ABSTRACT

Colour, is imparted to the skin by a variety of different substances which are visible to varying degrees in different people. The most important of these substances is the pigment, Melanin, which is produced in specialised cells called melanocytes within the skin. In the course of disease, the mucosal tissues can assume a variety of discolouration including brown, blue, gray and black. Such colour changes are often attributed to the deposition, production or increased accumulation of various endogenous or exogenous pigmented substances. However, although an area may appear pigmented, the discolouration may not be related to the actual pigment but rather to the deposition or accumulation of organic or inorganic substances.

KEYWORDS: Melanocytes, Discolouration, endogenous, exogenous, accumulation.

INTRODUCTION

Human head and neck skin and oral mucosa is not uniformly coloured and hence several degrees of chromatic variegation may be observed in physiological and pathological conditions. However the oral and perioral pigmentation can be physiological or pathological in origin. The term “Oro Facial Pigmentations” maybe applied to a wide range of entities caused by the accumulation of one or more pigments and featuring a change in colour of tissues.

Haemoglobin, hemosiderin and melanin represent the most common endogenous sources of mucosal colour change. Pigmented lesions that are of exogenous origin are usually
traumatically deposited directly into the submucosal tissues. The specific hue, duration, location, number, distribution, size, and shape of the pigmented lesion(s) may also be of diagnostic importance.\(^{[1,7]}\) Moreover, in order to obtain an accurate diagnosis, thorough dental, medical, family and social histories are required and various diagnostic and laboratory tests, including biopsy, may be necessary. Thus, an understanding of the various disorders and substances that can contribute to oral and perioral pigmentations is essential for the appropriate evaluation, diagnosis and management of the patient.\(^{[1]}\)

**PIGMENT**

A **Pigment** is a material that changes the colour of reflected or transmitted light as the result of wavelength-selective absorption. Pigments appear the colours they are because they selectively reflect and absorb certain wavelengths of visible light. When this light encounters a pigment, parts of the spectrum are absorbed by the chemical bonds of conjugated systems and other components of the pigment. Some other wavelengths or parts of the spectrum are reflected or scattered. The new reflected light spectrum creates the appearance of a colour. Ultramarine reflects blue light, and absorbs other colours. Pigments, unlike fluorescent or phosphorescent substances, can only subtract wavelengths from the source light, never add new ones. A pure pigment allows very little white light to escape, producing a highly saturated colour.\(^{[4, 8, 9, 26, 27]}\)

- The normal colour of the oral mucosa is pale pink and the range of colour depends on factors like.
  1. *Melanogenesis and distribution of melanin pigment.*
  2. *Keratinization.*
  3. *Depth of epithelialization.*
  4. *Degree of vascularity.*\(^{[3]}\)

Pigmentations could be either physiological or pathological conditions affecting the oral mucous membrane and are given as follows:

- **Local or ethnic pigmentation- associated with environment, race and ethnic factors.**
- **Oral pigmented manifestations of systemic diseases.**
- **Pigmentations associated with drugs.**
- **Pigmentations associated with neoplasms**\(^{[3]}\)
However for easier study, diagnosis and planning of treatment, pigmentation of oral mucous membrane is broadly classified into 2 groups according to the origin of the pigments namely, Endogenous Source and Exogenous Source.

The most common cause of oral pigmentations are genetic, related to ethnicity, and those caused by accidental amalgam implantation (Table: 1)

**TABLE 1: Pigmentations Of Facial Skin And Oral Mucosa**[^3]

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Macular</th>
<th>Nodular</th>
<th>Papillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>Amalgam tattoo, Graphite tattoo, melanotic macule, melanoacanthoma, Ephelis, Junctional nevus, Blue nevus, Ecchymosis, petechia, Macular hemangioma, Kaposi sarcoma.</td>
<td>Compound and intradermal (mucosal) nevi, Seborrhoeic keratosis (skin), Angiomas, varices, Kaposi sarcoma and Melanoma.</td>
<td>Acanthosis nigricans, Black or brown hairy tongue</td>
</tr>
</tbody>
</table>

**TABLE 2: Clinical Classification Of Oral Pigmentations**[^10]

<table>
<thead>
<tr>
<th>Colour</th>
<th>SOLITARY Focal</th>
<th>SOLITARY Diffuse</th>
<th>MULTIFOCAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue/Purple</td>
<td>Varix, Hemangioma</td>
<td>Hemangioma</td>
<td>Kaposi’s sarcoma, Hereditary hemorrhagic telangiectasia.</td>
</tr>
<tr>
<td>Gray/Black</td>
<td>Amalgam tattoo Graphite tattoo Nevis Melanoma</td>
<td>Amalgam tattoo, Melanoma, Hairy tongue</td>
<td>Heavy-metal ingestion pigmentation</td>
</tr>
</tbody>
</table>

Pigments can be placed in three categories: **Artifacts of Fixation, Exogenous and Endogenous** (table 3).
TABLE 3: Categories of Pigments[38]

<table>
<thead>
<tr>
<th>Fixation Artifacts</th>
<th>Exogenous Pigments</th>
<th>Endogenous Pigments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formalin pigment</strong> (in and near blood)</td>
<td><strong>Carbon</strong> (in lungs and associated lymph nodes, especially of city dwellers, coal miners) - <strong>BLACK</strong></td>
<td>Melanins (in normal skin, eye, some neurons; melanomas) -  <strong>BROWN</strong> to <strong>BLACK</strong></td>
</tr>
<tr>
<td>- <strong>BLACK</strong></td>
<td><strong>Mercury pigment</strong> (everywhere in the tissue) - <strong>BLACK</strong></td>
<td><strong>Hemosiderin</strong> (in cells that have phagocytosed blood; liver in diseases of iron metabolism) - <strong>DARK YELLOW</strong> to brown</td>
</tr>
<tr>
<td><strong>Picric acid</strong> (everywhere in the tissue)</td>
<td><strong>Inks used for tattoos</strong> (skin) - Various colors</td>
<td><strong>Lipofuscin</strong> (in older people, in cardiac muscle cells, neurons etc.) - <strong>YELLOW</strong> to <strong>LIGHT BROWN</strong></td>
</tr>
<tr>
<td>- <strong>YELLOW</strong></td>
<td><strong>Osmium dioxide</strong> (in most parts of tissues; darkest in fat cells, lipid droplets) - <strong>GRAY</strong> to <strong>BLACK</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 1: Biosynthesis of Melanin.**
TABLE 4: Endogenous Pigmentation In Oral Mucosal Disease[^9]

<table>
<thead>
<tr>
<th>PIGMENT</th>
<th>COLOUR</th>
<th>DISEASE PROCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMOGLOBIN</td>
<td>BLUE, RED, PURPLE</td>
<td>Varix, Hemangioma, Kaposi’s sarcoma, Angiosarcoma, Hereditary hemorrhagic Telangiectasia.</td>
</tr>
<tr>
<td>HEMOSIDERIN</td>
<td>BROWN</td>
<td>Ecchymosis, Petechia, Thrombosed varix, Hemorrhagic mucocele, Hemochromatosis.</td>
</tr>
<tr>
<td>MELANIN</td>
<td>BROWN, BLACK or GRAY</td>
<td>Melanotic macule, Nevus, melanoma, Basilar melanosis with incontinence.</td>
</tr>
</tbody>
</table>

Endogenous pigmentation are deposited or formed as a reaction of a chemical of endogenous origin ie., originate from within the body. They are broadly classified as **Hematogeneous** (from blood) or **Non-Hematogeneous** origin.

Eg: Haemoglobin, hemosiderin, melanin, carotene, blood and bile pigments and lipofuscin represent the endogenous source of mucosal colour change.

TABLE 5: Exogenous pigmentation of the Oral mucosa[^3]

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>COLOUR</th>
<th>DISEASE PROCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver amalgam</td>
<td>GRAY, BLACK</td>
<td>Tatoo, Iatrogenic trauma</td>
</tr>
<tr>
<td>Graphite</td>
<td>GRAY, BLACK</td>
<td>Tatoo, Trauma.</td>
</tr>
<tr>
<td>Lead, Mercury, Bismuth</td>
<td>GRAY</td>
<td>Ingestion of paint or medicinal.</td>
</tr>
<tr>
<td>Chromogenic bacteria</td>
<td>BLACK, BROWN, GREEN</td>
<td>Superficial colonization.</td>
</tr>
</tbody>
</table>

Exogenous pigments are deposited as such or formed as a reaction of a chemical of exogenous origin.

TABLE 6: Drugs associated with Oral Pigmentation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>PIGMENT</th>
<th>COLOUR</th>
<th>ORAL PIGMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazones</td>
<td>Oral</td>
<td>contraceptives</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
<td>Clofazamine</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>5- Fluorouracil</td>
<td></td>
<td></td>
<td>Premarin</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td>Clofazemine</td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
<td></td>
<td>Chlorhexidine</td>
</tr>
<tr>
<td>Minocycline</td>
<td></td>
<td></td>
<td>Carotene</td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
<td></td>
<td>Antimalarials</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ENDOGENOUS PIGMENTATIONS

A) FOCAL MELANOTIC PIGMENTATIONS

1. FRECKLE/EPHELIS\([1, 3, 10, 11, 13, 14, 16]\)

The common cutaneous freckle/ephelis, represents an increase in melanin pigment synthesis by basal layer melanocytes, without an increase in the number of melanocytes. On the skin, this increased melanogenesis can be attributed to actinic exposure. It is noticeable in 1st decade, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule that is often seen on the sun-exposed regions of the facial and perioral skin. Become darker during - periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months. Yet the increase in pigmentation is solely related to an increase in melanin production without a concomitant increase in the number of melanocytes. The intra oral counterpart to ephelis is the Oral Melanotic Macule.

2. ACTINIC LENTIGO\([3, 5, 15, 16]\)

Actinic lentigo is a brown macule that results from chronic ultraviolet light damage to the skin. Persons with facial freckles in childhood more likely develop Actinic Lentigines. It is found in more than 90% of Whites- older than 70 years of age. \([16]\) Does not occur within the mouth - is seen on the facial skin. It appears as uniformly pigmented brown to tan macules, well demarcated with irregular borders.

3. ORAL/LABIAL MELANOTIC MACULE (FOCAL MELANOSIS)\([1, 5, 15, 16, 17]\)

The oral melanotic macule is a flat, brown, mucosal discolouration produced by a focal increase in melanin deposition within the basal cell layer, lamina propria. Melanotic macules - more frequent in females (2:1), usually in the lower lip -33% (labial melanotic macule), buccal mucosa, palate and gingival .However, any mucosal site may be affected. Overall, melanotic macules tend to be small (<1 cm), well-circumscribed, oval or irregular in outline and often uniformly pigmented. Once the lesion reaches a certain size, it does not tend to enlarge further.

4. ORAL MELANOACANTHOMA (MELANOACANTHOSIS)\([1, 6, 15, 16, 31, 42]\)

Oral melanoacanthoma is another unusual, benign, melanocytic lesion that is unique to the mucosal tissues. It presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion, and most develop in black females. Although any mucosal surface may be involved, the buccal mucosa is the most common site of occurrence. Dermatosis papulosa
**nigra** is a relatively common facial condition that typically manifests in older black patients, often female, and represents multiple pigmented seborrheic keratoses.

### 5. MELANOCYTIC NEVUS

Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of **melanocytic growth and proliferation**. In the oral cavity, the **intramucosal nevus** is most frequently observed, followed by the **common blue nevus**.

**Compound nevi** are less common, and the **junctional nevus** and **combined nevus** (a nevus composed of two different cell types) are infrequently identified. **Cutaneous nevi** - common occurrence ➔ average caucasian adult patient may have several nevi.

#### VARIANTS OF MELANOCYTIC NEVUS

2. Halo Nevus.
3. Spitz Nevus (Benign Juvenile Melanoma).
4. Blue Nevus (Dermal Melanocytoma; Jadassohn – Tieche Nevus).

### 6. MALIGNANT MELANOMA

Malignant melanoma is the least common but most deadly of all primary skin cancers. Epidemiologic studies suggest that the incidence of melanoma is actually Multiple episodes of acute sun exposure, especially at a young age, immunosuppression, the presence of multiple cutaneous nevi, and a family history of melanoma are all known risk factors for the development of cutaneous melanoma. Melanoma-prone families have a high incidence of germline mutations in the tumor suppressor genes, CDKNA2/p16ink4a or, less commonly, CDK4.

Cutaneous melanoma is most common among white populations that live in the sun-belt regions of the world. Facial skin, the malar region - common site for melanoma - subject to significant solar exposure.

In general, the clinical characteristics of cutaneous melanoma are best described by the ABCDE criteria.
Asymmetry, irregular Borders, Color variegation, Diameter greater than 6 mm, and Evolution or surface elevation.

There are four main clinicopathologic subtypes of melanoma. These include

- Superficial Spreading Melanoma,
- Lentigo Maligna Melanoma,
- Acral Lentiginous Melanoma,
- Nodular Melanoma.

Tumor thickness (Breslow Tumor thickness), the level of tumor involvement in the dermis (Clark’s level of invasion), surface ulceration, vascular or lymphatic invasion, neurotropism, mitotic index, and absence of tumor infiltrating lymphocytes are all associated with a poor prognosis.

B) MULTIFOCAL/DIFFUSE PIGMENTATION

1. PHYSIOLOGIC PIGMENTATION

Physiologic pigmentation - most common source of multifocal or diffuse oral mucosal pigmentation. Dark-complexioned individuals, including Blacks, Asians, and South-Americans, frequently show patchy to generalized hyperpigmentation of the oral mucosal tissue. Although in many patients, the pigment is restricted to the gingiva, melanosis of other mucosal surfaces is not uncommon. If there is a sudden or gradual onset of diffuse mucosal pigmentation in adulthood, even in darker-skinned patients, other sources for the melanosis should be given consideration.

2. DRUG-INDUCED MELANOSIS

The chief drugs implicated in drug-induced melanosis are given in table. Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate or it can be multifocal and involve multiple surfaces. Sun exposure may exacerbate cutaneous drug-induced pigmentation.

3. SMOKER’S MELANOSIS

Diffuse melanosis of the anterior facial maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers. Most smokers (including heavy smokers) usually fail to show such changes.
However, it is probable that in certain individuals, melanin synthesis is stimulated by tobacco smoke products.\textsuperscript{[1,3,5,6]}

4. POST-INFLAMMATORY HYPERPIGMENTATION\textsuperscript{[1, 6, 9, 10, 53, 54]}
Post inflammatory hyperpigmentation is a well-recognized phenomenon that tends to develop more commonly in dark- complexioned individuals.\textsuperscript{[1, 6]} Most cases present as either focal or diffuse pigmentation in areas that were subjected to previous injury or inflammation. The acne-prone face is a relatively common site for this phenomenon. In addition to the typical microscopic features associated with lichen planus, there is also evidence of basilar hyperpigmentation and melanin incontinence.\textsuperscript{[6]}

5. MELASMA (CHLOASMA)/MASK OF PREGNANCY\textsuperscript{[1, 3, 6, 11, 12, 55]}
Melasma is a relatively common, acquired symmetric melanosis that typically develops on sun-exposed areas of the skin and frequently on the face.\textsuperscript{[1,3]} The cause is unknown but it is classically associated with pregnancy.\textsuperscript{[3]} Exposure to Exogenous Estrogen and Progesterone in the form of either oral contraceptives or hormone replacement therapy also may cause melasma. The forehead, cheeks, upper lips, and chin are the most commonly affected areas. Sun exposure tends to be an exacerbating, if not precipitating event. Rare cases of idiopathic melasma have also been described in females and, much less commonly, males.

C) MELANOSIS ASSOCIATED WITH SYSTEMIC OR GENETIC DISEASE
1. HYPOADRENOCORTICISM (ADRENAL INSUFFICIENCY, ADDISON’S DISEASE)\textsuperscript{[1, 3, 32, 33, 35, 36, 49, 56, 57]}
Addison disease is a rare disorder Male patients are affected with isolated AAD predominantly (70%) during the first two decades of life. Weakness, poorly defined fatigue, and depression are some of the typical presenting signs of the illness. Mostly, first sign of disease may be mucocutaneous hyperpigmentation. Generalized bronzing of the skin and diffuse but patchy melanosis of the oral mucosa are hallmarks of hypoadrenocorticism.

2. CUSHING’S SYNDROME/CUSHING’S DISEASE\textsuperscript{[1, 3, 11, 12, 33, 34, 35, 36, 58, 59]}
Cushing’s syndrome develops as a consequence of prolonged exposure to relatively high concentrations of endogenous or exogenous corticosteroids. It is more prevalent in female patients. However, prepubertal onset is more commonly seen in boys. Apart from the wide array of systemic complications, including weight gain and the characteristic “moon facies,”
diffuse mucocutaneous pigmentation may be seen in a subset of patients, specifically those whose pathology is associated with increased ACTH secretion.

3. **HYPERTHYROIDISM (GRAVES’ DISEASE)**\(^{(1, 3, 11, 12, 33, 34, 35, 36)}\)

Melanosis is a common consequence of hyperthyroidism (Graves’ Disease), especially in dark-skinned individuals. Studies suggest that at least 40% of black patients with thyrotoxicosis may present with mucocutaneous hyperpigmentation. In contrast, melanosis is very rarely observed in Caucasian patients with the disease.

4. **PRIMARY BILIARY CIRRHOSIS**\(^{(1, 3, 33, 34, 37, 58, 59, 60)}\)

Diffuse mucocutaneous hyperpigmentation may be one of the earliest manifestations of primary biliary cirrhosis. The mechanism by which melanosis develops is unknown. Hyperbilirubinemia often induces a yellowish discoloration of the skin, eyes, and mucous membranes.

5. **VITAMIN B12 (COBALAMIN) DEFICIENCY**\(^{(1, 3, 11, 12, 34, 58, 61, 62)}\)

Vitamin B12 deficiency may be associated with a variety of systemic manifestations, and diffuse mucocutaneous hyperpigmentation is a rare, and poorly recognized, complication of Vitamin B12 deficiency. The mechanisms by which melanosis develops are unknown. However, the pigmentation resolves following restoration of vitamin B12 levels.

6. **PEUTZ-JEGHERS SYNDROME**\(^{(3, 11, 12, 58, 59)}\)

Peutz-Jeghers syndrome is an autosomal dominant disease that is associated with mutations in the STK11/LKB1 tumor suppressor gene. Clinical manifestations include intestinal polyposis, cancer susceptibility, and multiple, small, pigmented macules of the lips, perioral skin, hands, and feet.

7. **CAFÉ AU LAIT PIGMENTATION**\(^{(1, 3, 11, 12, 58, 63, 64, 65, 66)}\)

Solitary, idiopathic café au lait (“coffee with milk”) spots are occasionally observed in the general population, but multiple café au lait spots are often indicative of an underlying genetic disorder. Café au lait pigmentation may be identified in a number of different genetic diseases, including Neurofibromatosis Type I, McCune-Albright Syndrome, and Noonan’s Syndrome. The classic-appearing café au lait spots are more characteristically seen in patients with the Noonan’s phenotype.
8. HIV/AIDS-ASSOCIATED MELANOSIS[1, 3, 11, 12, 58, 59, 60]
Diffuse or multifocal mucocutaneous pigmentation has been frequently described in Human Immunodeficiency Virus (HIV)-seropositive patients. The pigmentation may be related to intake of various medications, including antifungal and antiretroviral drugs, or as a result of adrenocortical destruction by virulent infectious organisms.

D) IDIOPATHIC PIGMENTATION
• LAUGIER-HUNZIKER PIGMENTATION[1, 3, 67, 68, 69]
Laugier-hunziker pigmentation (also known as laugier- hunziker syndrome) was initially described as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues specifically involving the lips and buccal mucosae. The fingernails are more commonly affected than the toe nails.

E) DEPIGMENTATION
• VITILIGO[1, 3, 12, 42, 58, 59, 70, 71]
Vitiligo is a relatively common, acquired, autoimmune disease that is associated with hypomelanosis. Although the etiology and mechanisms remain unknown, the end result is a destruction of the melanocytes. In some individuals, there may only be focal areas of depigmentation. In other patients, an entire segment on one side of the body may be affected. Occasionally, the skin and hair of most of the body may lose its pigmentation (vitiligo universalis).

F) HEMOGLOBIN AND IRON-ASSOCIATED PIGMENTATION
1. ECCHYMOSIS[1, 3, 11, 12, 19, 42]
Immediately following the traumatic event, erythrocyte extravasation into the submucosa will appear as a bright red macule or as a swelling if a hematoma forms. The lesion will assume a brown coloration within a few days, after the hemoglobin is degraded to hemosiderin.

2. PURPURA/PETECHIAE[1, 3, 11, 12, 42, 58, 72, 73]
Capillary hemorrhages will appear red initially and turn brown in a few days once the extravasated red cells have lysed and have been degraded to hemosiderin. The distinction between purpura and petechiae is - Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint and purpura as multiple, small 2 to 4 mm collections of extravasated blood. Within 2 weeks, the lesions should resolve. Failure to do so should
arouse suspicion of a hemorrhagic diathesis, a persistent infectious disease, or other systemic disease, and appropriate laboratory investigations must be undertaken.

3. **HEMOCROMATOSIS**[^1^, ^3^, ^11^, ^12^, ^72^, ^73^]

Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition (usually in the form of hemosiderin) in the liver and other organs and tissues. The cutaneous pigmentation is seen in over 90% of affected patients, regardless of the etiology of the disease. Increased melanin pigment may be seen in the basal cell layer, whereas golden or brown-colored hemosiderin can be seen diffusely scattered throughout the submucosal and salivary gland tissues.

**EXOGENOUS PIGMENTATION**

1. **AMalgAM TATTOO[^1^, ^3^, ^11^, ^12^, ^27^, ^28^, ^29^, ^30^]**

By definition, these are iatrogenic in origin and typically a consequence of the inadvertent deposition of amalgam restorative material into the submucosal tissue. Some studies suggest that amalgam tattoos may be found in up to 1% of the general population. They may be found on any mucosal surface. However, the gingiva, alveolar mucosa, buccal mucosa, and floor of the mouth represent the most common sites. The lesions are often found in the vicinity of teeth with large amalgam restorations or crowned teeth that probably had amalgams, around the apical region of endodontically treated teeth with retrograde restorations or obturated with silver points, and in areas in and around healed extraction sites.

2. **GRAPHITE TATTOOS[^1^, ^11^, ^12^, ^28^, ^29^]**

Graphite tattoos are an unusual source of focal exogenous pigmentation. They are most commonly seen on the palate and represent traumatic implantation of graphite particles from a pencil.

3. **ORNAMENTAL TATTOOS[^1^, ^11^, ^12^, ^42^]**

In certain tribal cultures, ornamental mucocutaneous tattooing is considered a rite of passage and esthetically pleasing. Female members of certain tribes are more likely to exhibit this form of exogenous pigmentation, usually in an effort to make themselves more attractive or desirable.
4. MEDICINAL METAL-INDUCED PIGMENTATION\textsuperscript{[1, 3, 11, 12, 75]}
Silver may cause a generalized blue-gray discoloration (argyria), whereas gold-induced pigment may appear blue-gray or purple (chrysiasis). In both cases, the pigmentation may be persistent, if not permanent, even following discontinuation of the substance. Rare examples of diffuse oral argyrosis have been reported. Chrysiasis does not involve the oral mucosal tissues since it is thought that exposure to ultraviolet light or other high-intensity light sources precipitates the pigmentation.

5. HEAVY-METAL PIGMENTATION\textsuperscript{[1, 3, 11, 12, 16]}
Diffuse oral pigmentation may be associated with ingestion of heavy metals. Nowadays, this phenomenon is unusually encountered. Yet it remains an occupational and health hazard for some individuals who work in certain industrial plants and for those who live in the environment in and around these types of facilities.

6. DRUG-INDUCED PIGMENTATION\textsuperscript{[1, 3, 15, 16]}
Minocycline, which is a tetracycline derivative and frequently used in the treatment of acne, is a relatively common cause of drug-induced non–melanin-associated oral pigmentation. Minocycline-induced soft tissue pigmentation may appear gray, brown, or black. Often the pigmentation is patchy or diffuse in its presentation.

GENODERMATOSES\textsuperscript{[1, 42, 47, 58, 59, 72]}
Genodermatoses are inherited genetics skin conditions often grouped into 3 categories namely chromosomal, single gene, poly genetic.\textsuperscript{[32]} The term genodermatoses refers to monogenetic diseases. In recent years, the causative genes and proteins have been identified for many genodermatoses. The genes that are associated with the onset of these diseases are called disease-related genes or predisposing factors; their importance to the disease is considerably different from that of monogenic causative genes for genodermatoses.

1. OCULOCUTANEOUS ALBINISM TYPE 1 (OCA 1)
Inheritance
Autosomal recessive, Tyrosinase gene on 11q 14-q21.\textsuperscript{[34]}
Clinical findings
Skin: Generalized pink white colour, solar keratoses, pink red nevi, squamous cell cancers, Basal cell cancer, melanoma; Hair: snow white colour; Eyes: blue to grey blue irides, severe nystagmus, photo phobia, strabismus, foveal hypoplasia.\textsuperscript{[33, 34]}
2. OCULOCUTANEOUS ALBINISM TYPE 2 (OCA 2)

Inheritance
Autosomal recessive, P gene on 15q 11.2 – 12.

Clinical findings
Skin: Generalized pink white to cream colour, multiple pigmented nevi, Ephelides, Lentigines, solar keratoses, squamous cell and Basal cell cancer; Hair: cream to yellow brown colour; Eyes : blue to yellow brown irides, nystagmus, photophobia, impaired visual acuity, foveal hypoplasia.\(^{[33,34]}\)

3. HERMANSKY – PUDLAK SYNDROME

Inheritance
Autosomal recessive, P gene on 15q 11.2 – 12.

Clinical findings
Skin: Generalized pink white colour, pigmented nevi, Lentigines, solar keratoses, squamous cell and basal cell cancer. Hair: cream to yellow brown colour. Eyes: severe nystagmus, impaired visual acuity, strabismus, foveal hypoplasia.\(^{[33,34]}\)

4. CHEDIAK HIGASHI SYNDROME

Inheritance
Autosomal recessive.

Clinical findings
Skin: light cream to slate gray colour, recurrent bacterial infections- Staphylococcus aureus more common. Hair: light blond with silver sheen. Eyes: photophobia, strabismus, nystagmus, decreased uveal pigment.\(^{[33,34]}\)

5. GRISCELLI SYNDROME

Inheritance
Autosomal recessive.

Clinical findings

6. PIEBALDISM

Inheritance
Autosomal dominant.
Clinical findings
Skin: depigmented patches on the forehead, central eyebrows, neck, anterior trunk, mid-extremities; often bilateral, sparing the hands, feet, back, shoulder, hips- islands of hyperpigmented to normally pigmented patches within and at the borders of hypopigmentation. Hair: white forelock. Rare: Hirschsprung disease, mental retardation, deafness, cerebellar ataxia.

7. WAARDENBURG SYNDROME
Inheritance
Autosomal dominant, Pax3 gene on 2q35.
Clinical findings
Skin: may have pigmented patches on body, Hair: white forelock (<50%).

8. HYPOMELANOSIS OF ITO
Clinical findings
Skin: unilateral and bilateral whorled marble cake hypopigmentation in Blaschok’s lines. Hair: Alopecia. CNS: seizures, mental and motor retardation; Eyes: strabismus, hypertelorism; Teeth: anodontia.

9. LEOPARD SYNDROME
Synonym
Multiple Lentigines syndrome.
Clinical findings
Skin: generalized multiple Lentigines; mucous membrane spared, Café au lait spots, Café noir spots. CVS: ECG conduction defects, aortic stenosis, obstructive cardiomyopathy; Growth retardation, abnormal genitalia, sensorineural defects.

10. CARNEY COMPLEX
Inheritance
Autosomal dominant.
Clinical findings
Skin: Lentigines, Blue Nevi, melanocytic nevi, Ephelides, Myxomas.
Cardiac: Atrial myxomas, CHF. Cushing’s syndrome, acromegaly, psammomatous melanocytic schwannomas.

11. McCUNE- ALBRIGHT SYNDROME
Inheritance
sporadic.
Clinical findings
Skin: Large segmental Café au lait macules with “coast of maine” border. Bone: polyostotic fibrous dysplasia- long bones and facial bones commonly affected, recurrent fractures, bowing of limbs, limb length discrepancies, and diffuse sclerosis at the base of the skull. Endocrine: hyperthyroidism, precocious puberty.

12. NEUROFIBROMATOSIS TYPE I
Inheritance
Autosomal dominant.
Clinical findings
Skin: Café au lait macules, greater than 6mm $\rightarrow$ NF I; freckling in axillary or inguinal folds, neurofibromas, pruritis over growing neurofibromas. Eyes: Lisch nodules- iris hamartomas, congenital glaucoma, choroidal nevi. Skeletal: sphenoid wing dysplasia, macrocephaly, scoliosis, vertebral disk dysplasia, short stature.

13. NEUROFIBROMATOSIS TYPE II
Inheritance
Autosomal dominant.
Clinical findings
Skin: Lentigines, Blue Nevi, melanocytic nevi, Ephelides, Myxomas. Cardiac: Atrial myxomas, CHF. Cushing’s syndrome, acromegaly, psammomatous melanocytic schwannomas.

CONCLUSION
Oral and perioral pigmentations may be focal, diffuse or multifocal. They may be blue, brown, gray, or black. They may be flat or tumefactive. Importantly, some are harbingers of internal disease; some are localized harmless accumulations of melanin, hemosiderin or exogenous metal. They may also range from extremely common and harmless (eg: amalgam tattoo) to the rare and deadly (eg: malignant melanoma). The differential diagnosis can be
lengthy particularly when the pigmentation is macular and diffuse or multifocal. Although biopsy is a helpful aid to diagnose, a thorough history, clinical examination and lab studies are necessary to arrive at a definitive diagnosis, thus posing a diagnostic challenge for the Oral Medicine specialist.

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