CHAPTER

# 18
# Disorders of Skin Pigmentation

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## Chapter Outline



Melanin is formed from the essential amino acids tyrosine and phenylalanine[Q] through a series of enzymatic steps in the liver and skin. Tyrosine is formed in the liver by the hydroxylation of the essential amino acid phenylalanine under the influence of phenylalanine hydroxylase which is in turn converted to DOPA and further into the pigment under the influence of tyrosinase enzyme (Fig. 18.1).

The melanin is made within the melanosomes (Fig. 18.2), which are of a size of 0.1 × 0.7 µm and are of two types—eumelanosomes (containing eumelanin), or pheomelanosomes (containing pheomelanin). These melanosomes pass into the dendritic processes of the melanocyte to be further transferred into neighboring keratinocytes (Fig. 18.2). The melanosomes are then engulfed into lysosomal packages (melanosome complexes) and distributed throughout the cytoplasm. The ratio of melanocytes to keratinocytes is about **1:36**, that is one melanocyte supplies melanin to about 36 keratinocytes.[Q]

**Clinical Pearl**

What determines a person's skin color is the activity of melanocytes and their interactions with their keratinocyte neighbors.[Q] Darker skin individuals have melanocytes that produce more and larger melanosomes. Also these melanosomes are efficiently transferred to keratinocytes and more slowly degraded in the melanosome complexes.[Q]

### Control of Melanogenesis

Melanogenesis can be increased by several stimuli, the most important of which is UVR. Tanning represents a protective mechanism of our skin against future UV damage and is of two types and involves two distinct reactions.

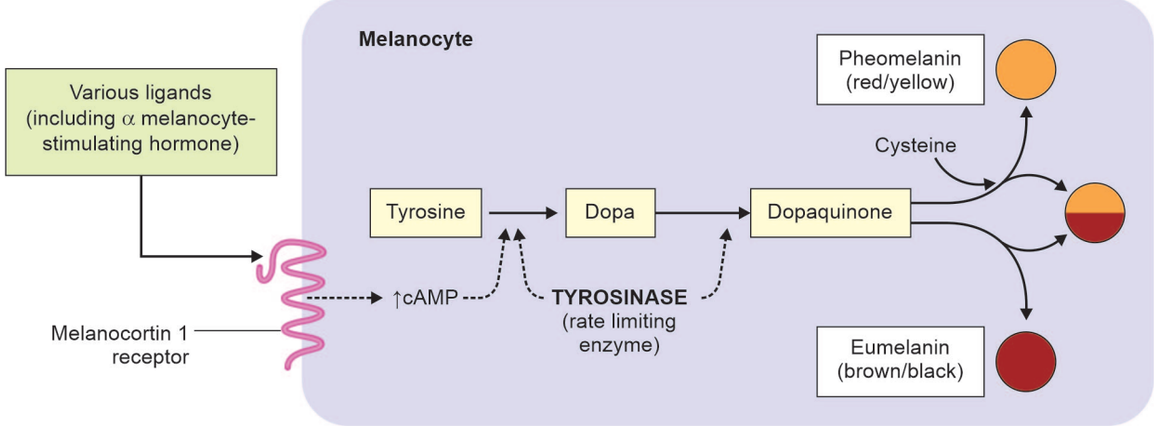



**Fig. 18.1:** Pathway of melanogenesis

for advanced learning

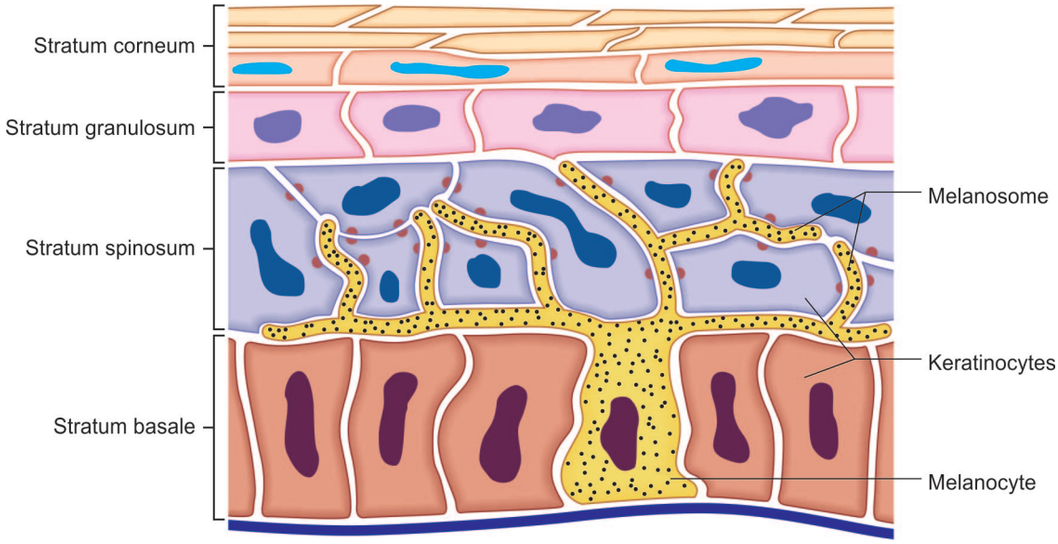



**Fig. 18.2:** Melanocyte and its interaction with keratinocytes. The melanosomes are transferred from the melanocyte to the keratinocyte

1. *Immediate pigment darkening* (*IPD*), also called the Meirowsky phenomenon, follows exposure to long wave ultraviolet (UVA 320–400 nm).Q This pigment darkening occurs over minutes to days, dependent on the UV dose and constitutive skin color, and is responsible for the well-known phenomenon of a 'false tan'. It is not caused by melanin synthesis but oxidation of preformed melanin and redistribution of melanin from perinuclear melanosomes to peripheral dendrites.
2. *Delayed tanning* (*DT*), the production of new pigment occurs some 3–4 days after exposure to medium-wave ultraviolet (UVB: 290–320 nm)Q and UVA and is maximal at 7 days.

- UVR results in DNA damage, which leads to the activation of p53.
- This in turn induces both keratinocytes and melanocytes in the skin to secrete pro-opiomelanocortin.
- Alpha melanocyte-stimulating hormone (α-MSH), a cleavage product of pro-opiomelanocortin, then binds the melanocortin 1 receptor on melanocytes and signals for the upregulation of microphthalmia transcription factor (MITF).
- MITF has a central role in melanogenesis by inducing the proliferation of melanocytes, increasing tyrosinase activity and melanosome production, and increasing the transfer of new melanosomes to their surrounding keratinocytes.

Estrogens and progestogens (and possibly testosterone too) may, in some circumstances, stimulate melanogenesis, either directly (by acting on estrogen and progestogen receptors in the melanocyte) or by increasing the release of MSH peptides from the pituitary.

### Classification

A simple method of classification is based on the onset of the disorder (congenital and acquired), the type of pigmentation and the etiology of the same, which depends on either melanin or melanocyte variations.

- *Hyperpigmentation*:
  - Excess melanin or other pigments (iron, silver, tattoos). If other pigments, then endogenous vs. exogenous.
  - Increased melanin production and transfer (café au lait macule) *vs*. increased number of melanocytes (lentigines, melanocytic nevi, malignant melanoma).
- *Hypopigmentation*: Loss of melanin (albinism) *vs*. loss of melanocytes (vitiligo).

## HYPOPIGMENTATION DISORDERS

There are various causes of a pigmentary loss in the skin depending on various steps of melanogenesis. A simple overview is given in Fig. 18.3 which is based on disorders that damage the melanocytes and those that affect tyrosinase.

A more elaborate classification is based on the distribution of the disorders (Fig. 18.4 and Table 18.1).

### Albinism

This is a family of disorders with disturbances in either melanin production or formation and transfer of melanosomes and typically affect skin and eyes.

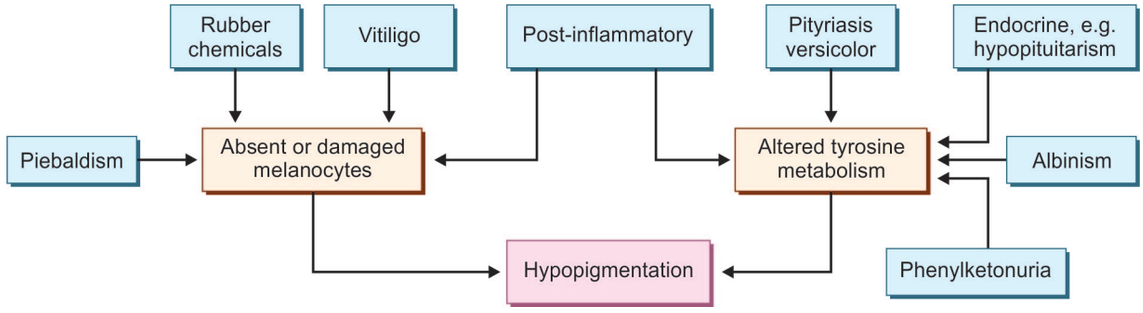



**Fig. 18.3:** Overview of hypopigmentation disorders based on the main pathogenetic steps

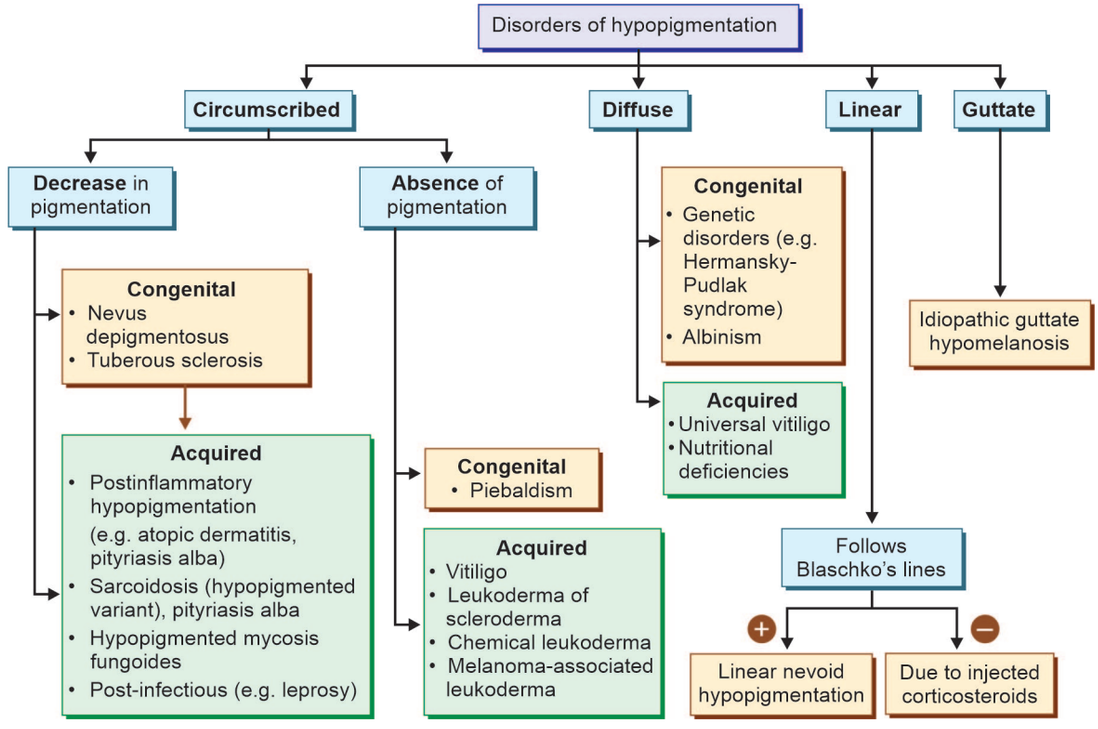



**Fig. 18.4:** Approach to diagnosis of hypopigmented disorders based on distribution

**TABLE 18.1** Disorders of hypopigmentation

| | | |
|---|---|---|
| Generalized involvement (whole body) | Congenital | Albinism, Chédiak-Higashi syndrome, Hermansky-Pudlak syndrome, phenylketonuria |
| | Acquired | Panhypopituitarism |
| Localized involvement | Congenital | Piebaldism Waardenburg syndrome, hypomelanosis of Ito, nevus depigmentosus, tuberous sclerosis |
| | Acquired | Vitiligo, postinflammatory hypopigmentation, pityriasis alba, idiopathic-guttate-hypomelanosis, chemical leukoderma |

In oculocutaneous albinism (OCA, autosomal recessive), melanin is missing in the skin, hair, and eyes. In ocular albinism, the defects are primarily in the eye.

### Tyrosinase-negative albinism

*Pathogenesis*: Mutation in tyrosinase gene; melanosomes contain no melanin.Q

*Clinical features*: Most severe form of albinism:Q

- Skin: White hair, white to pale pink skin, no pigmented nevi, risk for UV-induced tumors (actinic keratoses, squamous cell carcinomas).
- Eyes: Gray translucent iris, red reflex, photophobia, nystagmus, loss of vision.

*Diagnostic approach*: Hair bulb negative for tyrosine, ophthalmologic examination.

### Tyrosinase-positive albinism

*Pathogenesis*: Most common form of albinism;[Q] tyrosinase is present; melanin is formed and melanosomes start to form but rarely mature completely.

*Clinical features*:

- Skin: White skin and hair at birth; later slight pigmentation, often yellow-red hair; may have a few freckles.
- Eyes: Some pigment presence; defects less severe than above.

*Diagnostic approach*: Hair bulb positive for tyrosinase, ophthalmologic examination.

There are other types of albinism and are uncommon and can have associated systemic and immunological defects. These include:

- *Hermansky-Pudlak syndrome*: Tyrosinase-positive albinism plus platelet defects.
- *Chédiak-Higashi syndrome and Griscelli syndrome*: Pigmentary dilution[Q] with a gray sheen, macrophage defects with severe infections.

#### *Treatment*

Avoidance of sun exposure, and protection with opaque clothing, wide-brimmed hats and sunscreen creams, are essential and allow albinos in temperate climates to live a relatively normal life. Early diagnosis and treatment of skin tumors is critical.

### Piebaldism

Uncommon genodermatosis with circumscribed hypomelanosis; autosomal dominant[Q] inheritance.

Mutation in KIT gene on chromosome 4q12 that causes altered migration of melanocytes from the neural crest to the skin during embryogenesis.

#### *Clinical Features*

These patients often have a white forelock of hair[Q] and patches of depigmentation lying symmetrically on the limbs, trunk and central part of the face, especially the chin[Q] (Fig. 18.5). Typically, patients have pigmented islands within white patches.[Q]

**Associated syndromes:** *Waardenburg syndrome*:[Q] Piebaldism (with a white forelock in 20% of cases), dystopia canthorum (lateral displacement of the inner canthus of each eye), a prominent inner third of the eyebrows, irides of different[Q] color and deafness.

### Nevus Depigmentosus

Localized area of hypo- to depigmentation, usually following Blaschko lines, caused by aberrant transfer of melanosomes.

#### *Clinical Features*

Sharply demarcated permanent area of hypopigmentation present at birth, which grows with child; usually respects the midline[Q] (Fig. 18.6).

#### *Differential Diagnosis*

Nevus anemicus is a pharmacologic nevus,[Q] which is pale because of vasoconstriction. Thus nevus depigmentosus becomes red with rubbing; nevus anemicus does not. Diascopy can also be used to differentiate between the two.

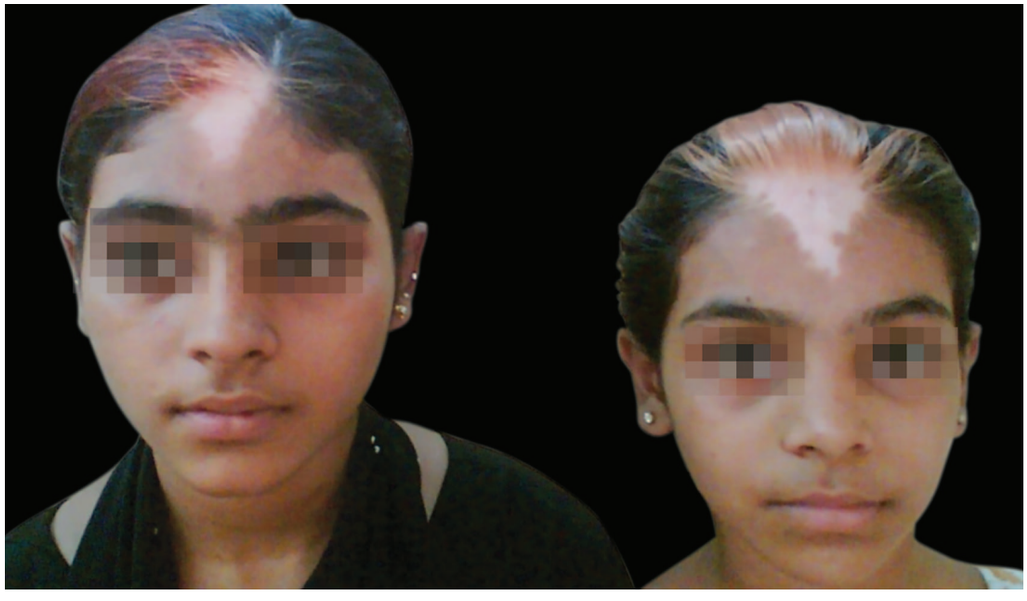


**Fig. 18.5:** White forelock with a characteristic, triangular amelanotic patch on the mid-forehead in a case of piebaldism

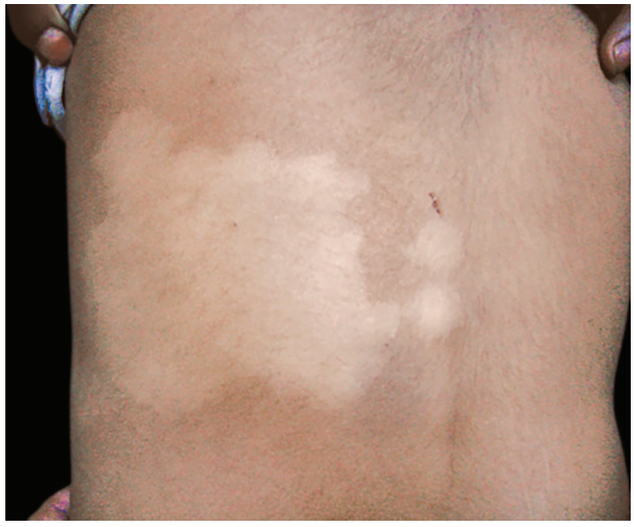


**Fig. 18.6A:** Nevus depigmentosus. Hypomelanotic patch with a decrease but not absence of pigmentation. The segmental nature can be confused with hypomelanosis of Ito

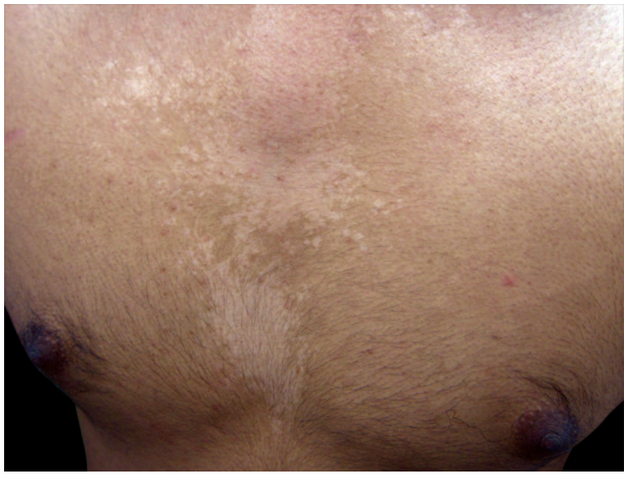


**Fig. 18.6B:** Another case of nevus depigmentosus

*Therapy*

Camouflage with cosmetics as for vitiligo.

### Hypomelanosis of Ito

This is not a single disease, but is best described as a manifestation of genomic mosaicism, and thus associated with wide variety of underlying defects, including mental retardation and severe neurological defects.

*Clinical Features*

Widespread areas of hypopigmentation following Blaschko lines (Fig. 18.7); individual lesions identical to nevus depigmentosus.

*Diagnostic Approach*

History, extensive physical examination, cytogenetic testing.

### Vitiligo DR2.1

Acquired localized depigmentation of skin, hair, and occasionally mucosa, of unknown etiology, characterized by complete loss of melanocytes.Q

*Pathogenesis*

Etiology not well understood. Theories include (Fig. 18.8A):

- Genetic predisposition
- Autoimmune destruction of melanocytes.
- Neural pathways,Q because of relation to stress and segmental type.
- Metabolic abnormalities: Accumulation of toxic metabolites and oxidants that damage melanocytes.
- Self-destruction of melanocytes (autocyto-destructive) theory because of aberrant tetrahydrobiopterin and

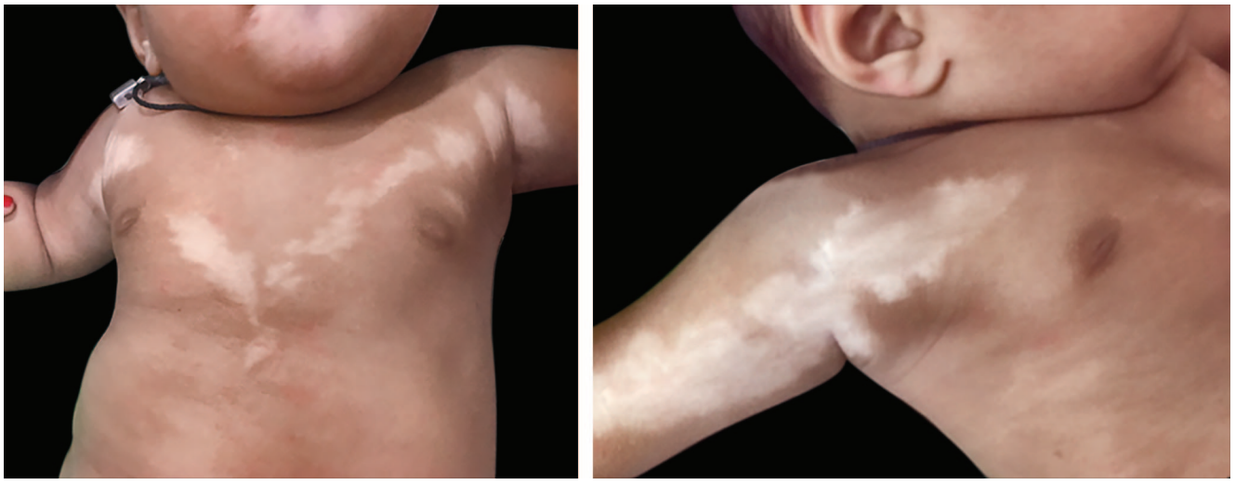


**Fig. 18.7:** Hypomelanosis of Ito: 'S'-shaped whorled pattern of hypopigmented macules along lines of Blaschko in an infant

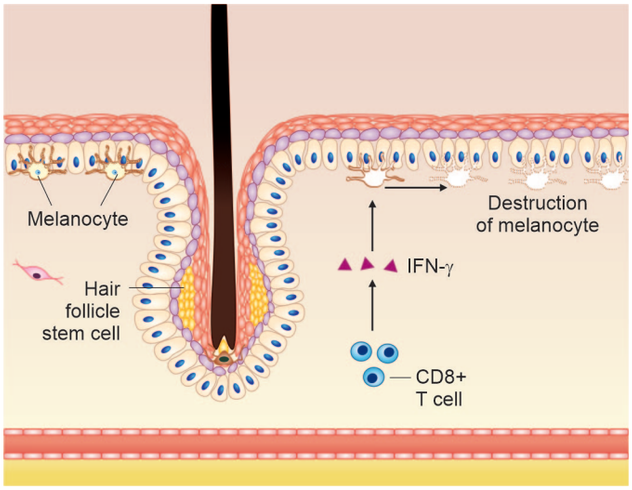



**Fig. 18.8A:** Vitiligo: Epidermis—complete *absence* of pigment and melanocytes. Dermis—normal. The left panel is the normal state and autoimmune damage leads to destruction of melanocytes

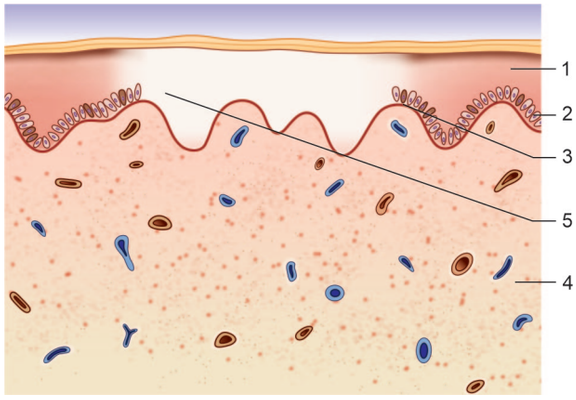



**Fig. 18.8B:** Vitiligo: (1) Epidermis shows (2) basal cells with (3) melanocytes, while the (4) dermis is normal. In (5) vitiligo, there is complete absence of melanocytes (centre of image)

catecholamine synthesis. Absence of melanocytes explain the histology of vitiligo (Fig. 18.8B).

## *Clinical Features*

The most common presentation of vitiligo is totally amelanotic (i.e. milk- or chalk-white)[Q] macules or patches surrounded by normal skin. The borders are usually 'scalloping' convex, as if the depigmenting process were 'invading' the surrounding normally pigmented skin.

**Trichrome vitiligo**[Q] features a hypopigmented zone between normal and totally depigmented skin (Fig. 18.9A). The intermediate zone does not have a gradation of color from white to normal, but rather a fairly uniform hue. The number of melanocytes is also intermediate in this zone, suggesting slower centrifugal progression than in typical vitiligo.

In **quadrichrome vitiligo**[Q], a fourth darker color is present at sites of perifollicular repigmentation (Fig. 18.9B).

**Pentachrome vitiligo**[Q] with five shades of color black, dark brown, medium brown (unaffected skin), tan and white has also been described.

One of the manifestations of vitiligo is the isomorphic Koebner phenomenon, characterized by the development of vitiligo at the sites of trauma (e.g. a laceration, burn or abrasion).[Q]

## *Classification*

Degree of involvement highly variable, ranging from a few macules to almost complete depigmentation (Fig. 18.10) and some representative images are depicted in Fig. 18.11:

1. **Localized:**
   - *Focal*: One or more patches in the same area.
   - *Segmental*: Limited to a dermatome or Blaschko lines.
   - *Mucosal*: Only affected mucous membranes (rare).

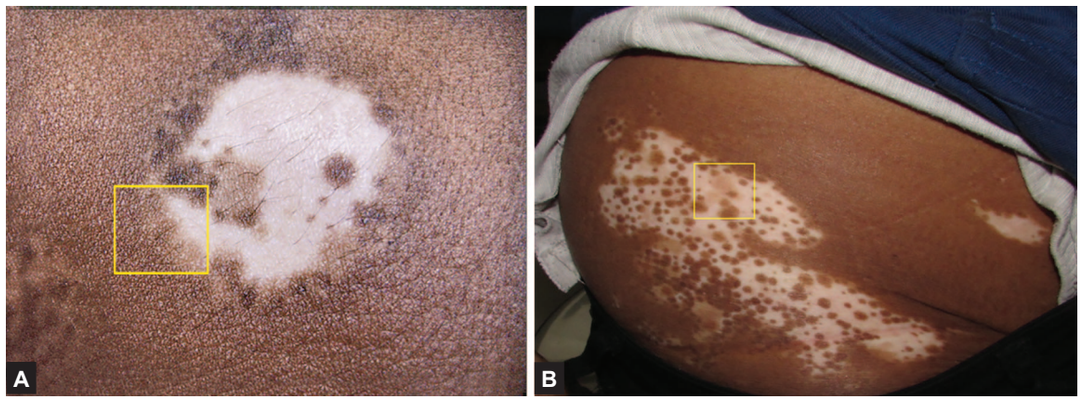



**Fig. 18.9A and B:** Trichrome vitiligo see box (A) with 3 zones of color—normal skin, transitory zone and complete loss of color. Note the presence of pigmented hair which is a good prognostic sign; (B) Treatment leads to a fourth color known as quadrichrome vitiligo. where apart from the three zones at the periphery (trichrome), there is also perifollicular pigmentation

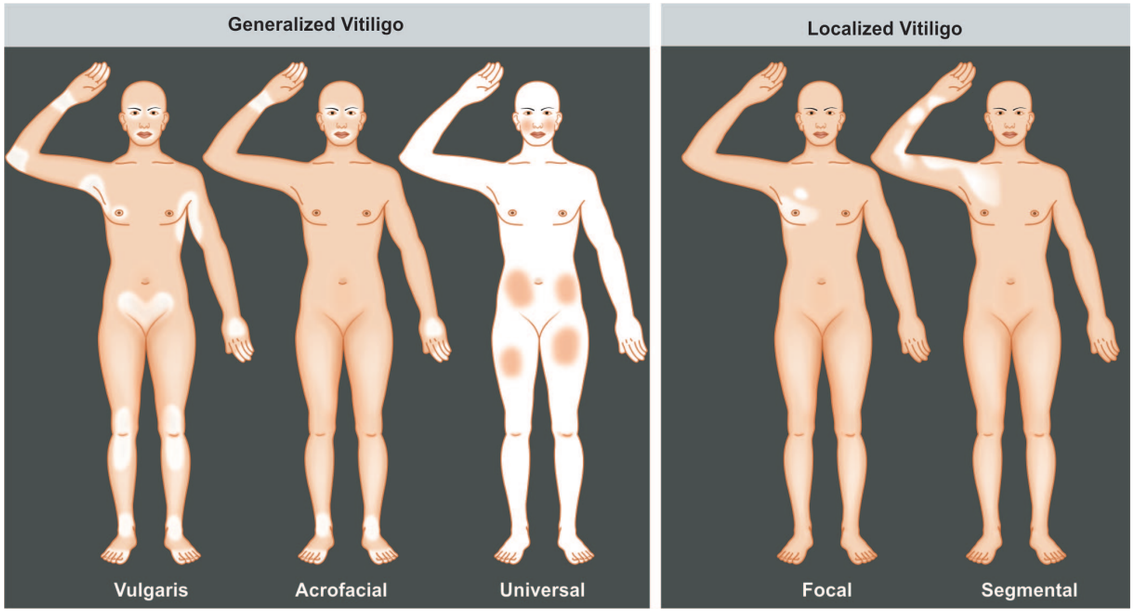



**Fig. 18.10:** Classification of vitiligo

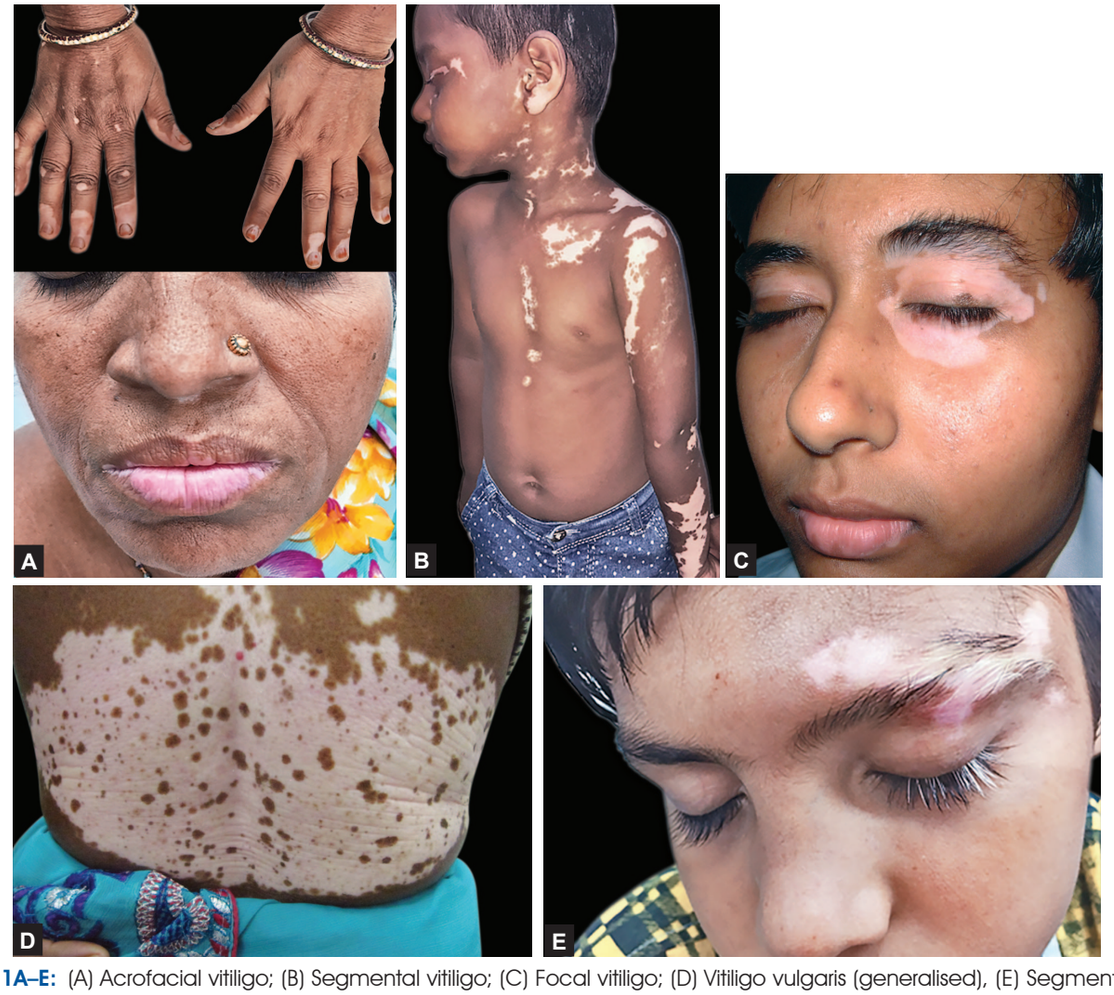



**Fig. 18.11A–E:** (A) Acrofacial vitiligo; (B) Segmental vitiligo; (C) Focal vitiligo; (D) Vitiligo vulgaris (generalised), (E) Segmental vitiligo with leukotrichia

2. **Generalized:**
   - *Acrofacial*: Distal extremities and facial, especially periorificial.
   - *Vulgaris* (*means common*): Disseminated lesions without region predilection.
   - *Universal*: Complete or almost complete depigmentation.

### Prognosis

Course highly variable and unpredictable. Spontaneous repigmentation that is cosmetically satisfactory for the patient occurs only rarely. Speckled repigmentation in a patch indicates that melanocytes from the outer root sheath of the hair follicle are producing melanin. Important to establish, if the vitiligo is stable or progressive, as this influences choice of therapy.

**Laboratory evaluation:** Thyroid function tests including autoantibodies, anti-parietal cell antibodies, total IgE, ANA, and blood sugar.

### Treatment DR2.2

The cosmetic disfigurement from vitiligo can be devastating to affected patients specially in India. Treatment is often unsatisfactory for those with extensive and long-standing disease. In the white patches, pigment cells are only present deep in the hair follicles and treatments mostly try to get melanocytes to divide and migrate into affected skin. The established therapy of vitiligo can be described as varially effective, an overview is given in Table 18.2.

The *aims* of vitiligo *treatment* are repigmentation and stabilization of the depigmentation process. The choice of therapy depends on the extent, location, and activity of disease as well as the patient's age, skin type and motivation to undergo treatment. In general, a period of at least 2–3 months is required to determine whether a particular treatment is effective. The areas of the body that typically have the best response to medical therapy are the face, neck, mid-extremities and trunk, while the distal extremities and lips are the most resistant to treatment.

#### Medical therapy

1. *Corticosteroids*: It is administered in vitiligo when it affects <20% of the body surface area and can achieve >75% repigmentation with either class 1 (superpotent) or class 2–3 (high-potency) topical corticosteroids.

   Oral steroids has been used in a pulse form, but should be used *only* for cases with documented *instability* of disease. Though a common practice is to give betamethasone (1 mg) twice a week, a safer alternative is to administer a short-acting steroid to avoid side effects. An option that we follow is to administer deflazaort or (0.25–1 mg/kg) in an alternate day dosage.
2. *Topical drugs* like tacrolimus 0.1%, topical calcipotriol are useful, if given as an alternative to topical steroids to avoid side effects. Good results are obtained when these agents are used for facial lesions and/or combined with sun exposure.
3. *Topical PUVA* is an option but unless supervised tend to cause side effects. Topical 8 methoxyposralen can be administered but requires careful sunlight exposure after 20 minutes beginning with 1 minute alternate day, gradually increasing to 5 minutes over months.
4. *Oral PUVA*: This form of therapy was first used by the Egyptians and ancient Indians. In India, PUVA-Sol is still the most cost-effective option for treating vitiligo, which uses sunlight as the source of UV light.

Psoralen photochemotherapy involves the use of psoralens combined with UVA. The psoralen most commonly utilized is 8-methoxypsoralen (8-MOP, methoxsalen), though if sunlight is the source (PUVAsol) 4,5′, 8-trimethylpsoralen (TMP, trioxsalen) should be administered.

Oral PUVA treatments using 8-MOP (0.4–0.6 mg/kg) are typically administered two times weekly. For patients with vitiligo, the initial dose of UVA is usually

TABLE 18.2 Treatment of vitiligo

| *Age* | *Type* | *Ist choice* | *2nd choice* |
|---|---|---|---|
| <5 years | Focal (<5%) | Topical steroids | UVB (311 nm), topical PUVA |
| | Segmental | Topical steroids +UVA | |
| | Widespread (>5%) | Topical steroids + NbUVB | |
| >5 years | Focal (<5%) | Topical corticosteroids (+UVA) | UVB (311 nm), topical |
| | Segmental | Minigrafts | PUVA, oral PUVA (>12 years), minigrafts (if stable) |
| | Widespread (>5%) | UVB (311 nm) | |
| Adults | Eyelids, lips, nipples, penis | Minigrafts | Oral PUVA (>12 years), topical corticosteroids (+UVA) |
| | Resistant, involving >80% | Total depigmentation | |

0.5–1.0 J/cm$^2$, which is gradually increased until minimal asymptomatic erythema of the involved skin occurs. A cheaper protocol, if sunlight is used, is to give TMP (Neosoralen Forte) 0.6 mg/kg/d and after 2 hours expose to sunlight (11 AM–3 PM) for 5–10 minutes on alternate days.

The response rate of PUVA is variable; although the majority of patients obtain cosmetically acceptable improvement, complete repigmentation is achieved in only a few patients. The total number of PUVA treatments required is generally between 50 and 300.

**Phototherapy:** NB-UVB (311 nm)Q has become the gold standard of therapy for vitiligo. The mean repigmentation achieved is 41–68% with 3 to 6 months of therapy. It has consistently been shown to be effective, although is not curative.

**Surgical modalities:** Where pigment is absent in hair follicles or in skin without hair follicles, autologous skin grafts can be performed. The two most common procedures transplant either minigraft implants of 1 mm cylinders or epidermal roofs of suction-raised blisters from unaffected skin. Melanocyte and stem cell transplants, in which single cell suspensions are made from unaffected skin and applied to dermabraded vitiliginous skin, are also useful but are still being investigated.

### Postinflammatory Hypopigmentation

This is a common consequence to eczema, pityriasis versicolor, psoriasis, sarcoidosis and lupus erythematosus (Fig. 18.12). It may also result from cryotherapy or a burn. In general, more severe the inflammation, more likely pigment is to decrease rather than increase. These problems are most significant in darker-skinned individuals.

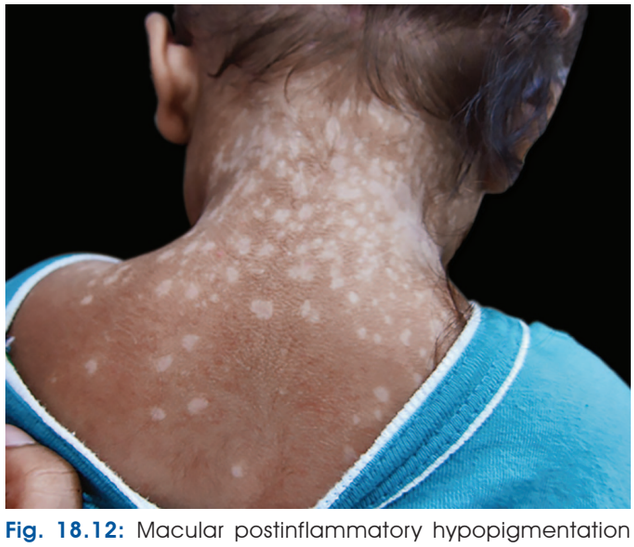


**Fig. 18.12:** Macular postinflammatory hypopigmentation consequent to pityriasis versicolor

### Pityriasis Alba

This disease mainly affects children between the age of 3 and 16 years and is clinically obvious in dark-skinned individuals.

#### *Pathogenesis*

The exact cause is unknown, though it is formally recognized as a postinflammatory hypomelanosis.

The following factors have been incriminated:

- Excessive and unprotected sun exposure.
- Frequent bathing with hot water, frequent washing of face with soap-based cleansers.
- Cutaneous signs of atopy which are associated with pityriasis alba.

#### *Clinical Features*

Pityriasis alba is characterized by multiple ill-defined hypopigmented macules and patches surmounted by fine,Q 'bran-like' (pityron, Greek for bran) scalesQ (Fig. 18.13) and may persist for months or years before resolving spontaneously. The early lesion is a mildly erythematous, slightly scaling patch with an indistinct elevated margin. In children, the face is the most common area of involvement, although it can occur at any location and may have one to several lesions. The lesion/patch appears to get worse and flakier in winters, when the skin is dry. However, it is more noticeable in the summer when the pale skin stands out against a tan.

#### *Differential Diagnosis*

Diagnosis is based on the clinical examination. In children, face is involved in one-third of cases of tinea versicolor. Thus, in doubtful cases, KOH skin scrapping can be performed. The white spots in vitiligo are

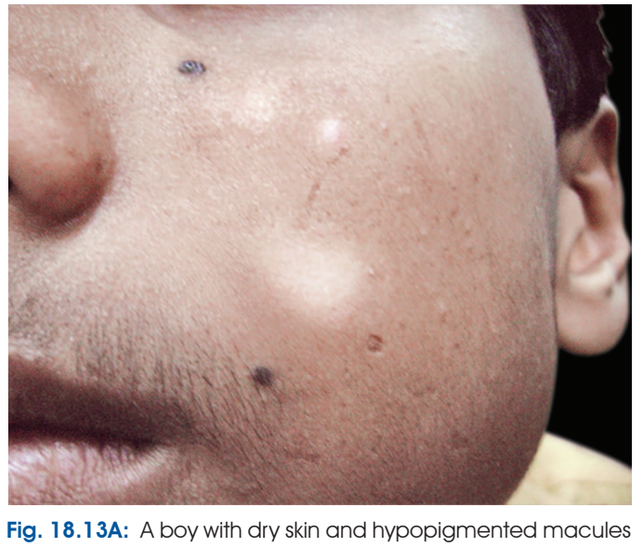


**Fig. 18.13A:** A boy with dry skin and hypopigmented macules (pityriasis alba)

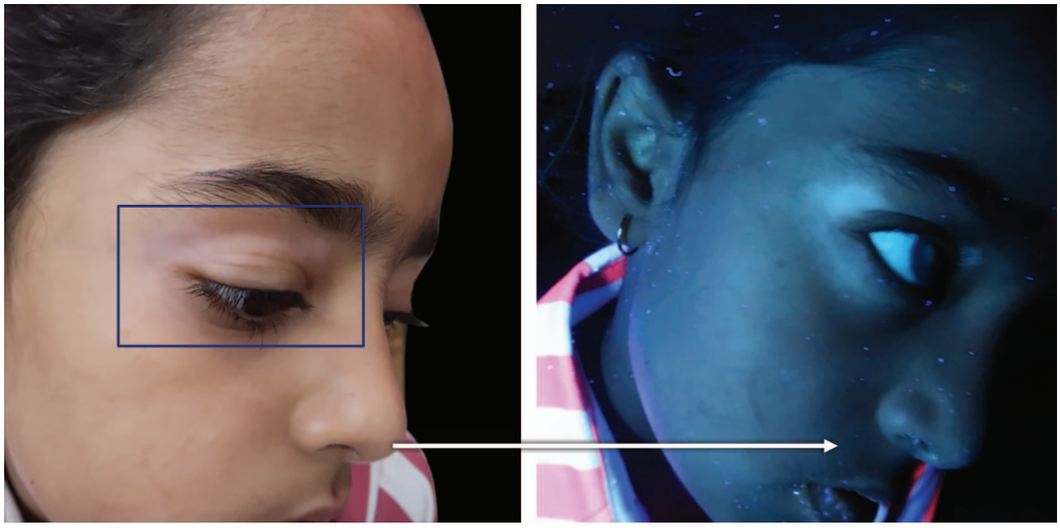


**Fig. 18.13B:** Wood's lamp can be used to differentiate the lesions in doubtful cases of vitiligo where clinical examination does not clearly define the lesion. A chalky white color is seen in vitiligo

distinguished by sharp demarcation, complete depigmentation and lack of scales. Occasionally a Wood's lamp examination can diagnose vitiligo from P alba (Fig. 18.13B).

### *Treatment*

Treatment is not often necessary as spontaneous resolution occurs. Emollients can be used for the dry scaling, and 1% hydrocortisone cream is used for the inflammatory reaction.

## Chemical Depigmentation

It usually occurs as an occupational leukoderma[Q] in workers exposed to phenols.

P-tertiary-butylphenol[Q] is the most important agent, especially in 'Bindi-induced' depigmentation. Other phenols that can cause this condition are monobenzyl-ether of hydroquinone (used in treatment of hyper-pigmentation) and 4-tertiary butyl catechol. These cause a lethal effect on melanocytes.

The dorsa of hands and feet (Fig. 18.14A and B) are commonly affected though it can occur on sites that are not exposed to the chemical.

## Idiopathic Guttate Hypomelanosis

Idiopathic guttate hypomelanosis (IGH—white spots on the arms and legs) is characterized by 2 to 5 mm **porcelain white spots** with sharply demarcated borders. They are located on the exposed areas of hands, forearms, and lower legs of middle-aged and older people (Fig. 18.15). The pathogenesis of IGH is not clearly known.

It could be a part of the normal ageing process. Chronic exposure to UV radiation can be another factor as lesions occur on sun-exposed sites.


**Fig. 18.14A and B:** (A) Chemical leukoderma due to rubber chappals; (B) A patient with hydroquinone-induced depigmentation, the HCl-based cream was used for melasma

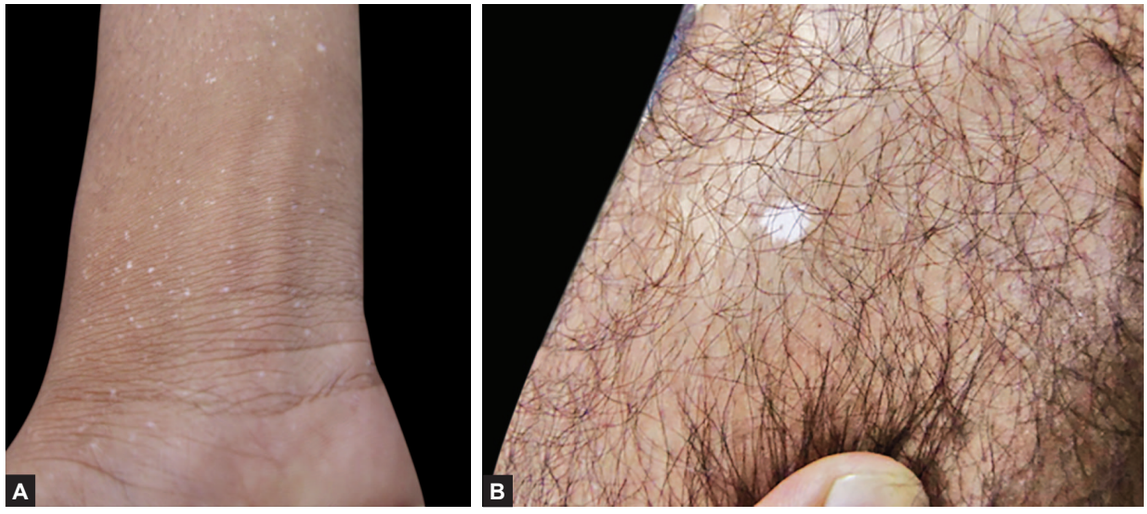



**Fig. 18.15A and B:** Idiopathic guttate hypomelanosis—sharply demarcated depigmented macules

## DISORDERS OF HYPERPIGMENTATION

These disorders can be classified clinically according to the distribution of the lesions and the onset of lesions (Fig. 18.16). A simpler method is to classify them on the basis of the color, where a brown color denotes epidermal disorders and bluish color is imparted by dermal disorders (Table 18.3).

### Brown Hyperpigmentation

#### *Café au lait Macule* (CALM)

Circumscribed tan macule, usually present at birth (Figs 18.17 and 18.18).

**Clinical features:** Irregular tan macules and patches of variable. More than five café au lait[Q] macules >1.5 cm

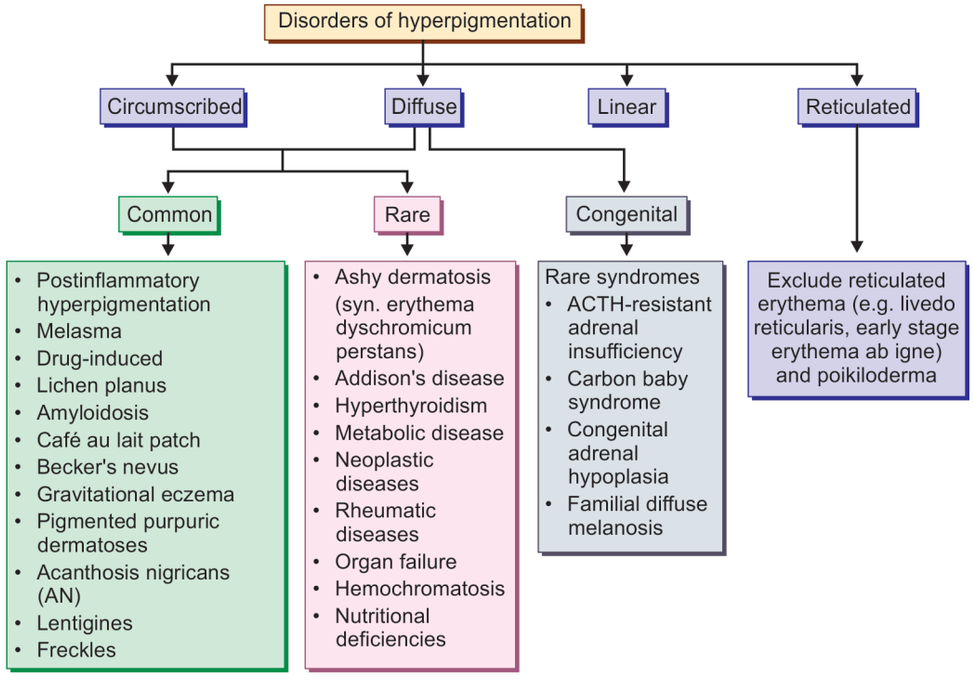



**Fig. 18.16:** Overview of hyperpigmentation disorders based on the distribution and onset of disease

TABLE 18.3 Classification based on predominant color

| | | |
|---|---|---|
| **Brown hyperpigmentation** | Diffuse | **Metabolic:** Hemochromatosis, Wilson disease,Q porphyria, hepatic failure, renal failure, Addison disease, tumors producing MSH or ACTH, ACTH therapy.<br>**Drugs or chemicals:** Antimalarials, arsenic, chlorpromazine, estrogens, minocycline,Q phenytoin, phenothiazine, psoralens (with UV); chemotherapy agents (busulfan, 5-fluorouracil, cyclophosphamide).<br>**Disease-related:** Systemic sclerosis, Whipple disease, mycosis fungoides, Sézary syndrome |
| | Localized | • Tumors and nevi: Freckle, lentigo, syndromes with lentigines, café au lait macule, seborrheic keratosis, melanocytic nevus, Becker nevus<br>• Melasma<br>• Phototoxic dermatitis: Berloque dermatitisQ<br>• Medications: Bleomycin (flagellate streaksQ), 5-fluorouracil (over veins)<br>• Burns, ionizing radiation, trauma<br>• Postinflammatory hyperpigmentation following dermatoses or trauma |
| **Gray or blue hyperpigmentation** | Diffuse | Hemochromatosis, metastatic melanoma with circulating melanin, bismuth, silver, gold, systemic ochronosis |
| | Localized | Nevus of Ota,Q nevus of Ito,Q Mongolian spot,Q blue nevus, incontinentia pigmenti, macular amyloidosis, fixed drug reaction, erythema dyschromicum perstans, exogenous ochronosis |

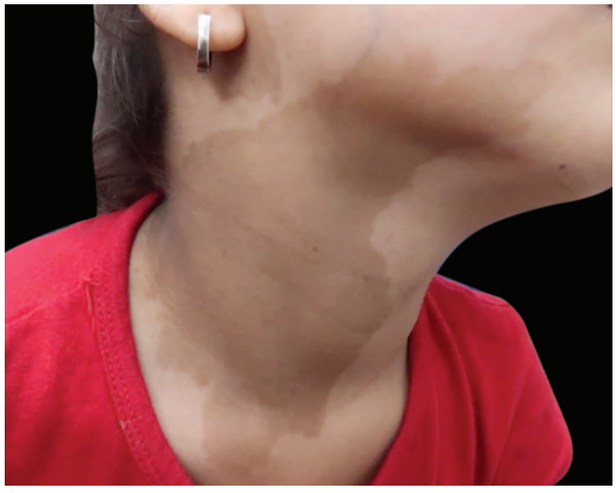


**Fig. 18.17:** CALM on the face and neck

**Fig. 18.18:** A single CALM on the face in a patient

are suggestive of neurofibromatosis 1, but the macules can be sporadic or associated with a variety of syndromes.

**Histology:** Increased pigment in basal layer, normal number of melanocytes, giant melanosomes.

### *Freckles*

Localized hyperpigmentation caused by sun exposure; waxes and wanes with seasons.

**Clinical features:** Much more common in skin types I and II; especially among redheads. Usually appear in childhood, flaring each summer; irregular brown macules of varying shades of tan and brown.

**Histology:** Increased melanin,Q normal melanocytes (Fig. 18.19A to C).

**Differential diagnosis:**

- Lentigo and junctional nevus can look like a freckle.
- *Actinic lentigo*: This does not darken with sun exposure and is acquired later in life. In contrast, freckles darken after sun exposure and are present from early childhood.
- *Lentigo simplex*: This is acquired in childhood, but the lentigines are not confined to sun-exposed skin.
- *Junctional nevi*: Darker pigmentation and lack of change after sunlight exposure favor a diagnosis of junctional nevus.

**Therapy:** Sunscreens, light avoidance, as freckles are marker for increased risk of skin cancers.

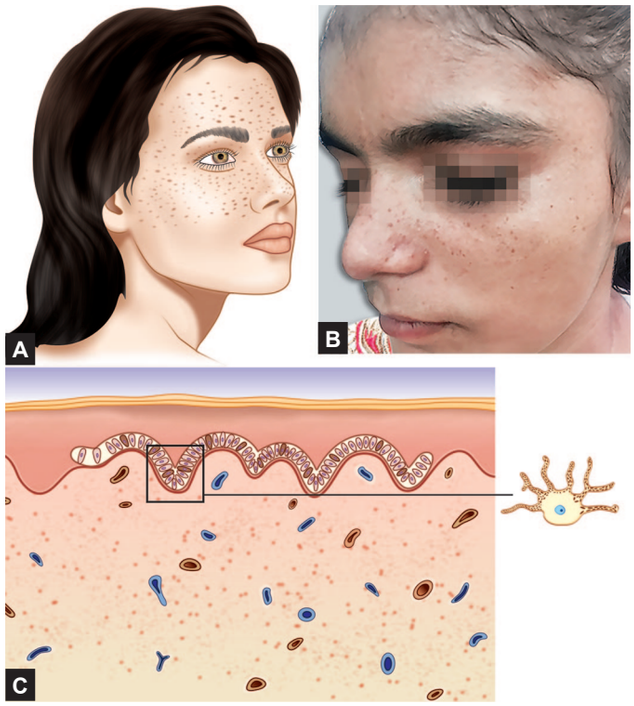



**Fig. 18.19A–C:** (A and B) Ephelides, also known as freckles, are most frequently encountered in fair-skinned individuals on sun-exposed skin. Sun exposure causes accentuation of lesions; (C) Histology of a freckle with increased melanin in the normal melanocytes

Others believe that freckles should be accepted as normal. Prevention by sunlight avoidance is effective but not always practical.

### *Lentigo*

They are light or dark brown macules, ranging from 1 mm to 1 cm across. Although usually discrete, they may have an irregular outline. Lentigo simplex presents with a dark brown small macule with increased melanocytes[Q] in the basal layer (Fig. 18.20A).

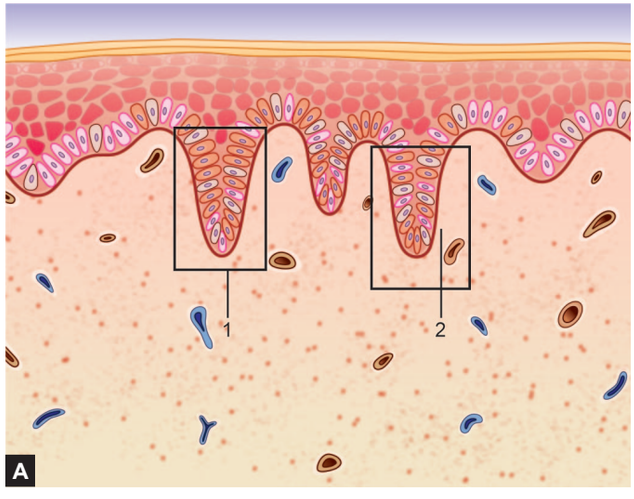
*Simple lentigines* arise most often in childhood as a few scattered lesions, often on areas not exposed to sun, including the mucous membranes (Fig. 18.20B).

*Senile* or *solar lentigines* are common after middle age on the backs of the hands (age spots or liver spots) and on the face.

Sometimes they are associated with systemic findings and a few important syndromes are:

- *Peutz-Jeghers syndrome*[Q]: Profuse lentigines on and around the lips, buccal mucosa, gums, hard palate, hands and feet. The syndrome is associated with polyposis of the small intestine, which may lead to recurrent intussusception and, rarely, to malignant transformation of the polyps. 10% of affected women have ovarian tumors.
- *Cronkhite-Canada syndrome*: This consists of multiple lentigines on the backs of the hands and a more diffuse pigmentation of the palms and volar aspects of the fingers. Other findings include gastrointestinal polyposis, alopecia and nail abnormalities.
- *Leopard syndrome (LEOPARD)*:[Q] This is an acronym for generalized lentiginosis associated with cardiac abnormalities demonstrated by ECG, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and deafness.

**Differential diagnosis:** In contrast to freckles, lentigines have increased *numbers* of *melanocytes* (Fig. 18.20A). They should be distinguished from freckles, from junctional melanocytic nevi and from lentigo maligna.



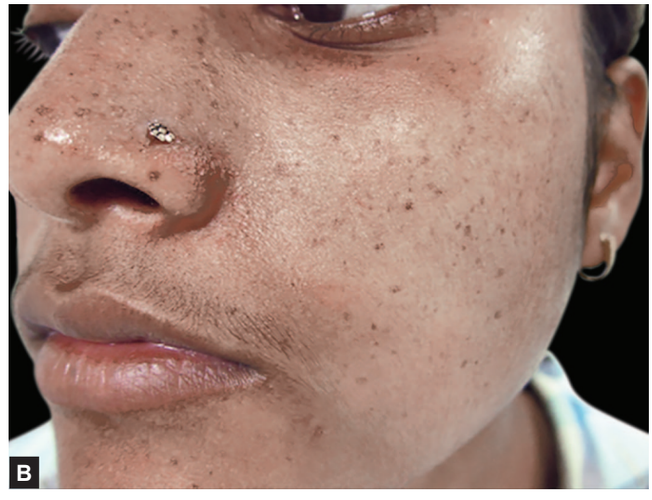




**Fig. 18.20A and B:** (A) Actinic lentigo. Epidermis—increased basal layer pigmentation resulting from increase in melanocytes and melanin; rete ridges are elongated;[Q] (B) Multiple lentigines in a female

**Treatment:** Treatment is usually unnecessary and prevention, by sun avoidance and the use of sunscreens, is the best approach. Melanin-specific high energy lasers (e.g. Q-switched ruby laser, 694 nm; Q-switched alexandrite laser,Q 755 nm; Nd:YAG laser,Q 1064 nm) can be used.

Topical therapies are also effective for lightening lentigines such as daily application of 0.1% tretinoin cream, 2–4% hydroquinone or a combination of these with or without a retinoid, alpha-hydroxy acid, or topical corticosteroid.

## *Melasma*

*Synonyms*: Chloasma, mask of pregnancy.Q

This is a common disorder with combined epidermal and dermal hyperpigmentation of forehead, cheeks, and perioral areaQ (Fig. 18.21A–C).

**Pathogenesis:** Risk factors include:

- Sun exposure
- PregnancyQ
- Use of oral contraceptivesQ (or tumors secreting estrogens)
- Rarely caused by phenytoin

The exact cause of melasma is unknown. The theory is that the melanocytes in the affected skin produce greater amounts of melanin than they do in the uninvolved skin. This hyperfunctioning of the melanocytes is thought to be triggered by UV exposure,Q hormonal or other systemic conditions such as thyroid disease. These stimuli can cause increased levels of nitric oxide, which stimulates tyrosinase activity, causing increased localized melanin production.

**Clinical features:** Irregular brown hyperpigmentation, sometimes with blue tones, often speckled. Sometimes mask-like pattern. Typically worsens with sun exposure.

**Three patterns** of hypermelanosis are observed and are described as centrofacial, malar, and mandibular. The central facial pattern is the most commonQ, affecting the forehead, cheeks, nose, upper lip, and chin. The malar and mandibular patterns exclusively affect the cheeks, nose, and the mandible.

The melanocytes in the areas of involvement are increased in number as well as in activity, producing a greater number of melanosomes.

**Therapy:** It is difficult to treat melasma as the melanin is present at varying depths in the dermis and epidermis. Also minor sun exposure can reactivate the process which is an issue in India. Any treatment regimen must include strict sun avoidance, including broad-spectrum sunscreen and hats.

1. *Topical agents*: HQ (hydroquinoneQ) is useful and the optimal effect is achieved with preparations containing 2–5% hydroquinone applied for 6–10 weeks. After this, maintenance treatment should be with preparations containing no more than 2% hydroquinone. Commonly the hydroquinone may be combined with a topical steroid and a retinoid for short-term use. Caution

**Clinical Pearl**

- Despite advanced and expensive therapies, melasma is often recalcitrant, recurrent and persistent.
- Caution is advised as over treatment or aggressive therapies that cause inflammation, may in turn cause more hyperpigmentation, specially in Indian skin.

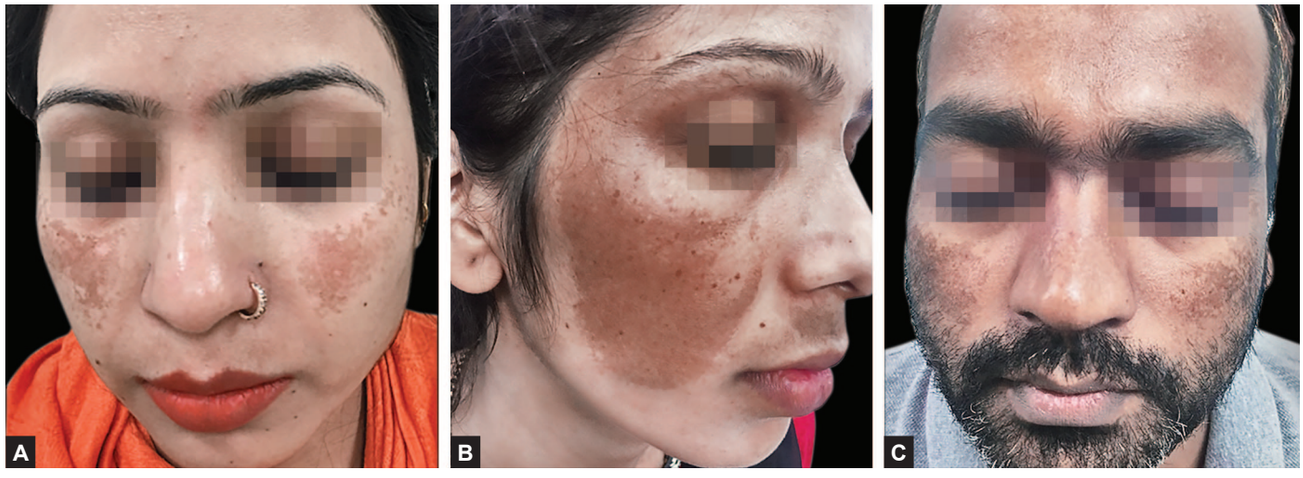



**Fig. 18.21A–C:** (A) A young female with melasma involving the malar area. The lesions started in pregnancy; (B) A 35-year-old female with malar and mandibular melasma. Also note the presence of freckles of cheeks; (C) Malar melasma in a 35-year-old male. Melasma is rare in men. Unlike females, hormones play little role in pathogenesis. UV light and mustard oil are implicated as causative factors in male melasma

should be observed as prolonged unsupervised application of HQ can cause exogenous ochronosis.

Fluocinolone 0.01% plus hydroquinone 4% plus tretinoin 0.05% solution is a commonly used preparartion (modified Kligman regimen[Q]).

Other topical lightening agents include tyrosinase inhibitors such as kojic acid and azelaic acid.

2. *Superficial chemical peels*[Q] help to remove epidermal melanin and are thus a useful adjunct to topical treatment. Glycolic acid peels are the most efficacious of the peeling agents but require expertise for proper application and in Indian skin salicylic acid peels are better.
3. Lasers have a variable effect (Q-switched ruby, Q-switched alexandrite, $CO_2$ and Er:YAG,) and in Indian skin can worsen melasma and result in dyspigmentation. New fractionated lasers show promising results but not in Indian skin.

Laser treatment has not been consistently effective, and the side effects may be greater than the benefits.

### *Becker's Nevus*

Becker's nevus is a relatively common anomaly affecting 0.5% of young men and women.

#### Clinical features

*Site*: Usually occurs in the scapular region.[Q] It can occur on other sites of the body like face, neck, and distal extremities.

It usually develops in adolescence as an irregular asymmetrical area of hyperpigmentation which may later thicken and develop coarse dark hairs[Q] (Fig. 18.22). The prominence in adolescence with increased hair growth (hypertrichosis) shows that it is androgen dependent.

**Treatment:** It can be treated with[Q] switched Nd:YAG or alexandrite laser.

## Blue and Gray Hyperpigmentation

### *Erythema Dyschromicum Perstans/Ashy Dermatosis*

This is a poorly understood dermatosis with inflammatory phase and a late postinflammatory dermal melanosis. It is often confused with lichen planus pigmentosus, which some authors believe to be the same entity.

**Clinical features:** Early lesions are erythematous macules favoring the trunk; they slowly evolve into blue-gray (ashy) macules with indistinct borders, often coalesce (Fig. 18.23). Totally asymptomatic.

**Therapy:** Nothing well established; both chloroquine and PUVA have proponents.

### *Deposition of Metallic Salts/Drugs*

A number of heavy metals can be deposited in the skin, usually imparting various shades of blue and gray. The most common agents are shown in Table 18.4. Hyperpigmentation caused by medications is also listed in Table 18.5.

### *Exogenous Ochronosis* (EO)

EO is a cutaneous disorder that occurs due to use of chemical substances on the face.

**Clinical findings:** EO is characterized by the presence of asymptomatic bilaterally symmetrical speckled blue black to gray brown macules (Fig. 18.24) on the face mainly the malar areas, lower cheeks, temples and neck. In early stages, it resembles melasma.

EO most commonly occurs due to use of topical hydroquinone (used as a skin lightening agent) but has also been described with use of phenol, resorcinol,

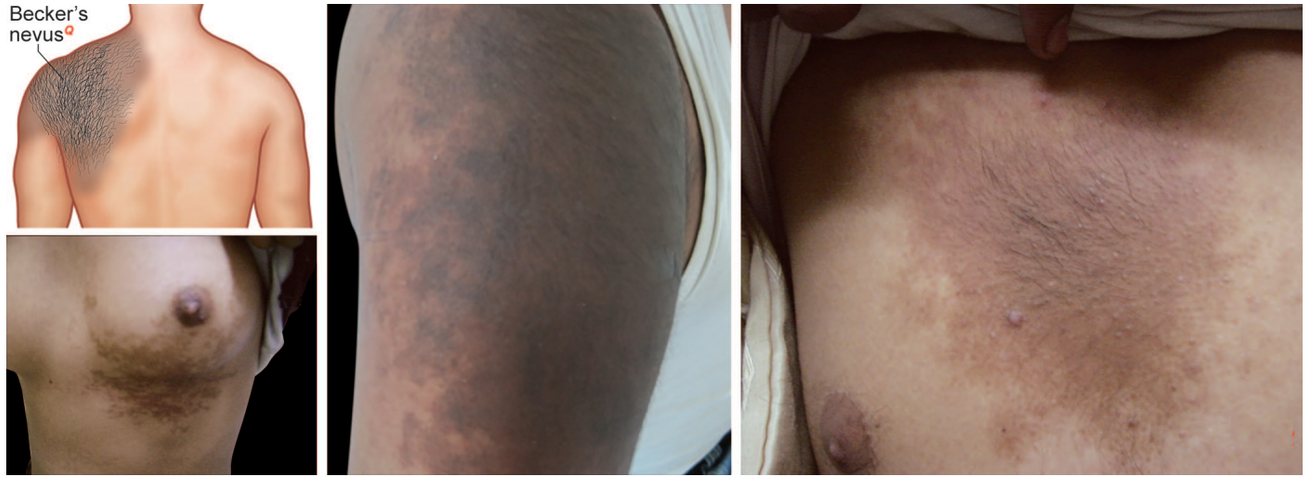



**Fig. 18.22:** Becker's nevus presents as a brown to black lesion, which can be hypertrichotic ( increased hair) or nonhypertrichotic and is seen commonly on the chest and arms

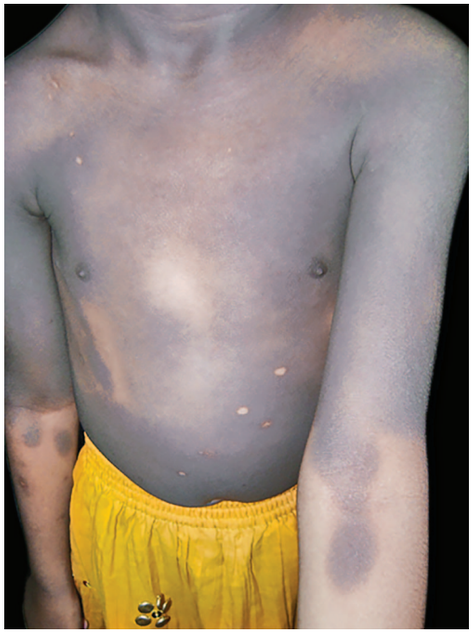


**Fig. 18.23:** Bluish macule on the trunk in a child with EDP

**TABLE 18.4** Hyperpigmentation caused by heavy metals[Q]

| | | |
|---|---|---|
| Silver | Nose drops, silver nitrate sticks | Argyria |
| Gold | Arthritis medication | Chrysiasis |
| Iron | Multiple blood transfusions, excessive ingestion | Siderosis |
| Arsenic | Fowler solution, skin tonics, old insecticides | Arsenical melanosis |
| Lead | Paints with lead | Plumbism with gingival[Q] hyperpigmentation |

**TABLE 18.5** Pigmentation due to drugs[Q]

| | |
|---|---|
| Amiodarone | Diffuse blue-gray hyperpigmentation in sun-exposed areas[Q] |
| Minocycline | • Dark blue to black macules in acne scars or over cysts<br>• Hyperpigmented patches in light-exposed areas (slowly reversible)[Q]<br>• Hyperpigmentation of mucosal surfaces, especially mouth |
| Antimalarials | Gray hyperpigmentation, especially facial and pretibial, as well as on gingiva and palate. |
| Chemotherapy agents | • Generalized hyperpigmentation: 5-fluorouracil<br>• Localized hyperpigmentation: Bleomycin, cyclophosphamide<br>• Linear hyperpigmentation: 5-Fluorouracil (over veins), bleomycin (flagellate, presumably following scratching) |

quinine, mercury, picric acid and oral antimalarials. The cause is competitive inhibition of the enzyme homogentisic oxidase by hydroquinone leading to accumulation of homogentisic acid and its metabolic products that polymerise to form the ochronotic pigment in the papillary dermis.

**Treatment:** Laser therapy is the only viable option with variable results.

### *Dermal Melanocytosis*

Blue-gray usually congenital lesions contain dermal melanocytes. The deeper location of the melanin is responsible for the blue-gray-black tones.

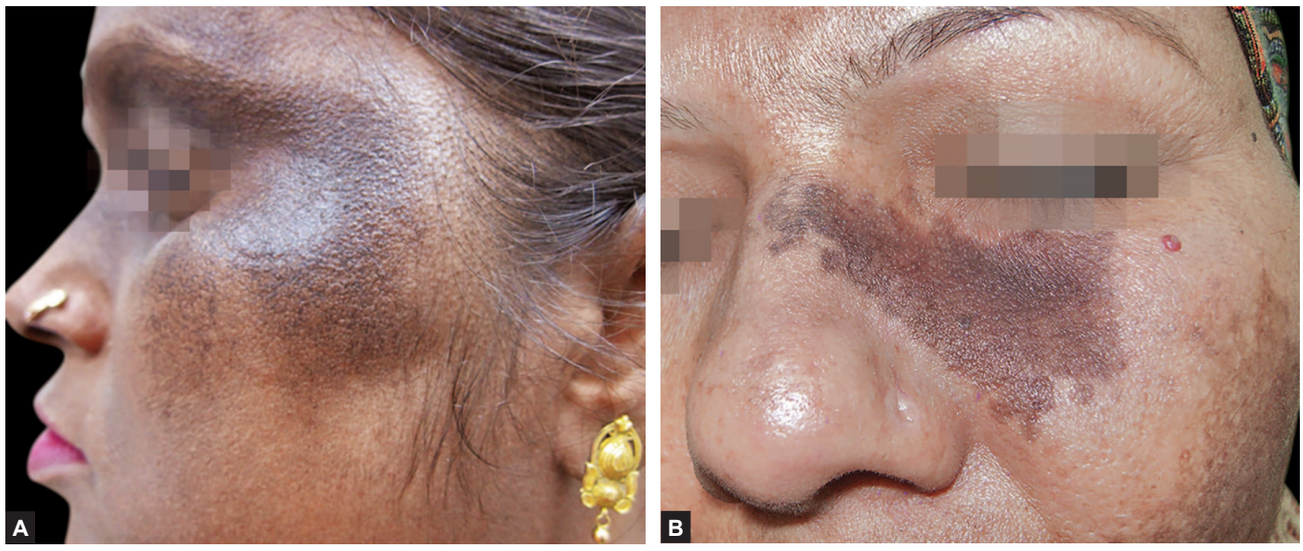



**Fig. 18.24A and B:** Blue-gray pigmentation: (A) Ochronosis due to use of fairness creams containing hydroquinone; (B) A case of localized ochronosis due to use of HQ 4%

**Nevus of Ota[Q]:** It is a dermal melanocytic[Q] hamartoma that presents as bluish-brown patchy hyperpigmentation on the face along the first or second branches of the trigeminal nerve (Fig. 18.25). The blue color is consequent to the tyndall effect due to the dermal placement of melanophages.

*Clinical features*: Lesions are usually present at birth or occur during the first year of life. It can also appear around puberty.

The condition is characterized by unilateral, irregular, patchy bluish gray to brown hyperpigmentation in the periorbital region, temple, malar prominence, nose and forehead (Fig. 18.26).

Ocular involvement occurs in 60% of cases in the form of scleral and conjunctival pigmentation. Rarely, bilateral lesions can occur.

*Treatment*: Q-switched lasers[Q] are the mainstay of treatment but results depend on the age of the patient and the depth of pigmentation.

**Mongolian spot:** A blue-gray patch over the sacrum,[Q] which is present in 90% of Asian, but uncommon in white babies; it tends to regress.

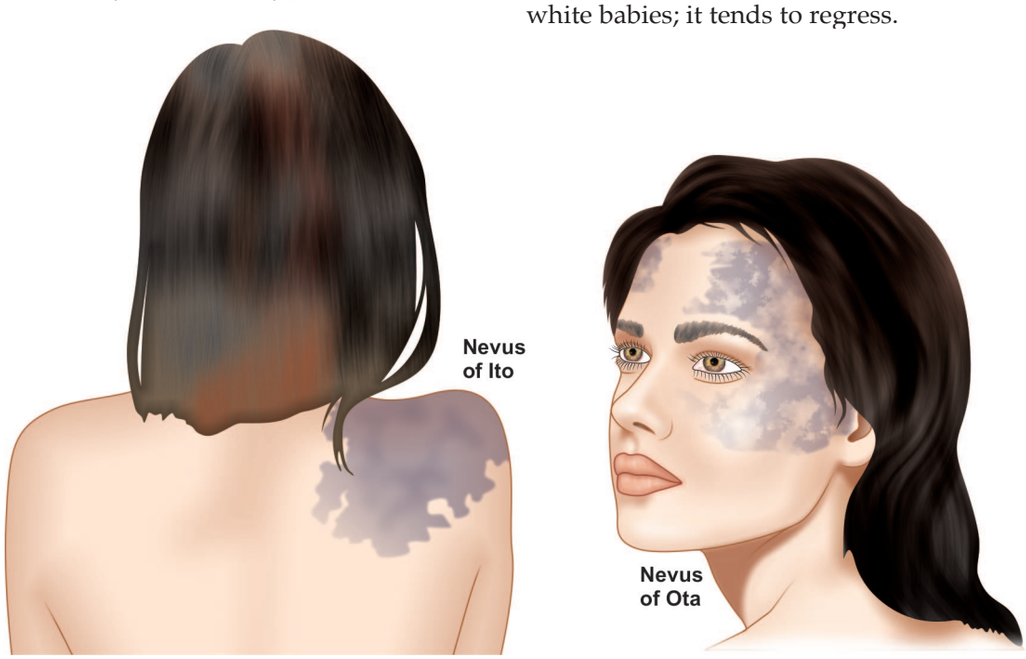



**Fig. 18.25:** Depiction of nevus of Ota and Ito

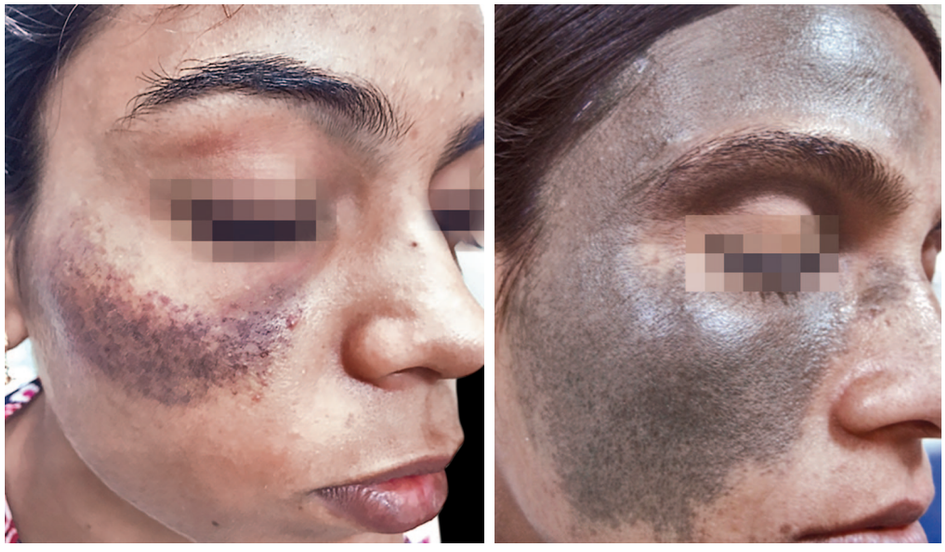


**Fig. 18.26:** Female patients with nevus of Ota

**Nevus of Ito:** Unilateral blue-gray patch on the shoulder and scapular region; also occurs most frequently in Asians.

## MELANOCYTIC NEVI AND THEIR VARIANTS

A nevus **(mole)** is a benign neoplasm of pigment-forming cells, the nevus cell. In this section, nevus signifies melanocytic nevus. They may be congenital or acquired. Most appear at puberty or in young adulthood. They may flare during pregnancy. Nevus cells are derived from the neural crest.Q Morphologically, one can recognize the nevus cell because it has no dendritic processes and groups together in nests within the epidermis and dermis (Fig. 18.27).

Nevi are traditionally classified on their histological pattern:

- Junctional nevi—melanocytes at the dermal–epidermal junction (DEJ)
- Dermal nevus—melanocytes in the dermis
- Compound nevus—melanocytes in both sites.

There are numerous other clinical variants which are described as special type of nevi.

### Clinical Features of Benign Nevi

The junctional nevus is a light to dark brown macule. (Fig. 18.28A).

Compound and intradermal nevi are flesh-colored or brown, smooth- or rough-surfaced papules that occur in older children and adults (Fig. 18.28B and C).

Nevi can occur anywhere on the body, but are increased on areas of sun exposure. The lesions have a continued progression thus they begin as junctional nevi, and in adolescence and adulthood, some (not all) of the nevus cells migrate downward into the dermis forming the compound nevi and then finally in adulthood, these nevi may continue to migrate so that all of the nevus cells relocated in the dermis (to form the intradermal nevi).

### Special Types of Nevi

1. Spitz
2. Blue

**Clinical Pearl**

The clinical appearance of benign nevi changes with aging and they involute or fade around the sixth or seventh decade.

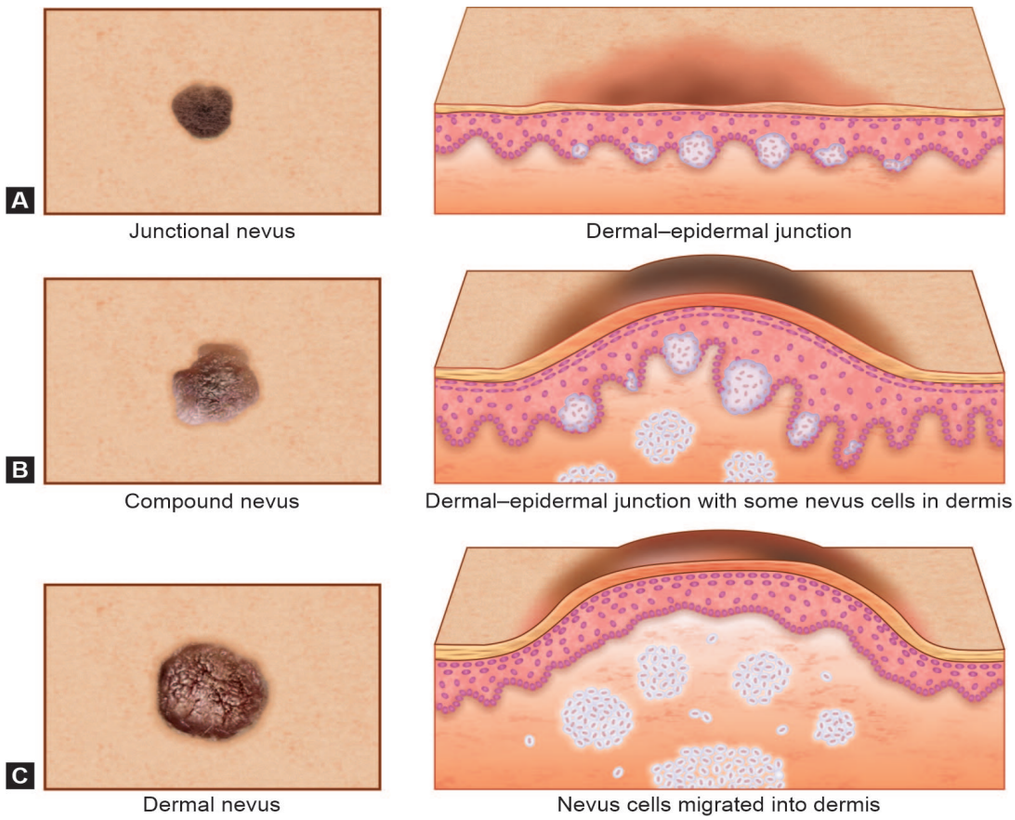



**Fig. 18.27A–C:** Depiction of the clinicohistological appearance of common acquired melanocytic nevi, the classification depends on the location of nevus cells

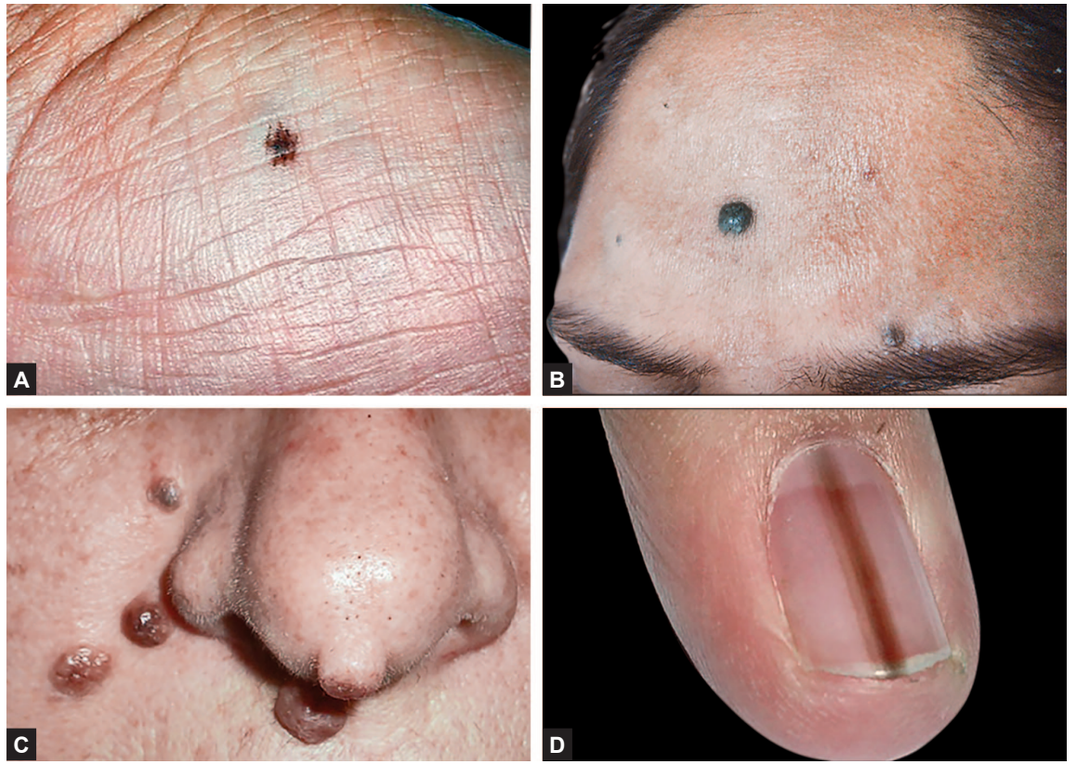



**Fig. 18.28A–D:** (A) Junctional nevus; (B) Compound nevus; (C) Skin-colored dermal nevi; (D) Melanonychia striata due to junctional nevus

3. Dysplastic/atypical
4. Congenital
5. Halo nevi

**Spitz:** The Spitz nevus (benign juvenile melanoma) is composed of spindle and epithelioid nevus cells. It is a smooth, round, slightly scaling, pink nodule that occurs most frequently in children (Fig. 18.29). The most important aspect of dealing with this lesion is to recognize that it is a nevus and not a melanoma, and to avoid extensive surgical intervention.

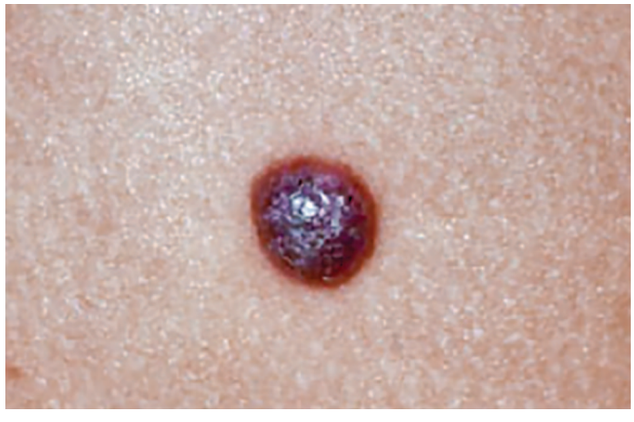


**Fig. 18.29:** Spitz nevus presenting as a solitary dome-shaped, hyperpigmented nodule

**Blue nevi** are small, steel-blue macules, papules, and nodules that usually begin early in life. Their importance in diagnosis is their similar appearance to nodular melanoma.

**Congenital nevi** (Fig. 18.30) are present at birth or shortly thereafter; they are usually elevated and have uniform, dark brown pigmentation with discrete

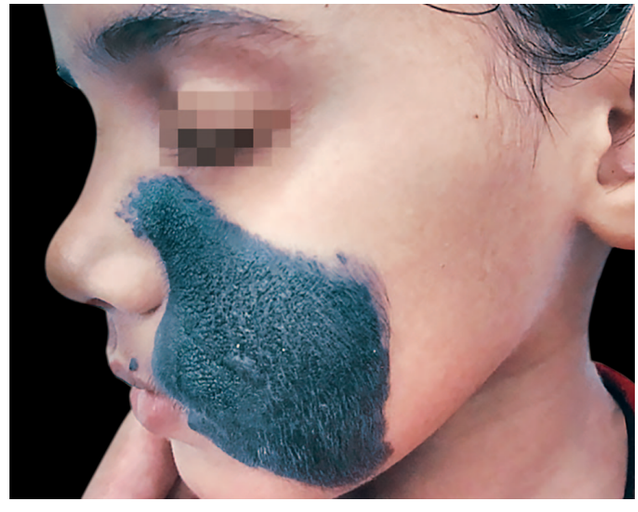


**Fig. 18.30:** An intermediate-sized congenital melanocytic nevus in a 6-year-old girl. Note the hair growth on the lesion

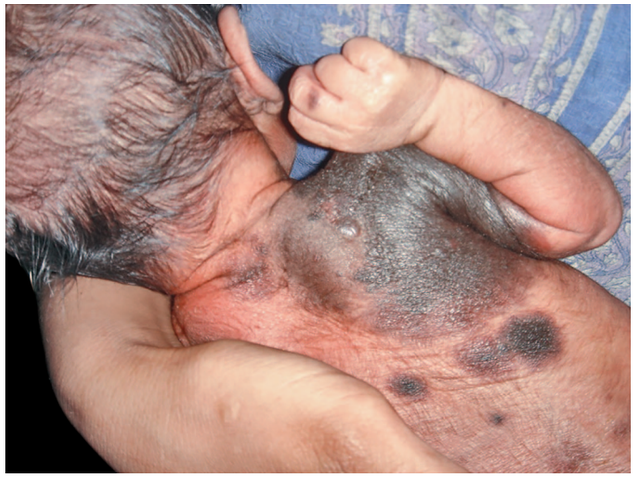


**Fig. 18.31:** Congenital nevus with thickening of skin and hypertrichosis

borders.[Q] Of newborns, 1% have congenital nevi. Often they contain hairs (Fig. 18.31).

They have been divided into **three types**—small (<1.5 cm in diameter}, medium (1.5–20 cm), and large (>20 cm). Congenital nevi are melanoma precursors.[Q] The risk is very small for small lesions (<1%) but large congenital nevi (>20 cm across or covering 5% of body area) have a 6 to 12% chance of developing into a malignant melanoma.[Q]

Giant lesions covering a large portion of the body (bathing trunk nevus)[Q] including the dorsal midline are at risk for neurocutaneous melanosis (Fig. 18.32).

Small congenital nevi have a little to no increased risk of transformation into melanoma and, therefore, do not need to be removed prophylactically.

**Dysplastic nevi:** Occasionally, patients have multiple large atypical nevi that continue to develop throughout life. Clinically, the *atypical mole* is more than 5 mm, is variegated in color with a pink background, and has an irregular, indistinct border.

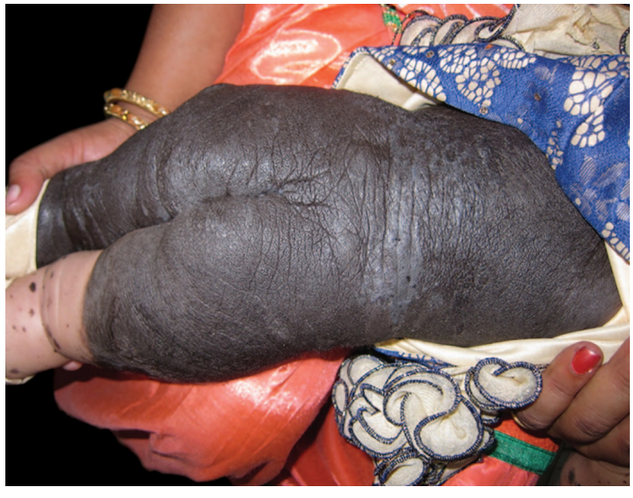


**Fig. 18.32:** Bathing trunk nevus[Q]

**Atypical moles** were initially recognized as markers for increased risk of melanoma in family members with inherited malignant melanoma, the familial atypical mole and melanoma syndrome or dysplastic nevus syndrome. In these families, virtually all members with atypical moles developed a melanoma in their lifetime, whereas family members without atypical moles did not.

Subsequently, investigators discovered that approximately 5% of the healthy Caucasian population in the United States has atypical moles. The risk of developing a melanoma in these individuals, is unclear, and in majority of them, melanoma never develops.

The clinical[Q] **ABCDE** rule is helpful for separating unequivocally benign nevi from dysplastic or atypical nevi and melanomas. It is not helpful for separating the latter two groups (Fig. 18.33):

- **A**symmetry
- **B**order (irregular, leakage of pigment)
- **C**olor (multiple colors)
- **D**iameter (>5 mm).

Some experts add the 'E' (evolution) to this rule.

**Clinical Pearl**

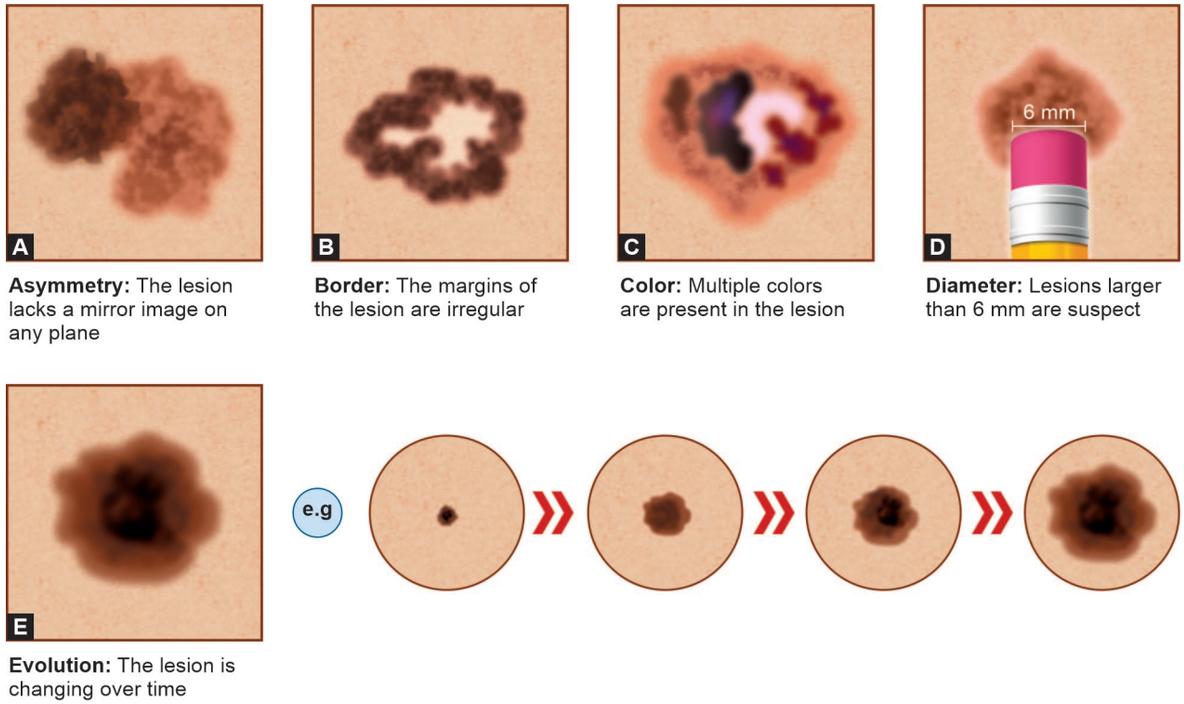
Another method of identifying an atypical nevi is the so-called 'ugly duckling sign'[Q], that is identifying a mole that is different from the others.

**Halo nevus[Q]:** Also known as Sutton nevus, this lesion is surrounded by a halo of depigmentation (Fig. 18.34). The nevus may become pale or even disappear. Adults with multiple halo nevi should be checked for a melanoma, which may trigger an antimelanocyte immune response.

## Treatment

In Indian skin, the risk of melanoma is negligible. There is no indication to remove common melanocytic nevi (moles) unless they are irritated. But in most clinical set ups, removal of moles is possibly the commonest cosmetic procedure and most patients who ask for removal do it for no medical reason. We have analysed our data and found that for small moles possibly lasers (ablative) may be useful but for a larger lesion, RF is a good option. In ideal situations, the excised lesion should be analysed histologically for melanoma.

For congenital nevi, a staged excision is advisable. For dysplastic nevi, a histological evaluation is necessary.




**Asymmetry:** The lesion lacks a mirror image on any plane

**Border:** The margins of the lesion are irregular

**Color:** Multiple colors are present in the lesion

**Diameter:** Lesions larger than 6 mm are suspect

**Evolution:** The lesion is changing over time

**Fig. 18.33A–E:** Depiction of the ABCDE rule for diagnosing cases of melanoma

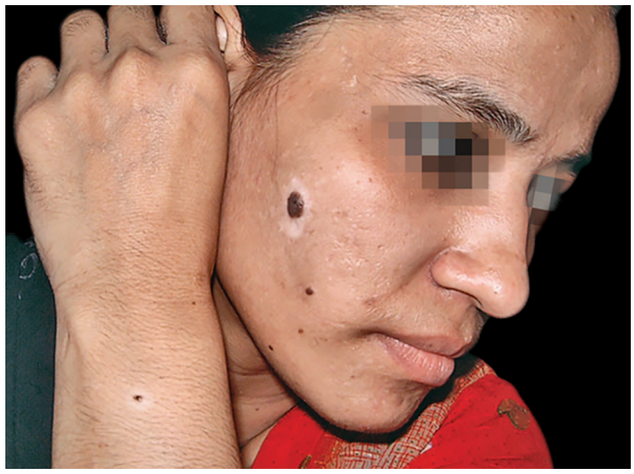


**Fig. 18.34:** Halo nevus[Q]

## MALIGNANT MELANOMA

Malignant melanoma is a cancerous neoplasm of pigment-forming cells, melanocytes, and nevus cells.

### Epidemiology

Its incidence is 15–20:100 000 in Northern Europe and USA; this is a lifetime risk of developing melanoma of 2%. The risk is inversely related to skin color.

The peak age is around 60 years but this varies with the type of melanoma; superficial spreading melanoma appears much sooner than lentigo maligna melanoma. Acrolentiginous melanoma is equally common in all races, and thus the most common melanoma of darker individuals.[Q]

Over half of all melanomas are <0.75 mm thick, so that >95% of patients never develop metastases.

### Pathogenesis

A brief overview is given here (Fig. 18.35A), though in pigmented skin, the incidence is less. Thus most of these factors apply largely to Caucasian skin.

- *Both UVB and UVA* increase the risk of melanoma. Intermittent excessive exposure—such as bad sunburns during childhood—correlates better with superficial spreading and nodular melanoma, while chronic long-term exposure fits with lentigo maligna melanoma.
- *Genetic contributions* are usually complex. For example, pale-skinned individuals with mutations in the MCR1 gene have a 17-fold increased risk of developing a melanoma with BRAF mutation.

**Clinical Pearl**

Familial atypical mole and melanoma syndrome should be suspected:

1. Personal or family history of melanoma and
2. Numerous (>50) atypical nevi

**Clinical Pearl**

Rule of 3s for familial melanoma genetic testing:
- 3 melanomas in a family,
- 3 melanomas in an individual,
- 3 cancers (melanoma or pancreatic) in a family.

- *Melanoma genes*: A series of gene mutations have been associated with melanoma. Mutations involve either signal transduction of a tyrosine kinase receptor (c-Kit, EGFR. FGFR, ErbB-2) (Fig. 18.35B).

Genetic testing may be considered when three family members have melanoma; an individual has three melanomas, or three cancer events (melanoma or pancreatic cancer) occur in a family.

## Clinical Features

The various types are depicted in Table 18.6 and Fig. 18.36.



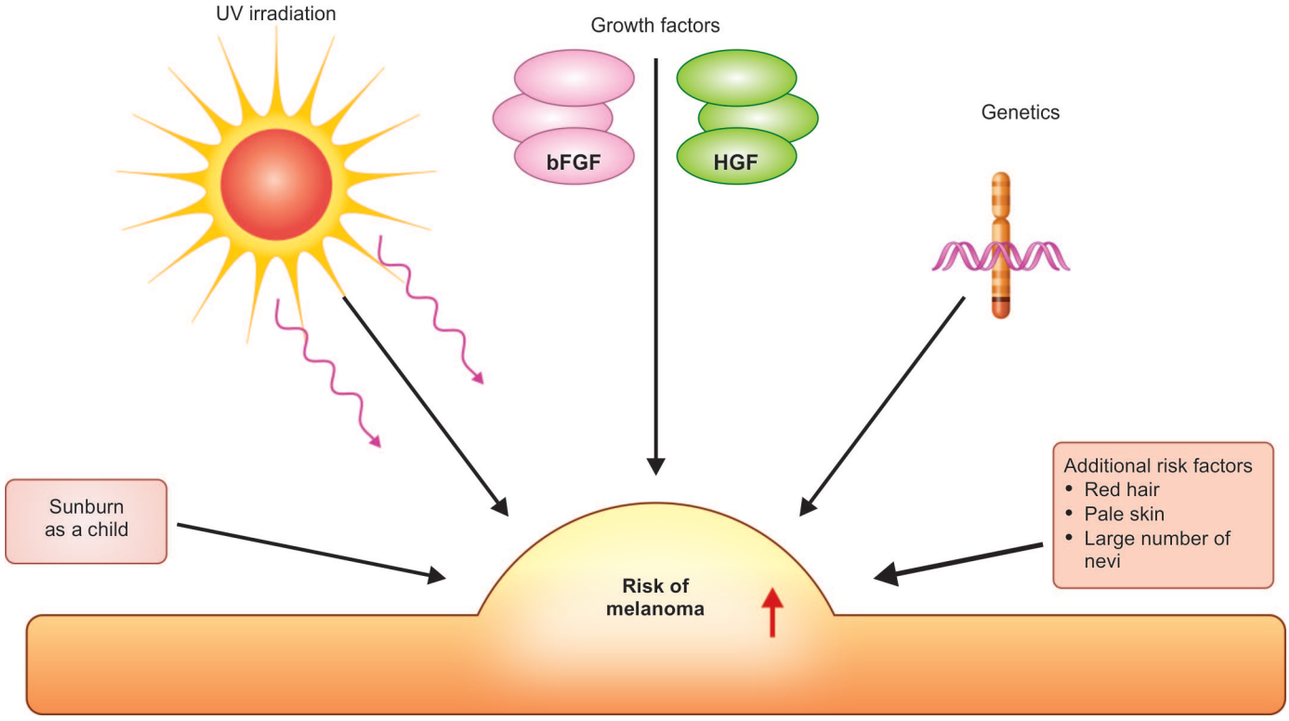



**Fig. 18.35A:** Overview of the factors that can increase the risk of melanoma

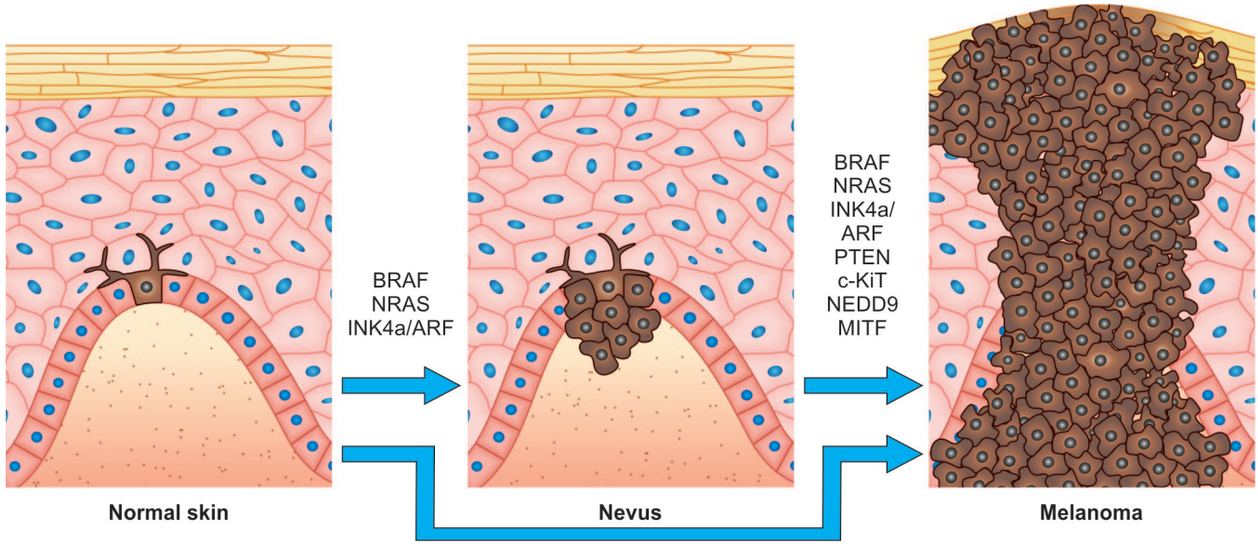



**Fig. 18.35B:** Gene mutation that predict melanoma

TABLE **18.6** Clinical features of melanoma

| *Type* | *Location* | *Median age (years)* | *Premetastatic* | *Frequency (%)*[a] | *Ethnicity* |
|---|---|---|---|---|---|
| Lentigo maligna | Sun-exposed surfaces (head, neck) | 70 | 5–15 years | 10 | Caucasian |
| Superficial spreading | All surfaces (back, legs) | 47 | 1–7 years | 27 | Caucasian |
| Nodular | All surfaces | 50 | Months to 2 years | 9 | Caucasian |
| Acral lentiginous | Palms, soles, nail beds | 61 | Months to 8 years | 1 | Blacks, Asian |

[a]53% of melanomas are unclassified.

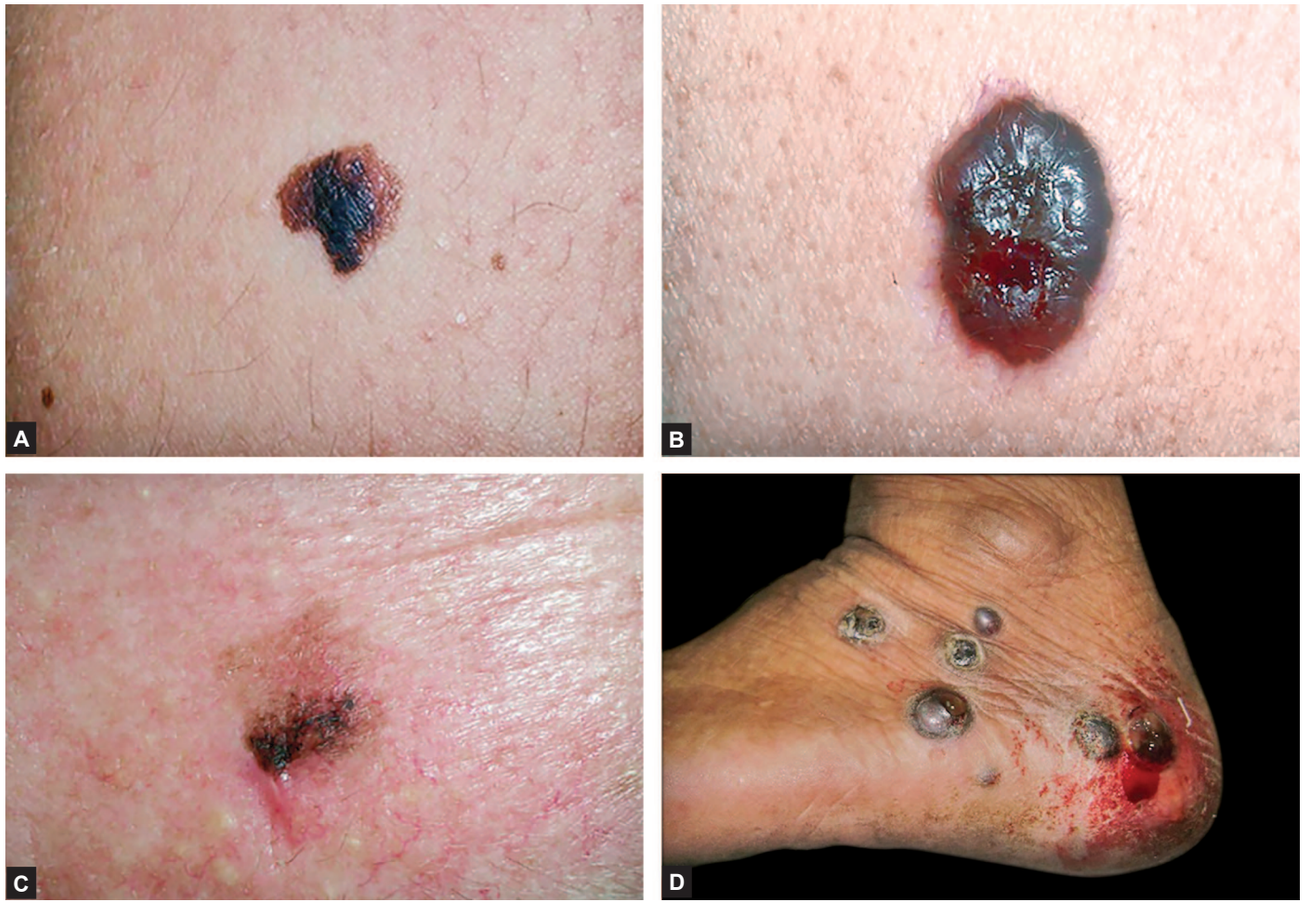



**Fig. 18.36A–D:** (A) Superficial spreading melanoma *in situ*; (B) Nodular malignant melanoma; (C) Lentigo maligna presenting as a hyperpigmented lesion with irregular borders located on the forehead; (D) Acral variant

**SSM** (Fig. 18.36A): The most common type of melanoma is the superficial spreading melanoma.[Q] This lesion is irregular in color (red, white, black, dark brown, and blue), surface (macule, papule, or nodule), and border (notched), and may occur anywhere on the body. It is found most frequently on the upper back in males, and on the upper back and lower legs in females.

**Nodular melanoma** (Fig. 18.36B and D) is a rapidly growing, blue-black, smooth or eroded nodule. It occurs anywhere on the body. It begins in the vertical growth phase, so is less likely to be diagnosed in a premetastatic stage.

**Lentigo maligna melanoma** (Fig. 18.36C) occurs on sun-exposed skin, especially the head and neck. It is multicolored, with dark brown, black, red, white, and blue hues, and it is elevated in areas. It is preceded by lentigo maligna (*in situ* melanoma[Q]), which extends peripherally and is an unevenly pigmented, dark brown and black macule. Lentigo maligna often reaches a diameter of 5 to 7 cm before showing signs of invasion.

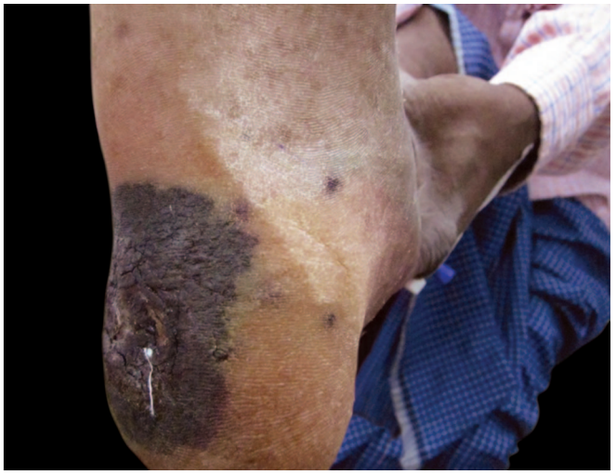


**Fig. 18.36E:** Acral lentiginous melanoma on the sole in a 45-year-old male

**Acral lentiginous melanoma** (Fig. 18.36E) occurs on the palms, soles, and distal portion of the toes or fingers. It is an irregular, enlarging, black growth similar to a lentigo maligna melanoma. The vertical growth phase in this type of melanoma can be deceptive, showing only a small degree of papular elevation associated with a deep component. In contrast to the other melanomas, acral lentiginous melanoma is most frequent in the Black and Asian populations.Q

## Diagnosis

**Biopsy:** All suspicious pigmented lesions must undergo biopsy, by excision with narrow 2 to 3 mm margins of normal skin or by deep shave biopsy. Definitive treatment by wide surgical excision should not be undertaken until confirmation of malignant melanoma has been made histologically.Q

Clark and BreslowQ correlated survival with tumor thickness. Breslow, using an ocular micrometer, measured tumor thickness from the stratum granulosum to the depth of invasion.Q These measurements predict 5-year survival (Fig. 18.37).

**Investigative approach:** This varies with the type of melanoma. The usual approach is to excise a suspicious lesion, get a histological diagnosis and then plan the definitive surgery.Q

An investigative approach is detailed in Fig. 18.38.

## Therapy

The survival of patients with malignant melanoma depends on early diagnosis, when surgical excision is often curative. An overview of the therapy is given in Fig. 18.39.

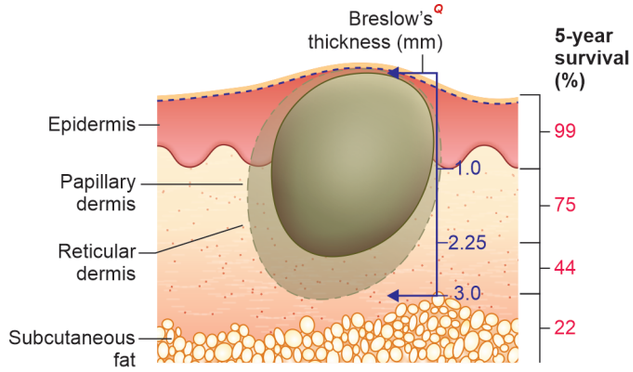



**Fig. 18.37:** Survival is related to depth of invasion (thickness measured in millimeters)

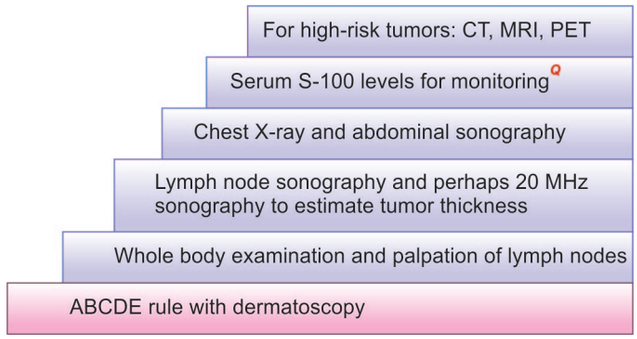



**Fig. 18.38:** An investigative approach in melanoma

### *Surgical Excision*

The margin of normal skin excised around the melanoma increases with the depth of invasion, or thickness: *in situ*, 0.5 cm margin; thickness less than 2 mm, 1 cm margin; thickness more than 2 mm, 2 cm margin.

### *Oncological Therapy*

Numerous medical agents have been tried largely for a malignant melanoma that has metastasized, and is best managed by a medical oncologist familiar with these agents—chemotherapy, radiation, immunotherapy, kinase inhibitors, and oncolytic virus (Box 18.1).

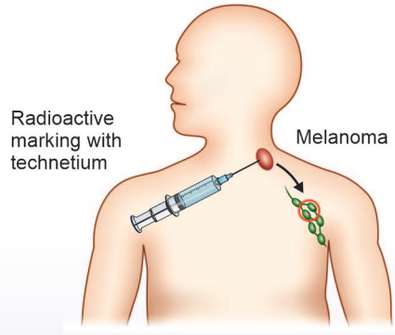
Radiation therapy is used for palliation of bone and brain metastasis, and when lentigo maligna is so large that surgical removal is technically difficult.

**Box 18.1 Oncotherapy for metastasis**

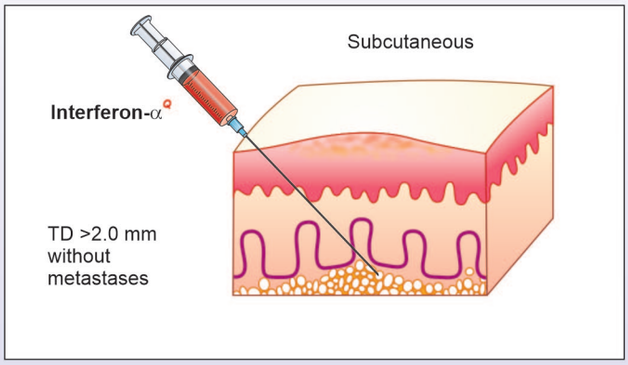
- Immunotherapy—interferon-α-2b, interleukin, ipilimumab, nivolumab, pembrolizumab
- Kinase inhibitors—vemurafenib, dabrafenib, trametinib, cobimetinib
- Oncolytic virus—talimogene laherparepvec

| Tumor depth (Breslow) | Safety margin |
|---|---|
| *In situ* | 0.5 cm |
| <2 mm | 1 cm |
| >2 mm | 2 cm |

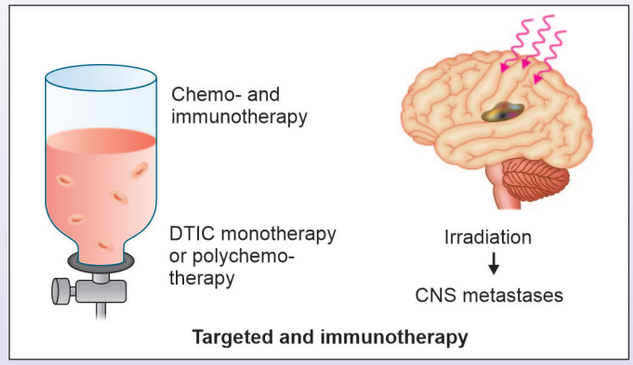
**Excision of primary tumor**




**Sentinel lymph node biopsy**




**Adjuvant immunotherapy**




**Targeted and immunotherapy**

**Treatment of metastases**

**Fig. 18.39:** Overview of treatment of melanoma