Blue, gray, and black skin and mucosal pigmented lesions are usually attributable to exogenous tattoos or melanin. Brown pigmentations are represented by either melanin or hemosiderin. Yellow discolorations may be the result of bilirubin deposition or the ingestion of large amounts of β-carotene. Blue and purple discolorations are generally the consequence of vascular lakes within the dermis or submucosal connective tissues. Pigmented lesions may be focal and macular or raised, or they may be diffuse or multifocal. In general, diffuse and multifocal pigmentation is attributable to melanosis, and there may be systemic or pharmacologic factors in the etiopathogenesis. The most common causes of oral pigmentations are genetic, related to ethnicity, and those caused by accidental amalgam implantation (Table 22–1).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Macular</th>
<th>Nodular</th>
<th>Papillary</th>
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<tbody>
<tr>
<td>Focal</td>
<td>Amalgam tattoo</td>
<td>Compound and intradermal (mucosal) nevi</td>
<td>Malignant melanoma</td>
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<td></td>
<td>Graphite tattoo</td>
<td>Seborrheic keratosis (skin)</td>
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<td></td>
<td>Ephelis, melanotic macule, melanoacanthoma</td>
<td>Angiomas, varices, Kaposi sarcoma</td>
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<td></td>
<td>Junctional nevus</td>
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<td>Melanoma</td>
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<td>Blue nevus</td>
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<td>Echymosis, petechia</td>
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<td>Macular hemangioma, Kaposi sarcoma</td>
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<td>Diffuse</td>
<td>Physiologic (ethnic) pigmentation</td>
<td>Malignant melanoma</td>
<td>Acanthosis nigricans</td>
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<td></td>
<td>Addison disease, Cushing syndrome</td>
<td>Kaposi sarcoma</td>
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<td></td>
<td>McCune-Albright syndrome</td>
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<td>Black or brown hairy tongue</td>
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<td>Peutz-Jeghers syndrome</td>
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<td>Smoker’s melanosis</td>
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<td>Melasma, chloasma</td>
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</table>

Table 22–1 Pigmentations of the Facial Skin and Oral Mucosa
Molecular and pathologic correlates of disease

Exogenous pigments in the oral mucosa are iatrogenic or traumatically introduced; amalgam is the most common. Cavity preparation of a tooth with an existing restoration results in the entrapment of fine particles in the fissures of the rotary bur. Laceration of the soft tissue deposits the particles in the submucosa (Figure 22–1). The silver particles in the amalgam slowly leach out and stain reticulum fibers. If there are other materials admixed with amalgam particles, a foreign body giant cell reaction is seen microscopically. There are no untoward effects of amalgam tattoos, the pigment remaining in place for the patient’s lifetime. Graphite, from lead pencils, is another source of exogenous pigment. Deposition usually occurs in the palate when some poor unfortunate sole has placed their pencil between the upper and lower teeth with the lead resting against the hard palate. Someone accidently bumps them and the graphite is fractured off the pencil tip and deposited into the palatal tissues.

Blood pigments are deposited in the connective tissues as a consequence of extravasation. Erythrocytes are lysed, releasing hemoglobin. The hemoglobin is converted by enzymes into hemosiderin, which in turn is broken down to bilirubin and biliverdin, which are phagocytized and cleared in the spleen. Blood pigments are usually cleared from the skin or mucosa within 2 weeks. The extravasation is attributable to trauma, capillary fragility, platelet defects, or clotting-factor disorders.

Melanocytic lesions all involve synthesis of melanin pigment granules by melanocytes. When there is no melanocytic proliferation, only increased synthesis of melanin in melanocyte-containing melanosomes, the pigment is released into the basilar keratinocytes, and when their capacity to retain this pigment is exceeded, pigment spills into the underlying connective tissues. These processes are referred to as basilar melanosis and melanin incontinence, respectively (see Figure 22–1). Keratinocytes containing melanin migrate to the surface. During this maturation process, the melanin is broken down by intracellular proteolytic enzymes.

On skin, melanosis occurs in response to excessive sun exposure. In the mouth, melanosis may occur in traumatized areas, and the traumatized epithelia that regenerate may do so with concomitant overproduction of melanin by melanocytes that repopulate the region. Other stimuli for melanin production are certain hormones and drugs. The adrenal cortical–hypothalamic axis is affected by hypofunction of the adrenal cortex. As serum corticosteroid levels decline, adrenocorticotropic hormone (ACTH) production by the posterior pituitary increases, and because ACTH has melanocyte stimulatory function, it can induce melanosis. Minocycline is a tetracycline derivative that is used to treat acne. It has been shown to stimulate mucosal melanocytes to produce excessive amounts of melanin pigment; the mechanism is unknown.

Melanin pigment is synthesized in melanocytes by a progression of molecular events that take place within small membrane-bound organelles, the premelanosomes. As the biochemical processes progress, the pigment becomes compacted into electron dense melanosomes. Tyrosinase is a key enzyme required for the synthesis of melanin pigment; the corresponding gene is mutated in albinism. Thus, albinos contain normal numbers of melanocytes, but they are unable to produce melanin. On the other hand, vitiligo is a term describing acquired depigmented patches caused by a diminished number of melanocytes.

Proliferation of melanocytes occurs in benign nevi and in melanoma. Melanocytic nevi develop during childhood and rarely arise in adult life. Most nevi originate as basal layer melanocytes that proliferate in the lower strata of the epithelium along the junction with the connective tissue, and are therefore termed junctional nevi (Figure 22–2 and Figure 22–3, A). Later, the nevocytes (melanocytes) drop off into the connective tissue to form theques and islands, a feature that labels them as compound nevi. Their eventual fate is to leave the surface epithelium entirely, whereby all the clusters of nevus cells reside in the dermis or submucosa as
intradermal or intramucosal nevi (Figure 22–3, B). Junctional activity is generally lost by age 18. Blue nevi are unique in that they arise from dermal or mucosal melanocytes that remained in the connective tissues during embryonic neural crest migration and, therefore, did not evolve from junctional nevi. Blue nevi are comprised of spindle-shaped melanocytes that synthesize copious amounts of melanin pigment (Figure 22–3, C).

Malignant transformation of melanocytes can often be attributed to genetic alterations that result from solar radiation. The earliest change is junctional. In an adult, junctional proliferation with nuclear atypia is referred to as atypical melanocytic hyperplasia. When cytologic atypia becomes more advanced, the lesions are superficial spreading melanomas (Figure 22–3, D). When invasion of the connective tissue ensues, they are invasive or nodular melanomas and metastatic potential has been reached. There are pathologic stages that correlate the depth or level of invasion with survival. The Clark classification system for skin is commonly used for this purpose (Figure 22–4). Malignant melanocytes confined to the epithelium represents level I, invasion into the superficial papillary dermis is level II, invasion through the papillary dermis down to the reticular dermis is level III, invasion through the reticular dermis is level IV, and deep invasion of the subcutaneous fat is level V. The Breslow system utilizes a micrometer to precisely measure depth of invasion.

Focal pigmentation

Melanotic macule, ephelis

Ephelides, or freckles, are generated or intensified by sun exposure to the skin. They are commonly seen on the faces of redheads and appear as small brown macules. Focal macular pigmentations of the oral mucosa and lower lip are mucosal equivalents to the ephelis and are termed oral melanotic macules. On the lip, there is often a history of trauma. Intraoral melanotic macules are most often seen on the gingiva, palate, and lips, but can be found anywhere in the mouth, including the tongue. They are usually small, brown or black, and have smooth borders (Figure 22–5). Biopsy confirmation is recommended to rule out a melanocytic proliferation. Melanotic macules are focal forms of basilar melanosis, a nonproliferative process. A unique form of melanotic macule is the melanoacanthoma, a lesion usually encountered in persons of native African descent. This form of macule is microscopically characterized by basilar melanosis with concomitant presence of dendritic, pigment-forming melanocytes spread throughout an acanthotic spinous cell layer.

The differential diagnosis on the skin includes senile lentigo or age spots, melanoacanthoma, and superficial spreading melanoma. The latter two can arise in oral mucosa.

Melanocytic nevi

As previously discussed, junctional, compound, intramucosal, and blue nevi can arise on the face or in the mouth. Junctional nevi are macular and brown, whereas blue nevi are black or blue, because the melanin pigment is deep within the connective tissue (Figure 22–6). Compound and intramucosal nevi typically present as nodules that are round and symmetric. Most, yet not all, compound and intramucosal nevi are pigmented. On the face, nevi can arise in any location. In the mouth, nevi are more often encountered on fixed mucosa of the palate and gingiva. Biopsy is recommended to confirm the diagnosis, because unlike skin nevi, oral nevi are rare, and it is prudent to obtain histologic confirmation.

Amalgam and graphite tattoo

Tattoos are iatrogenic or factitial and represent the most common focal pigmentation of the oral mucosa.
Amalgam tattoos are introduced during condensation of amalgam fillings or cavity preparation of an existing alloy-filled tooth, or caused by fragments that may break away during tooth extraction and fall into open extraction sites. Another source is through leaching of a retrofilled endodontically treated tooth in which there is an opening from the cortex to the gingiva or vestibule. The pigment is usually black or gray, unlike the brown pigmentation seen with melanin and blood pigments (Figure 22–7). In general, amalgam tattoos are located adjacent to a restored tooth. A radiograph is recommended to confirm the presence of foreign metallic particles. When there is no evidence of amalgam on the radiograph and there is no adjacent restored tooth, biopsy is recommended to rule out a melanocytic lesion. It should be recalled that failure to detect an opacity from an amalgam tattoo may be encountered when the imbedded particles are below the resolution of dental radiographs.

Graphite tattoos are black or gray and are typically found in the hard palate where a pencil lead was accidentally and traumatically implanted. This usually occurs in individuals who hold pencils between their teeth with the pencil point inside the mouth. Both amalgam and graphite are inert, yet a foreign body reaction is sometimes encountered.

**Echymosis**

Trauma to the soft tissues of the skin and mucosa often lead to venous severance with extravasation of erythrocytes. These bruises or ecchymoses are bright red if the traumatic episode is recent and superficial, or after 2 days they are “black and blue” or, more often, brown, owing to conversion of hemoglobin to hemosiderin (Figure 22–8). If there is no history of trauma, a coagu-
Pathology or platelet disorder should be suspected, and a hematologic evaluation (prothrombin time, partial thromboplastin time, platelet count, and platelet aggregation assay) should be obtained (see Chapter 7). Because the blood pigments are extravascular, diascopy or point-pressure yields no blanching.

**Angiomas**

Vascular anomalies are discussed in more detail in Chapter 25. Blood vascular growths (hemangiomas) are usually raised nodules or multinodular lesions that are red, blue, and purple; however, some are flat and macular. These macular hemangiomas can be red or purple. Trauma to the lower lip often damages venous channels, with forma-

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**Figure 22-4** Diagram showing Clark classification of levels of invasion in cutaneous malignant melanoma. This classification is not applicable to mucosal melanomas, since the submucosal tissue layers are different.

**Figure 22-6** A, Intramucosal nevus; B, intraoral blue nevus.

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**Figure 22-5** Oral melanotic macule.

**Figure 22-7** Amalgam tattoo.
tion of a varix (Figure 22–9, A). Diascopy of the lesions usually produces blanching, since the erythrocytes yielding the pigment changes are located within the lumens of vessels. In children, treatment is generally withheld, since most hemangiomas spontaneously regress after puberty. The hemangiomas seen in the Sturge-Weber syndrome, port-wine stains, and the blue rubber bleb nevus syndrome do not regress. In persistant small hemangiomas and varices of the oral cavity and face, sclerotherapy with injection Sotradecol® or laser ablation are treatment options. Kaposi sarcoma appears as a red, blue, purple, or brown mucosal lesion that can be macular or tumefactive (Figure 22–9, B). This unique form of human immunodeficiency virus (HIV)-associated angiosarcoma is described in detail in Chapter 14. Lymphangiomas and hemangiomas are discussed in Chapter 25.

Melanoma
Melanomas of the facial skin are commonly found on the forehead and malar skin, areas that are prominent and subject to direct sun exposure. Early lesions are macular, can vary greatly in size, and are characterized by two major clinical findings that distinguish melanoma from nevi. First, they tend to show pigment heterogeneity. The pigment varies from black to brown to gray, and there are foci of depigmentation. Secondly, the borders tend to be irregular. Melanotic freckle of Hutchinson is the term applied to these flat early melanomas that are histologically represented by super-
ficial spreading melanoma (Figure 22–10, A). These variegated lesions may ultimately progress to nodular lesions that are also pigmented, tumefactive, and often ulcerated. Nodular melanoma is microscopically invasive, and the prognosis worsens with increasing Clark or Breslow levels of invasion (Figure 22–10, B).

Oral melanomas are extremely rare and can present as macular superficial spreading lesions or as invasive nodular tumefactions (Figure 22–11). For unknown reasons, they are more common in certain islands of Japan than in other parts of the world. Oral melanomas have a predilection for the anterior maxillary gingiva and palate. However, they can occur on any mucosal surface. They are black, gray, or brown and, like skin, may harbor foci of depigmentation. Because of the poor prognosis for oral melanomas, treatment requires extensive surgical excision, often followed by radiation therapy. Vaccines remain experimental. Although melanomas are rare in the mouth, suspicious pigmented lesions should be biopsied. There is no concrete evidence that an incisional biopsy encourages metastases.

Diffuse and multiple pigmentations

Diffuse pigmentations are generally forms of basilar melanosis and appear brown or gray. The facial skin and oral mucosa may appear yellow in jaundice (see Chapter 6) and yellow-orange in patients who consume excess carotenoids, primarily beta carotene.

Physiologic pigmentation

Most Caucasians and Asians manifest coral pink oral mucous membranes. Black individuals, many Mediterranean region Caucasians, Asians, and Hispanics who are dark skinned often have pink mucosa with widespread diffuse macular fields of brown, gray, or even black pigmentation. This physiologic melanosis can be found anywhere in the mouth, the facial gingiva being the most common location (Figure 22–12).

Black or brown hairy tongue

Elongation of the filiform papillae is accompanied by superficial pigments in the condition known as hairy tongue. These pigments are derived from foods and endogenous oral bacteria (Figure 22–13). This condition is described in Chapter 25.

Smoker's melanosis

Patchy brown macular pigmentations are sometimes present in the buccal mucosa among heavy cigarette smokers. These macules are 0.5 to 1.0 cm spots that are multiple and bilateral (Figure 22–14). Microscopically they are forms of basilar melanosis without melanocyte proliferation. The mechanism for this association is unknown.

Addison disease

Adrenal cortical insufficiency is the consequence of destructive pathologic processes, such as neoplasms and inflammatory lesions. Decreased corticosteroid production leads to increased ACTH, a hormone with melanocyte stimulatory action. As a consequence, the skin darkens or becomes bronzed and multifocal pig-
Pigmentations appear in the mucous membranes of the oral cavity, conjunctiva, and genital regions (Figure 22–15). A tumor of the posterior pituitary or certain small cell carcinomas may also secrete excessive amounts of ACTH with the same pigmentary changes. In ACTH-secreting tumors, the patient manifests features of the Cushing syndrome (see Chapter 9).

Café au lait pigmentation
Bronze and tan diffuse and multifocal macular pigmentations appear on the skin in neurofibromatosis, an autosomal dominantly inherited disease characterized by multiple skin nodules or even pendulous tumors. These pale brown macules may be several centimeters wide (Figure 22–16). They can occur anywhere, including the face and neck, and occasionally, oral mucosal pigmentations arise. Owing to their pale brown color, they are referred to as café au lait spots. Similar pigmented lesions occur in the McCune-Albright syndrome, an osseous disease with endocrine accompaniments. Severe fibrous dysplasia is polyostotic in this syndrome and may affect the jaws and facial bones. In addition, patients can develop thyroid goiter, and females may undergo precocious puberty.

Acanthosis nigricans
The diffuse pigmentations seen in acanthosis nigricans are encountered in the context of papillary surface changes. This disease can affect the oral mucosa as well as skin and may be a harbinger of gastrointestinal cancer. It is discussed in more detail in Chapter 15.

Minocycline melanosis
The tetracycline derivative minocycline is used to treat acne and is, therefore, a drug that is consumed over a long period. In some patients undergoing minocycline therapy, oral pigmentations evolve. They are broad brown, gray, or black foci of pigmentation accounted for by the presence of basilar melanosis. Most minocycline melanotic lesions are located in the palate (Figure 22–17).
oral macular pigmentation around the mouth and on the fingers (Figure 22–19). When these lesions are encountered, the patient should be questioned about any gastrointestinal complaints and a family history of polyps. No treatment is necessary.

**Suggested reading**


