing and maintaining the collagen fibers (Types I, III, V, and VI)[57] and also the ground substance that consists of proteoglycans (eg, hyaluronan, heparan sulphate, syndecan, decorin)[58] and glycoproteins (eg, fibronectin, tenascin).[59] The collagen fibers in the lamina propria are thin and loosely arranged in lining mucosa but are arranged in bundles in masticatory mucosa.

Other cells found in varying numbers depending on the site include leukocytes, macrophages, mast cells, and numerous blood vessels in the form of capillaries that loop into the connective tissue papilla. There are also lymphatics and neural elements. The latter include intraepithelial nerve fibers, organized nerve endings (lamellar, coiled, or glomerular) and Merkel cell–neurite complexes.[60,61] The junction of the reticular layer of

the lamina propria with the underlying tissues varies depending on the type of mucosa. In the gingiva and anterior aspects of the hard palate, the lamina propria is bound to periosteum (Fig 3c) and tooth, while in the posterolateral aspects of the hard palate it is bound to a fibrous submucosa containing salivary glands and fat (Fig 3d). The lamina propria of lining mucosa is attached to a submucosa of connective tissue associated with muscles (lips, cheeks, tongue, and soft palate) (Fig 5a), fat (soft palate, cheek, and labial mucosa) (Fig 4a), and salivary glands (lips, cheeks, palate, and tongue) (Figs 3d and 5b).

## Relating Clinical Appearance to Histological Structure

The clinical appearance of the oral mucosa varies depending on the distribution of superficial blood vessels, the type and thickness of epithelium, components of the submucosa, presence of pigmentation and appendages, various surface features of the mucosa, functional adaptations, and disease. Other articles in this issue discuss diseases affecting the oral mucosa and will not be dealt with here.

### *Color of Oral Mucosa*

Clearly, the pink/red color of oral mucosa is derived from the extensive blood supply to these tissues. The distribution of blood vessels is also important in imparting the level of redness—for example, while the epithelium of the vermilion border of the lip is keratinized, it is thin, like interfollicular skin. The capillaries in the numerous connective tissue papillae are, however, superficially located just beneath the epithelium, imparting the red color to this tissue (Fig 3b). The vermilion border of the lip is at risk of ultraviolet damage, especially the lower lip in fair-skinned individuals. Changes in color and texture may be noted, in particular the blurring of the junction between the vermilion border and skin, patches of increased keratinization with loss of redness and loss of elasticity of the tissues due to degeneration of the collagen, and increase in thickened elastic fibers.[62] These changes may indicate early changes associated with malignancy (refer to other articles in this issue).

Generally there are many more cell layers in oral epithelium compared with epidermis of interfollicular regions of thin skin (eg, abdominal skin), which has a reported thickness of approximately 100 to 120 μm (Fig 3a).[10] However, as the thickness of epidermis varies in different regions, so the oral mucosa displays variation in epithelial thickness, which is related to the number of cell layers. For example, cheek mucosa has comparatively thick epithelium (580 ± 90 μm) (Fig 1c), resulting in a pinker clinical appearance compared with the epithelium in the floor of mouth, which is very thin (190 ± 40 μm) (Fig 1e). The thickness of the hard palate epithelium is somewhere in-between these two regions (310 ± 50 μm).[10]

The keratinized layer of the hard palate and the gingival tissue reduces the level of redness from the underlying blood vessels, such that these tissues appear pink clinically. However, if they are inflamed, the vascular response associated with inflammation results in a red appearance. The presence of fat in the submucosa (posterior-lateral regions of the hard palate, soft palate, and cheek) also imparts a yellow color to the mucosa in these regions (Fig 1d). Because of the apposition of mucosae with different types and thicknesses of oral epithelium and submucosal tissues, the color of the oral mucosa changes between regions—for example, there is a clearly defined mucogingival junction between the gingiva and alveolar mucosa (Fig 1b), whereas there is a gradual transition from the hard to the soft palate (Fig 1d).

As noted above, melanocytes are found in the basal layer of oral mucosal epithelium; however, the presence of pigmentation varies greatly between and within individuals,[53] being related to the level of skin pigmentation.[63] Though many areas of the oral mucosa are reported to contain melanocyte products,[53] pigmentation may not always be visible clinically such that light-skinned individuals rarely display pigmentation related to melanocyte activity. The gingiva, buccal mucosa, hard palate, and tongue most frequently display oral pigmentation.

Another major difference between the appearance of skin and oral mucosa results from an absence of skin-like appendages in oral tissues. An exception are sebaceous glands found in approximately 80% of adults.[62] They become clearly evident after puberty and are found symmetrically in the upper lip (rarely lower) and cheeks. They are referred to as *Fordyce spots* or granules and appear as yellowish spots or occasionally plaques that may be slightly raised above the otherwise pink mucosa.

As noted in Table 1, the expression of specific cytokeratin proteins for nonkeratinizing epithelium does not preclude the expression of cytokeratins specific for keratinizing epithelium.[23] This is evident in the whitish ridges/lines, consisting of keratinized epithelium, that may be found in the buccal mucosa at the level of the contact between upper and lower teeth. It is considered that this change in epithelial differentiation pattern is due to increased friction, related to cheek biting.

## Oral Mucosal Surface Features

Structural features of the oral mucosa, which are specific to these tissues, include the palatal rugae, the papillae of the dorsal surface of the tongue, and the attachment of the gingivae to teeth. The palatal rugae

are located in the anterior hard palate and consist of a series of raised connective tissue ridges covered with keratinized epithelium (Fig 1a). These structures are well developed in some animals, but they are probably of no major importance in humans.

### *Lingual Papillae*

As noted above, the anterior two-thirds of the dorsal surface of the tongue have three types of papillae that differ in gross and histological structure (Fig 5). The predominant type is the *filiform papillae*, which are thread-like projections of keratinized epithelium, contributing to the masticatory function of tongue (Figs 1f and 5a). Dotted between these papillae are the redder *fungiform papillae*, which consist of a well-vascularized connective tissue core, covered dorsally with keratinized epithelium and with taste buds located laterally (Figs 1f and 5a). The remaining few papillae on the dorsal surface are the *circumvallate papillae* (8 to 12 in number), located at the junction of the anterior two-thirds and posterior third of the tongue. They are mushroom-shaped structures, surrounded by deep troughs into which salivary gland ducts open. Their dorsal surface is keratinized with taste buds located on the nonkeratinized lateral aspects, overlying a connective core (Fig 5b). Located on the posterior aspect of the lateral borders of the tongue are foliate papillae, which consist of vertical mucosal folds/ridges separated by grooves containing taste buds.

### *Gingivae*

Gingival mucosa surrounds the teeth on labial/buccal and lingual/palatal surfaces. The epithelial covering of the outer surface of the gingiva (ie, that facing the lips/cheeks or palate/tongue) consists of masticatory or keratinized epithelium. In contrast, the epithelium facing the tooth (ie, that forming one wall of the gingival sulcus/crevice) consists of the coronally positioned nonkeratinizing sulcular component adjacent to the deeper junctional component (Fig 2a). As noted, this latter epithelium is attached to the tooth via hemidesmosomal attachment to a basal lamina, which is specific to this site and does not contain type IV collagen. The gingival tissues can be divided into components or structures, based on the relationship of the tissue to the tooth, namely *free* and *attached gingivae* and *interdental papillae* (Fig 1b). As the terminology implies, the free gingivae are not attached to the tooth and form a short cuff around the teeth. The gap created by this cuff is referred to as the *gingival sulcus* or *crevice* and is about 0.5 to 2 mm deep in health. The nonkeratinized nature of the sulcular epithelium results from the mild inflammation of the mucosa in this region as a result of the response of the host to the continual presence of the oral microflora (Fig 2a).

The attached gingival mucosa is connected to the tooth and/or bone, depending on the health of the gingival tissues, via the junctional epithelial attachment to the tooth as well as collagen fiber bundles from the gingival connective tissues, which insert into the surface of the tooth root or the periosteum of the alveolar bone (Fig 2a). In health, the attached gingiva has a stippled appearance (small superficial depressions) due to collagen fiber bundles that attach the gingival connective tissues to the tooth root and bone. Located between the teeth are the interdental papillae consisting of keratinized epithelium on the facial/lingual aspects overlying connective tissue (Fig 1b). These papillae are located on both labial/buccal and palatal/lingual aspects and are joined by the col, which is located beneath the contact areas of adjacent teeth and has an epithelial covering consisting of JE. The margin of healthy gingiva in relation to the teeth is in the region of the cementoenamel junction and its appearance is generally pink, firm, well contoured, and stippled. In contrast, inflamed gingivae are red, swollen, puffy, nonstippled, and bleed readily.

Differences in the response of oral mucosa to clinical manipulations are related to tissue structure. For example, injection of fluid into the alveolar or buccal mucosa is relatively easy and, if performed slowly, causes limited discomfort due to the looser supporting connective tissue (Fig 4). In contrast, injection into gingival or palatal mucosa is difficult and tends to be painful as a result of the firm attachment of the mucosa to periosteum or fibrous submucosa (Fig 3c). The firm attachment of masticatory mucosa also means the cut edges of these tissues do not move; therefore, limiting the need for suturing and closure of wounds is not possible without raising a flap. The cut edges of buccal mucosa, however, tend to gape and require suturing.

### *Salivary Gland Ducts*

The oral mucosa differs from skin in that it is continually bathed with saliva, secreted by salivary glands of the oral submucosa. The minor salivary glands in the lip submucosa are notable as they contribute a lumpy texture to these tissues. Various surface features of the oral mucosa are associated with the openings of ducts of the major salivary glands. The bilateral parotid papillae are located in the cheek mucosa, opposite the permanent molars, while the sublingual papillae, which mark the opening of the submandibular ducts, are located in the floor of the mouth (Fig 1e). The sublingual folds produced by the submandibular salivary gland ducts represent the multiple sites of opening of the sublingual glands (Fig 1e).

## Age Changes in the Oral Mucosa

Limited evidence is available of clinical changes to the oral mucosa that can be attributed to age alone. The

majority of reports of atrophy of the oral mucosa with age have not been based on longitudinal studies of healthy subjects and probably indicate changes associated with medications, inadequate nutrition, and/or disease.[64] A cross-sectional study of epithelial thickness of subjects aged from 18 to 96 years generally showed a variable but small reduction in epithelial thickness with age, and with flattening of the epithelial–connective tissue junction.[65] Systematic study of human oral connective tissues with age has not been reported. In terms of cell turnover, evidence of changes in human oral mucosa with age is not available, and the evidence from animal studies is varied, although there is some evidence of reduced turnover in epidermis.[66] Increased permeability with age has been reported in skin, whereas results for oral mucosa overall have indicated some increase in permeability with age, but this is quite variable between subjects and regions of the oral mucosa.[67] Evidence of dryness of the oral mucosa in association with age is reported to be mostly associated with medications.[64]

## Concluding Remarks

In summary, within the confined regions of the oral cavity, the oral mucosa displays a range of regional differences that relate to its development and functional demands. A number of similarities between the epidermis and keratinized oral epithelium have been noted, although differences between skin and oral mucosa are evident. The oral mucosa represents some features that are specific to the oral environment, including the constantly moist surroundings, the presence of teeth protruding through the oral epithelium, and the ubiquitous presence of inflammation in this region, along with the consistent functional demands of eating and communicating. The reader is referred to more detailed discussions about the specific regions of oral mucosa or tissue components in recent dental histology texts[1] and specialist journals.[68] The remaining articles in this issue of the journal will draw on the basics of oral mucosal development and structure and discuss the many diseases affecting the oral mucosa.

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