Disorders of pigmentation — Part 1: Hyperpigmentation

This is the first of a two-part series on disorders of pigmentation. In Part 1, we discuss the nature of pigmentary disorders and then focus on hyperpigmentary disorders. In Part 2, we cover hypopigmentary disorders.

Overview of pigmentary disorders

Disorders of pigmentation are a common presentation in dermatology and general practice. The aesthetic appearance of either hyperpigmentation or hypopigmentation, especially in the visible parts of the skin, can have major psychosocial implications. Although it is more of a cosmetic problem, a disorder of pigmentation can occasionally be associated with an underlying systemic disorder. It is therefore important to recognise the causes of pigmentary disorders to achieve the best treatment outcome.

This article discusses pigmentary disorders in general including the underlying pathological mechanisms and management. It then looks at individual hyperpigmentary and hypopigmentary conditions in more detail.

The single most important substance determining human skin colour is the pigment melanin. Other compounds that may contribute to the skin colour include carotenoids and haemoglobin.

Melanin is produced by melanocytes during melanogenesis. This occurs within melanosomes, which are small membrane-bound packages. When melanosomes become full of melanin, they move along the arms of melanocytes and are transferred to the keratinocytes. One melanocyte supplies melanin to about 36 keratinocytes. People have the same number of melanocytes but their skin colour is determined by the amount and types of melanin the melanocytes produce. Melanocytes are found in the skin or epidermis, hair follicles, eye, nervous system, leptomeninges and the inner ear. Melanocytes in the skin and other body sites have a common embryological origin from the neural crest. They migrate from here into these different body sites.

The production of melanin is mainly regulated by the enzyme tyrosinase. Melanocytes produce two types of melanin that give the skin its colour. The most common form of melanin is eumelanin, which gives a brown-black colour and is more abundant in people with dark skin. Pheomelanin gives a red-yellow colour to the skin. Both the amount and type of melanin produced is controlled by several genes, such as the genes for the MSH cell surface receptor and the melanosomal P-protein. These genes can regulate the variability of the skin colour in humans by mainly regulating the level and activities of enzymes involved in the melanin biosynthesis, mostly the enzyme tyrosinase.


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Medication-induced hyperpigmentation

Dr Deepani Ratnayake
consultant dermatologist, Base Hospital Dambulla, Sri Lanka.

Professor Rod Sinclair
director and head, dermatology, Epworth Hospital, Melbourne, Victoria.
Disorders of pigmentation can be due to a variety of genetic and acquired causes. This is because there are many genes involved in the different stages of melanin production and transport abnormalities may arise from any of these stages. In piebaldism, for example, melanocyte migration from the neural crest is defective. Other abnormalities may occur in the formation of melanocytes and melanosomes, or during the secretion of melanosomes to keratinocytes. Certain pigmentary disorders such as Waardenburg syndrome may also be associated with visual and neurological defects, owing to the defects’ common embryological origin and migration from the neural crest.

Acquired conditions of pigment loss can arise from melanocyte destruction. This may be due to an underlying autoimmune disorder such as vitiligo, or inflammation by many factors such as UV radiation, drugs, inflammation and hormonal factors. Abnormalities in the other pigment compounds such as carotenoids and haemoglobin may also result in certain pigmentary disorders.

**Pathogenesis**

Lentigines

Lentigines are small, brown to black-coloured macular lesions. They have several points of difference to freckles: there is an increased number of melanocytes in lentigines, lentigines are darker, persist throughout the year, and do not darken on exposure to sunlight. There are several types of lentigines, as listed in the box below. Multiple lentigines can occur in association with an underlying genodermatosis (table 3).

Café au lait macules

Café au lait spots are macules varying from light brown to dark brown with smooth or irregular borders. While having a few small hyperpigmented lesions. However, figure 2 will help the clinician in approaching a patient.

**Patterns of hyperpigmentary disorders**

**Disorders of hyperpigmentation may be localised (circumscribed) or diffuse (table 2).** Certain conditions such as poikilodermatosus disorders cause reticulated and mottled type of pigmentation (figure 1). Because of their cosmetic significance, facial and periorbital pigmentation need special attention. There is no set algorithm or specific way to approach a patient with a hyperpigmented lesion. Formal counselling from a mental health professional may be helpful. Education about the disorder and treatment options should be fully provided so that the patients can form realistic expectations and participate in making important decisions about their medical care.

**Cosmetic camouflage is an option in some patients, especially on visible parts of the body.**

**Minimising sun exposure**

Patients who have depigmented or hypopigmented skin should minimise sun exposure and use a sunscreen that provides protection from both UVA and UVB light. Tanning makes the contrast between normal and depigmented skin more noticeable. Sunscreen helps prevent tanning and also helps protect from sunburn and long-term damage. Moreover, hyperpigmentary disorders such as melasma and freckles can deteriorate with sun exposure.

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**Table 1: Wood's lamp features in pigmentary disorders**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytagia versicolor</td>
<td>Yellowish-white or copper-orange fluorescence</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Bright areas with sharp borders, varying in location and extent</td>
</tr>
<tr>
<td>Tuberculosclerosis</td>
<td>Patches; characteristic ash-leaf shape</td>
</tr>
<tr>
<td>Hypermelanosclerosis of Ilot</td>
<td>Whorled or streaked patterns.</td>
</tr>
<tr>
<td>Erythema</td>
<td>Shows coral red fluorescence</td>
</tr>
<tr>
<td>Melasma</td>
<td>Pigments in the outer epidermal layer of the skin are accentuated while the colour of the deeper dermal pigments is decreased</td>
</tr>
</tbody>
</table>

**Table 2: Patterns of hyperpigmentary disorders**

<table>
<thead>
<tr>
<th>Circumscribed</th>
<th>Diffuse</th>
<th>Reticulate and mottled</th>
<th>Blaschoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freckles, lentigines, melanocytic naevi, melanoma, acanthosis nigricans, post-inflammatory, fixed drug eruption, café-au-lait macules, mastocytosis, phytophotodermatitis</td>
<td>Drug-related, endocrinopathies, haemochromatosis, HIV</td>
<td>Poliokidlerma of Civatte, erythema ab igne, genetic reticulate pigmentary disorders, poikilodermatosus disorders (eg, mycosis fungoides and dermatomyositis), confluent and reticulate papilomatosis, host disease, post-kala azar dermal leishmaniasis, systemic sclerosis</td>
<td>Pigmentary mosaicism, incontinentia pigmenti</td>
</tr>
</tbody>
</table>

**Table 3: Syndromes and genetic diseases associated with hyperpigmentation**

<table>
<thead>
<tr>
<th>Freckles</th>
<th>Xeroderma pigmentosum</th>
<th>Neurofibromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigines</td>
<td>Peutz–Jeghers syndrome</td>
<td>Leonard syndrome</td>
</tr>
<tr>
<td>Café au lait macules</td>
<td>Neurofibromatosis</td>
<td>McCune–Albright syndrome</td>
</tr>
<tr>
<td>Reticulate pigmentation</td>
<td>Dermatophagia pigmentosa reticularis</td>
<td>Dyskeratosis congenita</td>
</tr>
</tbody>
</table>

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**Freckles**

FRECKLES are small flat brown circular spots arising on the face and other sun-exposed areas. They usually fade in winter with less sun exposure and as the keratinocytes are replaced with new cells. They are most often seen in fair skinned, red-haired people. Genetic tendency and sun exposure can predispose to development of freckles. Freckles represent an increase in the amount of melanin, not an increase in the total number of melanocytes. Increased tendency to develop freckles is seen in genetic disorders such as xeroderma pigmentosum. Axillary freckles are a feature in neurofibromatosis (table 3).

While freckles are a harmless condition, some patients may be distressed by their appearance and seek treatment. Sun protection is essential in managing this condition if treatment is requested. There are several safe and effective methods that are available to help lighten or reduce the appearance of freckles. Treatment options include bleaching or fading creams (table 4), light application of liquid nitrogen, laser treatment and chemical peels. Frequently, multiple or a combination of these treatments may be required for the best results. Preventive photoprotection starting in early childhood is important because freckles can easily recur with repeated UV exposure.

**Diagnosis**

Many pigmentary disorders can be diagnosed clinically. A detailed history and examination is important and often gives clues to the underlying cause. A lesion presenting from birth may be a naevus or a genetic disorder. A family history of a similar disease also favours a genetic disorder. Diffuse types of pigmentary changes may be due to metabolic, hormonal or nutritional causes. A preceding rash or injury to the skin suggests post-inflammatory hyper- or hypopigmentation.
lesions may be normal, a greater size and number can point towards an underlying genetic disorder. The most commonly associated systemic disorder is neurofibromatosis type 1 (figure 3). Other syndromes associated with cafe au lait spots are listed in table 3.

The cafe au lait macules themselves do not require medical care. Pigment laser (Q-switched Nd:YAG) offers clearance in about 30% of cases when cosmetic treatment is requested. Discussion about the possible post-treatment complications should occur prior to treatment. The complications include transient hyperpigmentation and hypopigmentation, slight scarring, permanent hyperpigmentation and recurrence.

**Post-inflammatory hyperpigmentation**

Post-inflammatory hyperpigmentation is a frequent complication following various cutaneous disorders. These cutaneous disorders may be infections (eg, tinea), dermatitis, drug reactions and inflammatory skin disorders (eg, lichen planus). Epidermal post-inflammatory hyperpigmentation appears light-brown to black whereas deeper dermal pigmentation has a grey to bluish appearance. A variety of topical agents have been used to treat epidermal post-inflammatory hyperpigmentation, with varying degrees of success. These agents include hydroquinone, tretinoin cream, corticosteroids, glycolic acid (GA) and azelaic acid (table 4). A combination of topical creams and gels, chemical peels and sunscreens may be necessary and is only effective for epidermal hyperpigmentation. Laser treatment may be able to address dermal pigment deposition. Broad-spectrum sunscreen screens should be combined with any treatment regimen.

**Melasma**

Melasma presents as bilateral symmetric hyperpigmented macules commonly in the cheeks, the upper lip, the chin and the forehead (figure 4). The most significant cause of melasma is exposure to sunlight. Female hormones also play a role and appearance of melasma can be associated with pregnancy and contraceptive pills. There is a known genetic predisposition to melasma.

Melasma can be epidermal, dermal or mixed. Epidermal melasma has well-defined borders and is dark brown in colour. Dermal melasma is the common type with ill-defined borders and is bluish in colour. The mixed type has a combination of clinical features (see table 5).

Melasma can be difficult to treat and can be recurrent. There are several treatment modalities; these should always be combined with adequate sun protection. As shown in table 5, epidermal melasma has a good response to treatment while dermal melasma has a poor response.

**Types of lentigines**

- **Simple lentigines**
  - Very common condition
  - Benign, isolated pigmented macules
  - Seen in any part of the body including palms and soles
  - Independent of UV exposure
  - Usually do not need any treatment

- **Solar lentigines**
  - Small, discrete, irregularly shaped and uniformly brown macules
  - Typically seen in sun-exposed areas together with other features of chronic sun damage

- **PUVA lentigines**
  - Relatively large macular pigmentation
  - Develop as a complication of long-term PUVA (psoralen + UVA) therapy
  - May be a marker of increased future development of melanoma and non-melanoma skin cancer

- **INK spot lentigines**
  - Densely pigmented, relatively smaller macules
  - Often alarm both the patient and the doctor because of their clinical resemblance to melanoma

**Table 4: Depigmenting agents**

<table>
<thead>
<tr>
<th>Name and preparation</th>
<th>Clinical considerations</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinone 2% and 4% preparations</td>
<td>Clinical</td>
<td>Most effective inhibitors of melanogenesis acts by inhibiting tyrosinase*</td>
<td>Imitation</td>
</tr>
<tr>
<td>Tretinoin 0.025-0.1%</td>
<td>Topical therapy is not recommended</td>
<td>Acts by increasing keratinocyte turnover and thus limiting the transfer of melanosomes to keratinocytes</td>
<td>Photochemical enhancement</td>
</tr>
<tr>
<td>Azelaic acid 20% cream</td>
<td>Superior to 2% hydroquinone</td>
<td>Most competitive inhibitor of tyrosinase in vitro*</td>
<td>Skin irritation</td>
</tr>
<tr>
<td>Kojic acid — in concentrations of 1-4%</td>
<td>Twice daily application</td>
<td>A fungal metabolite that inhibits the catecholase activity of tyrosinase*</td>
<td>No photosensit or photoallergic reactions have been reported</td>
</tr>
<tr>
<td>Ascorbic acid 10-15% serum or cream</td>
<td>Takes 8-12 weeks to see a response</td>
<td>Has antistain properties and reduces melanogenesis</td>
<td>Implant contact dermatitis</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silymarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbutin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper mulberry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquorice extract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxy acids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Tyrosinase is the rate-limiting, essential enzyme in the biosynthesis of the skin pigment melanin; reduction of this enzyme leads to decreased production of melanin.

**Figure 3: Cafe au lait macules seen on the forehead of a patient with neurofibromatosis type 1. Note the neurofibroma on left of chin.**

**Figure 4: Melasma in a middle-aged woman, showing the classic bilateral hyperpigmented macules on the cheeks and other parts of the face.**

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**Ashy dermatosis (erythema dyschromicum perstans)**

Erythema dyschromicum perstans, also called lichen planus pigmentosus, causes ashy discolouration of skin and is therefore also known as ‘ashy dermatosis’. Ashy dermatosis is an asymptomatic eruption of oval, polycyclic, or irregularly shaped, grey-blue hyperpigmented macules on the trunk, the arms, the face, and the neck (figure 5). There are no systematic symptoms or associations. There are close similarities with lichen planus although the exact relationship is not clear. The disease is more common in Asian and Latin American people.

Different treatments have been tried but ashy dermatosis is usually resistant to treatment. Clofazamine has shown satisfactory results in some patients. Other treatments such as dapsone, potent steroids and bleaching creams have not shown satisfactory results.

**Acanthosis nigricans**

Acanthosis nigricans causes increased pigmentation with a soft velvety appearance on the sides of the neck, in the axillae and groin. There is also often an increased pigmentation of mucosal surfaces. The mechanism responsible for the pigmentation is unknown, but increased melanocytes-stimulating hormone activity is suspected. There are several types of acanthosis nigricans (see box, right).

The aim of treatment is to correct the underlying disease. This may involve multidisciplinary evaluation. Treatment of the lesions of acanthosis nigricans is for cosmetic reasons only. Topical medications that have been effective include keratolytics (eg, topical tretinoin 0.05%, ammonium lactate 12% cream, or a combination of the two) and triple-combination depigmenting cream (tretinoin 0.025%, hydroquinone 4%, fluocinolone acetonide 0.01%) nightly with daily sunscreen.

**Erythrasma**

Erythrasma is a chronic superficial infection of the intertriginous areas. The vascular type can present with red fluorescence of lesions and is a helpful bedside test.

**FACIAL hyperpigmentation**

FACIAL hyperpigmentation is one of the most common cosmetic complaints and requires special consideration. The presentation may be either diffuse or patchy. The causes may be multifactorial (see box, right), including genetic factors, sunlight, cosmetics and hormonal factors.

**Periorbital hyperpigmentation**

Dark circles around the eyes or periorbital hyperpigmentation can cause much psychological distress to the patient. Even though the condition is usually benign, it can be very resistant to treatment. It is a common condition and often familial. There are most likely multiple causative factors involved, including epidermal hypermelanosis, dermal melanosis, increased vasculature, and normal anatomic variants.

The vascular type can present with erythema predominantly involving the inner aspect of the lower eyelids, with prominent capillaries or telangiectasia. Blush discolouration of the lower eyelid can be seen as a result of visible blue veins. Constitutional type can present with a curved band of brownish to black hyperpigmentation with a velvety texture and often involving the upper eyelids (figure 8). Post-inflammatory hyperpigmentation may be secondary to contact or atopic dermatitis. Shadow effects due to an overhanging tarsal margin, eyelids or a deep tear trough can cause dark eye circles more commonly seen with ageing. Dry skin, hormonal disturbances, nutritional deficiencies and other chronic illnesses can also contribute. Treatments that have been tried include skin-lightening creams, chemical peels, intense pulsed light, Q-switched ruby laser, autologous fat transplantation, combinations of fat grafting and blepharoplasty, and fillers. However, none have provided a satisfactory treatment.

**Naevus of Ota**

Naevus of Ota is a hamartoma of dermal melanocytes presenting as a blue or grey patch on the face, within the distribution of the ophthalmic and maxillary branches of the trigeminal nerve. The naevus can be unilateral or bilateral, and, in addition to skin, it may involve ocular and oral mucosal surfaces (figure 9). Cosmetic camouflage makeup can minimise the disfiguring facial pigmentation. Other topical therapy is of no value. Pulsed Q-switched laser, Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:YAG laser have shown satisfactory results.

**Table 5: Melasma categorised by depth of pigmentation and ease of treatment**

<table>
<thead>
<tr>
<th>Melasma type by depth of pigmentation</th>
<th>Description</th>
<th>Relative response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal</td>
<td>Well-defined borders</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Dark brown in colour</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Becomes prominent with Wood’s lamp examination</td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Bi-defined borders</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Blush in colour</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Become less obvious with the Wood’s lamp examination</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Combined features</td>
<td>Partial</td>
</tr>
</tbody>
</table>

**Types of acanthosis nigricans**

- **Obesity-associated acanthosis nigricans**
  - Most common type
  - Associated with increased pseudo-acanthosis nigricans
  - May be a marker for higher insulin needs in obese women
  - May be an early marker for metabolic syndrome in paediatri patients

- **Syndromic acanthosis nigricans**
  - HARP-AN syndrome: hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN)
  - Polycystic ovarian syndrome
  - Uncontrolled diabetes mellitus
  - Ovarian hyperandrogenism

- **Acral acanthosis nigricans**
  - Hyperkeratotic velvety lesions
  - Found over the dorsal aspects of the hands and feet, with crinkle hyperpigmentation
  - Seen in otherwise healthy African-American individuals

- **Drug-induced acanthosis nigricans**
  - Examples include nictinic acid, systemic corticosteroids, oral contraceptives, fusidic acid

- **Malignant acanthosis nigricans**
  - Examples include gastric adenocarcinoma, Wilms tumour, osteogenic sarcoma
  - May present as lesions that arise rapidly, are more extensive, and in atypical locations
  - May be associated with tripe palms (thicker velvety palms that have the appearance of stomach lining of beef, pork or sheep)

**Step 1. Patient selection and counselling**

1. Discussion with the patient should include:
   - The procedure and the expected outcome
   - Possibility of unexpected complications like increased pigmentation, hypopigmentation
   - That treatment needs to be maintained

2. Take care in approach to patients with unrealistic expectations, active skin infections (HSV), ketodial tendency, uncooperative or non-compliant patients (careless about sun protection or maintaining treatment)

**Step 2. Skin preparation or priming**

1. Treat the pigmentation with 2-4% hydroquinone
2. Start a mild peeling agent like 0.025% retinoids, 6-12% glycolic acid
3. Start a sunscreen and avoid sun exposure
4. Stop the peeling agent three days before the peel

**Step 3. Post-procedural care**

1. Maintain adequate sun protection
2. Do not pick, scrub or peel off the skin
3. Gentle wash and cleanse
4. Start the maintenance treatment when skin returns to normal

*Proper post-procedural care is mandatory in achieving good results and in preventing complications*
Reticulate and mottled hyperpigmentary disorders

RETICULATE pigmentary disorders cause net-like patterns of cutaneous hyperpigmentation that are seen in both congenital and acquired conditions (see tables 2 and 3). A formal diagnosis of any underlying disorder should be made because it is the most commonly used treatment for this condition and achieve good results.

Riehl’s melanosis (melanodermatitis toxica)
Riehl’s melanosis is caused by frequent and repeated contact with small amounts of sensitising allergens in cosmetics at a concentration that is too low to produce typical eczematous dermatitis. However, the repeated contact over time and repeated sun exposure causes cumulative allergic contact dermatitis that results in basal cell damage and pigment incontinence. Many cases are preceded by mild erythema, oedema and pruritus, followed by a diffuse-to-reticulate pattern of hyperpigmentation.

Photo-patch testing
Patch testing and photo-patch testing will help in making a diagnosis. A photo-patch test is similar to a skin patch test except that the allergens are applied on the skin in duplicate. One set is exposed to a small dose of ultraviolet radiation (UVA) to detect a photosensitivity reaction. Standard patch test series, cosmetic series, fragrance series, and patient’s personal products can be used depending on the suspected allergens.

Other management measures
Complete avoidance of the suspected allergens is necessary, leading to a gradual improvement. Topical creams containing 2-4% hydrocortisone twice daily for 4-8 weeks combined with tretinoin may hasten the resolution of the hyperpigmentation.

Poikiloderma of Civatte
Poikiloderma of Civatte is a reddish-brown, reticulate pigmentation with atrophy of the skin and telangiectasia that occurs on the lateral cheeks and sides of the neck. It is seen more commonly in middle-aged women. Photosensitising chemicals in perfumes or cosmetics together with chronic sun exposure have been implicated in the pathogenesis of poikiloderma of Civatte. Hormonal changes related to menopause or low oestrogen levels may also be a causative factor.

There is no specific medical treatment for poikiloderma of Civatte. Educating the patient about avoiding sun exposure and the proper use of sunscreens is most important.

Berkloque dermatitis
Berkloque dermatitis has drop-like or streak-like hyperpigmentation on the face or forehead that arises from the application of perfumes and subsequently being exposed to the sun. The principal management is discontinuation of the offending substance and/or limiting the use of the perfumes to covered areas. A short course of systemic corticosteroids may help if there is inflammation and discomfort.

Diffuse or systemic causes of hyperpigmentation

DIFFUSE hyperpigmentation may be due to an underlying systemic disease (eg, Addison’s disease, hyperthyroidism, haemochromatosis) or it may be a side effect of medication use.

Addison’s disease
In Addison’s disease, hyperpigmentation occurs over the entire body with accentuation in old scars and in skin creases. The nail beds and the oral mucosa may also become hyperpigmented. The hyperpigmentation is caused by an increased activity of the melanocyte-stimulating hormone and adrenocorticotrophic hormone, both of which are capable of stimulating pigment production. Vitiligo, which is also an autoimmune disorder, can be associated in patients with Addison’s disease as part of a multiglandular deficiency syndrome.

Other systemic conditions
Hyperthyroidism causes a pattern of hyperpigmentation similar to that in Addison’s disease, especially in patients with darker complexion. Haemochromatosis, a disorder of iron storage and deposition, can cause a slate-grey hyperpigmentation owing to the deposition of haemosiderin. In scleroderma, hyperpigmentation is generalised, but there is accentuation of the brown colour on the dorsal surface of the arms and hands. Occasionally, vitiligo-like hypopigmentation will be interspersed within areas of darkened skin. Hyperpigmentation associated with malignancies is most commonly found with carcinoma of the lung. The pigmentation occurs because of the melanocyte-stimulating hormone-like activity of polypeptides produced by such tumours. Generalised melanosis may also be seen with advanced, widespread melanosis, in which case the colour is due to the pigmented compounds produced directly by the malignant cells.

Medication-induced hyperpigmentation

MANY drugs are known to cause diffuse or localised hyperpigmentation. These are summarised in table 6, see next page.

Drug-induced pigmentation
The following features point to a drug-induced pigmentation:
• The increased pigmentation starts gradually after initiation and fades when drug is discontinued.
• The hyperpigmentation shows photo-aggregation.
• Involvement of cartilage, mucosa, nail and scar.

Fixed drug eruptions
Fixed drug eruptions are common and have some unique features. They are typically of acute onset and appear as annular, oedematous, reddish-brown to violaceous macules or plaques. These erythematous patches or plaques gradually fade with residual hyperpigmentation. The centre of the patch may blister or become necrotic (figure 11). Their diagnostic hallmarks include residual hyperpigmentation and recurrence at previously affected sites following re-exposure to the same drug. Local symptoms may include pruritus, burning, and pain. The initial eruption is frequently located on the lip or genitalia.

The common medications that may cause fixed drug eruptions are analgesics, muscle relaxants, sedatives, anticonvulsants and antibiotics. Patients should be counselled on medication avoidance and possible cross-reactions to similar medications.
Table 6: Medications that cause hyperpigmentation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description of hyperpigmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimalarials (eg, chloroquine, hydroxychloroquine, amodiaquine and quinacrine)</td>
<td>Blush-grey or purple pigmentation in the prefrontal areas</td>
</tr>
<tr>
<td>Chemotherapy agents (eg, bleomycin, 5-fluorouracil, adriamycin, hydroxyurea)</td>
<td>Bleomycin causes a pigmented banding of the patient’s nails, generalised hypermelanosis to focal pigmentation of pressure points, linear or flogelated bands 5-Fluorouracil causes photosensitivity reaction in sun-exposed skin, followed by hyperpigmentation, hypermelanosis in the skin near infusion or portal irradiation sites Adriamycin causes pigmented patches in the oral mucosa and lateral aspect of the tongue Hydroxyurea causes nail bed and/or kurla hyperpigmentation and tongue pigmentation</td>
</tr>
<tr>
<td>Heavy metals (eg, silver, gold, iron)</td>
<td>Silver causes a generalised slate-grey pigmentation (argyria) that is most accentuated in sun-exposed areas and often involves a patient’s nails, sclera and mucous membranes Gold causes a blue-grey hyperpigmentation of sun-exposed skin, known as chrysis Iron causes a permanent blue-grey discolouration</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Tetracyclines cause a brown discoloration of the teeth in children Minocycline causes blue-black discoloration localised to scars, blue-grey pigmentation on the extremities, and a generalised ‘muddy’ brown hyperpigmentation in sun-exposed skin</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Blue- or violaceous pigmentation of sun-exposed skin and yellow-brown slipping of the cornea</td>
</tr>
<tr>
<td>Antiretrovirals — zidovudine</td>
<td>Reversible dyspigmentation of the nails, brown mucocutaneous hyperpigmentation</td>
</tr>
<tr>
<td>Clorafine</td>
<td>Violet-blue or bluish cutaneous pigmentation most apparent in lesional skin (figure 12)</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>Slate or blue-grey pigmentation in sun-exposed areas of the skin</td>
</tr>
</tbody>
</table>

**Conclusion**

**PIGMENTATION disorders are usually considered to be cosmetic in nature. However, it is important to recognise that they can cause psychological distress to the patient. It is also important to remember that some hyperpigmentation disorders may be associated with an underlying systemic disease or be caused by a medication. A thorough history and clinical examination is required, and investigations or specialist referrals should be made where appropriate.**

**Further reading**


**How to Treat Quiz**


1. Which TWO statements are correct regarding the pathophysiology of pigmentedary disorders?
   a) Melanin, carotenoids and haemoglobin all contribute to human skin colour
   b) Disorders affecting the enzyme tyrosinase may disrupt the production of melanin
   c) Melanocyte numbers are never affected in acquired conditions of pigment loss
   d) Darker skin colour is due to increasing numbers of melanocytes

2. Which THREE statements are correct regarding clinical features associated with pigmentedary disorder under Wood’s lamp examination?
   a) Phytosor may show a yellowish-white or copper-orange fluorescence
   b) Vitiligo has increased sharpness of borders
   c) Melasma has accentuated outer epidermal layer pigmentation
   d) Tuberculosis has ovoid yellow patches

3. Which THREE statements are correct regarding the general management principles of pigmentedary disorders?
   a) Formal counselling from a mental health professional is important
   b) Management of patient expectations is important
   c) Tanning is a good strategy to improve depigmented skin
   d) Sunscreen should be advised for both hypopigmentary and hypopigmentary disorders

4. Which TWO statements are correct regarding the clinical features of circumscribed hyperpigmentary disorders?
   a) Melanocytic naevi, acanthosis nigricans
   b) Retinoid hyperpigmentation
   c) Leukoderma (which has no underlying cause)
   d) Neurofibromatosis type 1

5. Which TWO statements are correct regarding the management of circumscribed hyperpigmentary disorders?
   a) Both epidermal and dermal melanoma have a good, curative response to treatment
   b) 60% of café au lait macules may clear with pigment laser
   c) Maintenance therapy is not required after a successful chemical peel for melanoma
   d) The primary aim of treatment of acanthosis nigricans is to correct the underlying disease

6. Which TWO statements are correct regarding the clinical features and management of reticulate and mottled hyperpigmentation disorders?
   a) Confluent and reticulate papilomatosis usually forms between the breasts and on the back of young women
   b) Erythema ab igne is usually caused by prolonged cold exposure
   c) Squamous cell carcinoma may develop as a long-term consequence of erythema ab igne
   d) Prurigo pigmentosa may be effectively treated with antihistamines and steroids

7. Which TWO statements are correct regarding the clinical features of facial hyperpigmentation?
   a) Porphyria cutanea tarda
   b) Drug-induced pigmentation usually occurs in areas not exposed to the sun
   c) Ophthalmology referral is essential for patients with Hori’s naevus
   d) The principal treatment for Berloque dermatis is discontinuation of the offending substance

8. Which TWO statements are correct regarding the management of facial hyperpigmentation?
   a) Photo-patch testing helps the management of Riehl’s melanosis by identifying the causative agent to avoid
   b) The principal treatment for Berloque dermatis is discontinuation of the offending substance
   c) Periorbital hypopigmentation is readily treated with a chemical peel
   d) Ophthalmology referral is essential for patients with Hori’s naevus

9. Which TWO statements are correct regarding the clinical features of medication-induced hyperpigmentation?
   a) Drug-induced pigmentation usually fade when the drug is discontinued
   b) Drug-induced pigmentation usually occurs in areas not exposed to the sun
   c) Fixed drug eruptions are usually gradual in onset
   d) Common medications that may cause fixed drug eruptions include analgesics and antibiotics

10. Which THREE medical conditions may cause diffuse or systemic hyperpigmentation?
    a) Lepromatous leprosy
    b) Addison’s disease
    c) Raynaud’s disease
    d) Hyperthyroidism

**Instructions**

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.

We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.


**NEXT WEEK** We conclude this series on disorders of pigmentation with a close examination of hypopigmentary disorders.