Skin colour disorders .

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The colour of the skin : normal skin colour is depended on :

1. **Haemoglobin –** both the oxygenated and reduced type (state) .
2. **Carotenoids –** yellow pigments , exogenously produced from plants & diet , present in epidermis and subcutaneous tissue .
3. **Melanin pigment –** which is the major colour determinant , the racial and ethnic difference in skin colour are related to the number , size , shape , distribution and degradation of melanin –laden organelles called **melanosomes ,** which are produced by the melanocytes and transferred to the surrounding epidermal keratinocytes . **There are two types of skin melanin pigmentation occurs in human :**

a. **Constitutive skin colour –** which is the amount of melanin pigmentation that is genetically determined in the absence of sun exposure and other influences .

b. **Facultative (inducible)-** skin colour or **'tan'** which results from sun exposure

Increased pigmentation can also be due to **endocrine causes (**such as occurs in pregnancy , and Addison's disease) and to **interaction of light and hormonal effects (as seen in melasma) .**

The wide variety of skin colour occurring in human can be objectively measured by reflectance **spectrophotometry .** In black people the abdomen is the darkest and the lumber region is the lightest , in white people , the darkest area is the upper thigh and the lightest is the lumber region , females are generally lighter than males .

A blue colour is seen in Mongolian spot , naevus of Ota , naevus of Ito and blue naevus , which is due to the presence of brown melanin pigment in the dermis .

Melanocyte :

Epidermal melanin unite – an epidermal melanocyte is surrounded by a group of keratinocytes , with which it maintains functional contact (**M:K about 1:36)** , so the melanin in human skin is produced by the melanocyte (melanogenesis) , which involve production of melanosomes transfer and distribution of these pigment granules to the surrounding epidermal keratinocytes .

Three different mechanisms may be involved in the control of skin colour changes:

1. **The pigment cell** may act as an independent effectors and responded directly to the stimulus of light , called the tanning processes , both **immediate (minutes -2hours)** and **delayed (48-72hours) .**
2. **The movement** of pigment within the melanophore (site of pigment) may be under nervous control .
3. **The activity of pigment cells** may be under hormonal influence ,***pituitary hormones** that cause expansion of melanophores or promote the formation of melanin in epidermal melanocyte , ***melatonin substance** occurs in high concentration in the mammalian pineal body , has similar function .

Distribution of melanocytes : melanocyte can be found in nearly every tissue , but are most common in the epidermis , hair follicles , dermis , eye , around blood vessels , peripheral nerves , the sympathetic chain , leptomeninges and inner ear . The total epidermal melanocyte population in a person is about 2multiply by 1000000000cells . The number of melanocytes is reduced with aging , about 6-8%/decade , the density of melanocytes is about twofold higher in exposed than in non-exposed skin .

Biochemistry of melanogenesis : melanin is usually classified into **two main groups :**

1. **The black and brown eumelanin –** which is soluble in all solvents , nitrogenous pigments arise by oxidative polymerization of 5,6-dihydroxyindoles , derived biogenetically from tyrosine via dopa .
2. **Phaeomelanins :** alkali-soluble pigments , ranging from yellow to reddish-brown , most of them contain sulpher in addition to nitrogen and arise by oxidative polymerization of cysteinyl-dopas via 1,4benzothiazine intermediates .

Red human hair contains in addition to phaeomelanins , small amount of intensely coloured pigments known as trichochromes , which are sulpher –containing pigments of well defined structure . **Both** eumelanins and phaeomelanins are derived from tyrosine by the same initial steps .

Tyrosine –tyrosinase (copper containing enzyme, by oxidation) 3,4dihydroxyphenylalanine(dopa) tyrosinase dopaquinone ------ cyclodopa (leukodopachrome) , +cysteine(SH) cysteinyldopa , +glutathione(polymerization) phaeomelanins , or glutathionedopa (colourless) . Cyclodopa change to dopachrome , than to 5,6dihydroxyindole , which by oxidative polymerization to eumelanin .

Alpha-melanocyte-stimulating hormone – produced by the pituitary gland , is the major hormone controlling melanin pigmentation , **also inflammatory mediators** e.g. fibroblast growth factor , leukotrienes C4,D4 , arachidonic acid , prostaglandins D2,E2 . Leukotrienes B4 and E4 may induce melanogensis , But IL-1alpha , IL-6 and TNF-alpha inhibit both melanocyte proliferation and melanogenesis , e.g. Nelson's syndrome (bilateral adrenalectomy) and Addison's disease , there are generalized marked hyperpigmentation , **estrogens also increase skin pigmentation .**

Melatonin (5-methoxy-N-acetyl-tryptamine)- is a hormone isolated from bovine pineal glands , although it is also present in much lower concentration in the hypothalamus and peripheral nerves , its action resembles that of adrenaline , noradrenalin , acetylcholine , serotonin and triiodothyramine , but is by far the most potent , being 100000times as effective as noradrenalin . Melatonin produced a visible lightening of the skin in melanotic dogs within 2days of 1mg/day , but in guinea pig epidermis even large doses have failed to alter the skin pigmentation . Human shows a clear daily rhythm , and a fall in nocturnal serum melatonin occurs during prepuberty and pubescence .

***Biological significance of melanin :**

Melanin is widespread through out the animal kingdom , where it appears to serve a variety of functions :

1. **Protection of tissue –** its major function in human is protection of the lower layers of the skin against UV light , so give protection against carcinogenesis and sunburn snow glare .
2. **Pigmentation increases the heat load in hot climates , so that black people** absorb 30% more heat from sunlight than do white people , so more profuse sweating , which is disadvantage .
3. **Pigmentation reduce the synthesis of Vit. D , so in areas** of poor nutrition , black children are more liable to rickets , also disadvantage .
4. **Pigmentation give some immunological protection** against certain disease e.g. malaria , parasites and tropical diseases , this is due to increase reticuloendothelial activity (increase serum alpha –globulin) .

5. **Melanin acts as stable free radicals ,** and can trap electrons and possibly free radicals , but also participate oxidation –reduction reactions .
6. **Melanin is phagocytized by** leukocytes , so circulating through the body and may influence intracellular metabolism (regarded as hormones) .

Pathogenesis of disorders of melanin pigmentation : disorders of melanin pigmentation can be divided on morphological grounds into two types :

a. **Hypermelanosis –** where there is an increased amount of melanin in the skin , which may be confined to the epidermis , when the skin appears browner than normal or it may be present in the dermis , producing a salty-grey or blue appearance .
b. **Hypomelanosis –where there is a lack** of pigment in the skin , which there for appears white or lighter than normal colour . **Amelanosis –** is the term applied when there is a total lack of melanin in the skin . **Depigmentation –** means a loss of pre-existing pigment from the skin . **Leukoderma –** is a white skin . Wood's light is often helpful in localizing abnormal variations in melanin , pigmentation in the skin and as an aid to the diagnosis of various disorders .

Changes in pigmentation can arise in a number of ways and can be due to a Varity of genetic and environmental factors , ways may involve :-

1. **Formation of melanosomes in melanocytes .**
2. **Melanization of melanosomes .**
3. **Secretion of melanosomes into keratinocytes .**
4. **Transport of melanosomes in the keratinocytes with and with out degradation in lysosome –like organelles .**

Light and electron microscopy studies have considerable value in the acknowledgement of the pathogenesis of many disorders of melanin pigmentation in humans caused by:-

a. Inflammatory disorders .
b. Genetic predisposition for many disorders of pigmentation .
c. Physical causes (thermal burns , ionizing radiation) and chemicals like phenol .

Racial variation , type of skin and response to sun exposure :

Genetic and racial factors play the primary role in determining the degree of pigmentation in human , so the main racial groups are : **Caucasoid (white) , Mongoloid (Oriental) , Negroid (black) and Australoid (Aboriginal) .** The skin response to sun exposure are :-

Skin type	**Sun sensitivity**	**Pimentary response**
Type-1	Very sensitive, always burn easily	Little or no tan
Type-2	= ====== = ==== = ====	Minimal tan
Type-3	Sensitive, burn moderately	Tan gradually (light brown
Type-4	Moderately sensitive , burn minimally	Tan easily (brown)
Type-5	Minimally sensitive , rarely burn	Tan darkly (dark brown)
Type-6	Insensitive , never burn	Deeply pigmented (black)

Hypermelanosis : of two types :-

1. **Either due to genetic and nevoid factors .**
2. **Or acquired types .**

Genetic and nevoid types :-

Periorbital melanosis – is some darkening of the skin around the eyes , not uncommon , familial , periorbital hyperpigmentation , is characterized by dark circular areas around the eyes and is determined by Autosomal dominant gene , first noted below the lower eyelids at the approach of puberty with wide variation in its ultimate extent and intensity .

Brown colour :

Ephelides (freckles) , Lentigines , multiple lentigines sy., Café-au-lait-spot and freckles of neurofibromatosis , Albright's sy. (melanotic macules) , Acanthosis nigricans (Juvenile type) , Xeroderma pigmentosum , Fanconi's sy. , Dyskeratosis congenital , Familial progressive hyperpigmentation , Peutz-Jeghers sy. .

Grey , slate or blue colour :

Mangolian spot , Nevus oh Ota , Nevus of Ito , Blue nevus , diffuse melanosis , Incontinentia pigmenti , Naegeli-Franceschetti- Jadassohn sy. .

Lentiginosis :

A lentigo is a benign pigmented macule in which there is an increased number of melanocyte , it is called lentiginosis , where there are a large number of lentigines , or in a distinctive distribution , it include :- *Generalized lentiginosis (non-genetic) , * Unilateral lentiginosis (zosteriform , no neurological involvement) , *Eruptive lentiginosis and *multiple lentigines sy. (Autosomal dominant) with a wide rang of developmental defects (e.g. cardiomyopathy , growth retardation , deafness , ocular and skeletal abnormalities) .

Ephelides (freckles):

***Definition* –** it is probably determined by **Autosomal dominant** gene , and most frequently seen in individuals with red or blonde hair and blue eyes , there is no increase in the number of melanocyte in the lesion , but their melanosomes are long and rod-shaped , like those found generally in dark skinned people (i.e. increase the quantity of melanin in the epidermis) . After exposure to sun –light more melanin is formed in the lesions , so become darker .

***Clinical features* –** freckles first appears at about the age of 5years as light –brown pigmented macules on light exposed skin and increasing in number , size and depth of pigmentation during summer times and are smaller , lighter and fewer in number in winter times . They may be cosmetically disfiguring or may enhance appearance .

***Diagnosis*-** D.D. lentigo , inherited and acquired disorders with freckles .

***Treatment* –** seldom required , removed by laser , retinoic acid .

Incontinentia pigmenti :

Definition- it is a complex hereditary sy. , inherited as X-linked dominant trait , characterized by vesicular , verrucous and pigmented Cutaneous lesions , which are associated with developmental defects of the eye , skeletal system an CNS , more than 95% of cases are females .

***Clinical features*-** the skin changes are often present at birth , have usually developed befor the end of the first week and rarely appears after the first 2months . The clinical stages recognized are :- ***Bullae , *papular and warty lesions , *pigmentation . However** their sequence is irregular , their duration variable and they may overlap .

The bulla are clear tense often in linear groups develop on the limbs , often in recurrent crops , less often they are generalized , the crops continue for a few days or for a month or two , they are accompanied or followed by smooth red nodules or plaques often irregularly linear , on the limbs and trunk , the plaques may be extensive and may precede the bullae , they may be bluish –purple in colour and may ulcerate . **The warty lesions** are linear may appear on the dorsa of hands and feet , particularly on the fingers and toes . **The pigmentation** are blue –grey or slate to brown , bizarre splashed or Chinese figure distribution , occasionally , multiple , linear and macular telangiectases have been present . Rarely the activity may present into adult life . 50% of cases with acute inflammatory skin changes have peripheral eosinophilia , with both neutrophil and lymphocyte dysfunction . The pigmentation persist for many years slowly fading until it is imperceptible by the second or 3rd decade . **Hypopigmentation** and atrophic streaks are not uncommonly found in the later stages of disease . 25%of cases have patches of cicatrical alopecia , nail dystrophy (rare) , keratoacanthoma .
Other organs involvement – dental defects , ocular defects (30%) CNS disorders (25%) , mental retardation , spastic tetraplegia epilepsy , skeletal abnormalities .
Treatment – not necessary .

Hypermelanosis in acquired disorders :

Causative factor	Brown	Gray, slate or blue
Metabolic	**Liver diseases (haemochromatosis , hepatolenticular degeneration, biliary cirrhosis) , Porphyria (porphyria cutanea tarda, variegate and erythropoietin)**	**Haemochromatosis**
Endocrine	**ACTH and MSH producing pituitary and other tumours , Addison's disease , ACTH therapy , Pregnancy , contraceptive pells ,estrogens and melasma**	
Chemicals	**Arsenic , Busulfan , bleomycin, cychlophosphamide, adriamycin, psoralin (Berloque and phytophotodermatitis**	**Minocycline, fixed drug eruption , barbiturates, phenolphthalein, phenothiazines , chlorpromazine .**
Physical	**UV light , ionizing radiation and trauma .**	
Nutritional	**Kwashiorkor , pellagra, sprue and Vit. B12 deficiency .**	**Chronic nutritional deficiency .**
Post-inflammatory	**Eczema , LP, DLE, lichen and macular**	**Pinta , erythema dyschromicum perstans .**

	amyloidosis , systemic sclerosis, morphoea .	
Tumours	**Malignant melanoma , Acanthosis nigricans with adenocarcinoma , malignant tumours .**	**Metastatic melanoma with melanogeuria .**

Facial melanosis :

It is hypermelanosis involving predominantly the face and the neck , relatively common and often presents a complex diagnostic problem , may be caused by :-

1. Genetic and racial factors are important (more in dark skin) .
2. Endocrine factors play a major role in melasma .
3. External agents (light and photodynamic chemicals) are essential in the occupational melanosis .
4. Cosmetics may occasionally cause facial melanosis .
5. It may be part of generalized melanosis e.g. addisonin pigmentation .

Melasma (Mask of pregnancy , chloasma):

Definition- it is a common acquired hypermelanosis seen mainly in women and occurs exclusively on the sun-exposed skin of the face , during the years of reproductive activity .

Aetiology- a. Genetic predisposition .

b.Pregnancy . c. Combined oral contraceptive pills . d. Ovarian disorders . e. Sun-light exposure . f. Endocrine causes .

Clinical features – the hypermelanosis affects the upper lip ,checks , forehead and chin , become more apparent following sun-light exposure , brown in colour , bilateral patches and frequently symmetrical .Clinically classified to three types : central (70%), maxillary (molar20%) and ramius (10%)type In some women it may be noticeable premenstrually . After labour or after stopping oral pills , the condition may fade but is often persistent . Up to10%of cases of melasma are seen in men particularly Latin Americans and those from Middle East or Asia .

Treatment- a variety of topical treatment are effective in lightening melasma , in combination with sun protective measures e.g. hydroquinone 2-4% , Retinoic acid 0.05% , 0.1% and sunscreens and cosmetic camouflage .

Hypomelanosis : of two types :

1. **Genetic and nevoid disorders .**
2. **Acquired hypomelanosis .**

1. Genetic and nevoid disorders :

a. Albinism (Oculocutaneous albinism ,OCA) :

There are many distinct types of OCA , each of which is characterized by partial or complete failure to produce melanin in the skin and the eyes . **Melanocytes are present** in normal distribution but fail to synthesize melanin adequately , these conditions are inherited as autosomal recessive disorders , one rare type with apparent autosomal dominant inheritance . OCA involved many types classified into :-

A. Tyrosinase negative albinism (hair bulbs after plucking and incubation with tyrosine fail to produce darkening) .
B. Tyrosinase positive albinism (plucked hair bulbs produce darkening) , this is the most common type .
C. Ocular albinism – only the eyes are clinically involved there are four different types (two X-linked , one Autosomal dominant and one recessive) .

Incidence : in UK 1/20000, USA and Caucasians 1/39000 , in Afro-Caribbean's 1/28000 and in Panama 63/10000 .

Clinical features – In all races there is marked dilution of the pigmentation of the skin , hair and eyes . In tyrosinase negative OCA the skin is pink , hair is white and the patients shows a prominent red reflex , this is the most sever variant of OCA . In tyrosinase positive OCA , some pigment is formed and with increasing age is to be found in the iris , skin and hair , latter often developing a flaxen-yellow colour , these patients may also tan , the iris is less translucent , and in black people the skin has a yellow –brown colour that with age develops dark-brown freckles and brown iris .

In both types , patients have **photophobia with a characteristic expression due to apparent squinting , errors of refraction** and almost all patients have horizontal or rotatory nystagmus , some times with head nodding .

In temperate climates , the prognosis for albino is good , but in tropics the fate of albinos is **grim** . At an early age most of them develop in solar exposed skin many actinic keratosis , SCC and occasionally , melanomas and death .

Treatment- no treatment is possible other than prescribing photoprotective preparations and limiting sun exposure , regular examination for the early detection and treatment of premalignant and malignant conditions of the skin .

b. Pibaldism :

Definition- it is a rare Autosomal dominant condition characterized by stable areas of vitiligo-like amelanotic skin associated with a white forelock . The incidence is less than 1/20000 , both sexes are affected equally and no race is spared . Ultrastructural studies have shown either an absence of melanocytes and melanosomes in the hypomelanotic areas or sometimes reduced numbers of abnormal large melanocytes and in the hypermelanotic islands in the areas of hypomelanosis , melanocytes are present that produce normal melanin .

Clinical features- patches of skin totally devoid of pigment are present at birth and usually remain unchanged throughout life , most common is a frontal median or paramedian patch , associated with a mesh of white hair (white forelock) , rarely this may be the only lesion , often , white patches occurs on the upper chest , abdomen and limbs , bilaterally but not necessarily symmetrically , occasionally on the face , particularly the chin . The hands , feet and back remains normal , islands of normal or hypermelanotic skin occurs in the white areas or less often on normal skin .

Diagnosis – D.D. vitiligo , nevus depigmentosus , albinism .

Treatment- only photoprotective preparations , cosmetic camouflage or skin dyes , skin grafts , minigrafts and grafts of autologous cultured melanocytes .

Vitiligo :

Aetiology- vitiligo affects all races , with 1% incidence of the world population , prevalence is 0.38% , more in pigmented skin races , both sexes are equally affected . About 30-40% of patients have a positive family history , the inheritance may be polygenic or determined by an Autosomal dominant gene of variable penetrance .

Various theories have been suggested for the aetiology of vitiligo :-

1. **Autoimmune hypothesis :** this is based on the clinical association of vitiligo with a number of autoimmune disorders e.g. thyroid diseases , pernicious anemia , Addison's disease , DM, hypoparathyroidism , myasthenia gravis , AA, morphoea , lichen sclerosus , halo nevus and malignant melanoma , with organ-specific autoantibodies .

2. **Neurogenic hypothesis –** this suggests that a compound is released at peripheral nerve ending in the skin , that inhibit melanogenesis and could have a toxic effect on melanocytes .
3. **Self-destruct theory of Lerner-** this suggests that melanocytes destroy themselves due to defect in a natural protective mechanism that removes toxic melanin precursors (chemical compounds causing vitiligo) .

Pathology- there is a marked absence of melanocytes and melanin in the epidermis . **E.M. shows replacement** of epidermal melanocytes by langerhans cells , the dermis shows lymphocytic infiltration in the upper dermis and in inflammatory vitiligo , there is a dense infiltrate of lymphocytes and histiocytes **.**

***Clinical features-* vitiligo** can begin at any age , but in 50% of cases it develops before the age of 20yeaes . The condition is gradually progressive , sometimes extending rapidly over a period of several months , sometimes and then remaining quiescent for many years . **Hypomelanotic macules** are usually first noted on the sun-exposed areas of skin ,on the face or on the dorsa of hands , these areas are prone to sunburn , rarely itching in the absence of sunburn may occur , **isomorphic or Kobner phenomenon is positive . The a melanotic macules in vitiligo** are found particularly in areas that are normally hyperpigmented , e.g. face , axillae, groins, areola and genitalla , also areas subjected to repeated friction and trauma are also likely to be affected : e.g. the dorsa of hands , feet , elbows , knees and ankle .

The distribution of the lesion is usually symmetrical , sometimes unilateral and may be dermatomal , rarely there is complete vitiligo . The pigment loss may be partial or complete , or both may occur in the same areas (trichrome vitiligo) . The macules have a **convex outline** , increased irregularly in size and fuse with neighboring lesions to form complex patterns , the hairs in the patches frequently remain normally pigmented , but in older lesions the hairs are often amelanotic , the margins of the lesions may become hyperpigmented , The main symptom is the cosmetic disability , but some patients presented because of sunburn in the amelanotic areas . Vitiligo commonly starts in children , who are likely to show segmental vitiligo , autoimmune disease or it have a family history of canities .

In 10-20% of patients , spontaneous regimentation is noted , particularly in sun-exposed and perifollicular areas , **premature graying , uveitis and deafness may be associated .**

Diagnosis- in DD. **piebaldism , TV. , lichen sclerosus , scleroderma , post inflammatory leukoderma , pityriasis alba , hypomelanotic macules in leprosy (**anesthetic) .

Treatment- the treatment of vitiligo is unsatisfactory , in sunny climates , sun screens are often necessary , which are of two types :

1. **Systemic –** a. **Psoraline (PUVA) ,** 4,5,8-trimethylpsoralin , 8-methoxypsoralin or 5-methoxypsoralin combined with exposure to sunlight or to light sources (long wave UV light) , dose of psoralin is 0.6mg/kg – 2hours before carefully controlled graduated exposure to sunlight , preferably around midday , continued for at least 6months and some times for several years . **b. Corticosteroid –** oral prednisolone or IM. Flucenolone acetonid .
2. **Topical -** ***Psoralin** –with or with out UVA (may cause blistering) .

   ***Narrow band UVB 311nm** phototherapy .

   ***Topical potent corticosteroid –** e.g. 0.1%betamethasone valerate and 0.05%clobetasol dipropionate .

   ***Topical 5% iodine tincture .**

3. Skin grafting , minigrafts and autologus cultured melanocytes (may cause Kobner phenomenon) .

Inpatients with extensive vitiligo , and only a few residual areas of hyperpigmentation , **skin bleaching creams** , such as 20%monobenzylether of hydroquinone are of use (benaquine) , to render the hole skin whit .

Halo nevus :

Definition :- Is a halo of hypopigmentation around a central Cutaneous tumour , usually a benign melanocytic nevus , neuroid nevus , blue nevus , neurofibroma , primary or secondary malignant melanoma , usually seen in children or young adults of either sex . It is frequent in patients with certain organ –specific autoimmune disorders as dose vitiligo.

Pathology- is of compound nevus with lymphocytic infiltration and absence of melanocyte in depigmented halo .

***Clinical features* –** consists of circular areas of hypomelanosis occurs around pigmented nevi , particularly on the trunk , less commonly on the head and rarely on the limbs , multiple lesions are common , the halos being about 0.5-1cm , usually seen in young people , the nevus tends to flatten and may disappear completely .

***Treatment* –** normally none is required ,or treated as in vitiligo .

Acquired hypomelanosis:

***Endocrine –** hypopituitarism , Addison's disease , thyroid diseases .

***Chemical factors-** occupational and therapeutic leukoderma , e.g. monobenzylether of hydroquinone , monomethylether of hydroquinone , chloroquine and hydroxychloroquine , arsenic , phenolic germicidal (no treatment is effective) .

***Nutritional factors –** chronic protein deficiencies , pernicious anemia .

***Post-inflammatory and infections-** eczema , pityriasis alba , psoriasis , TV, pinta , syphilis , yaws , leprosy , sarcoidosis , DLE , LP .

***Neoplasms-** halo nevus , malignant melanoma .

***Miscellaneous-** idiopathic Guttate hypomelanosis .

Tattoos:

1. **Accidental tattoos-** is an introduction of pigmented particles accidentally as contaminants of wounds or may at high velocity penetrate previously intact skin , producing a disfiguring tattoos . The lesions are treated by surgical excision , laser or by dermabrasion .
2. **Therapeutic agents tattoos -** e.g. iron salts used as solutions of ferric sulphate and ferric chloride in the treatment of dermatitis , give a reddish – brown tattoos .
3. **Cosmetic tattoos** – introduce substance like carbon for cosmetic purposes .

Complications :

Unhappiness , psychological and social burden , introduction of infections (bacterial, TB, syphilis, hepatitis B, HIV) , allergic reactions to pigments .

Treatment- surgical excision and grafting , laser , dermabration .