



Changes in color of the skin and systemic disease

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Abstract When looking for diseases of the skin, this is usually done in a holistic way, automatically and unconsciously, by recognizing localization, distribution, and appearance of the primary or secondary skin lesions. When Robert Willan (1757-1812) introduced the concept of morphology of skin lesions, it became the basis for the classification of dermatoses. Apart from ethnic factors, the various dermatoses comprise a rainbow of colors ranging from the most common red color to yellow, blue, brown, silver, green, black, and white.

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Introduction

The color of the skin is part of the individual identity and a lifelong ethnic signature. It is genetically fixed, diffuse, and permanent for life. This results from the distribution of pigment and structural elements of the skin, its density, packing of layers and the transparency through, and the reflection of light from the skin.

Unfortunately, ethnic color is often a reason for racism and disregard between so-called “white, yellow, brown/black, or red races.” The word “race,” however, should be discarded today and replaced by the term “biologic diversity,” which is a positive and colorful annotation of humankind.

Pathophysiology of skin color

From the broad spectrum of electromagnetic waves from x-rays to radio waves, only a small spectrum from the end

of ultraviolet (about 380 nm) to the beginning of infrared (about 760 nm) can be seen. The color that is seen is not just a characteristic emission of electromagnetic waves from the object but is also a question of the recipient’s eye, including the physiologic receptors, so-called cone cells with different spectral sensitivities, and their work up through the brain, which results in trichromatic color vision. In animals, evolution has adapted the visible spectrum according to their environmental needs. Deep-water fishes, being equipped with one receptor type only, see monochromatic darker or lighter gray, whereas most primates, including humans, see trichromatic; reptiles, birds, or insects see tetrachromatic; butterflies even see pentachromatic. The color that is seen is due to the reflection of light. It is not only a question of the object or subject being viewed but also a question of perception.

Changes of skin color due to diseases

From the earliest days of the study of skin diseases, color has played a role, however erratic and incomplete. Robert Willan (1757-1812) in “Description and Treatment of Cutaneous Diseases” (1798-1808) uses the changes of color in

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his descriptions. Mention of color has continued throughout the development of dermatology. When looking for diseases of the skin, it is usually done in a holistic way, automatically and unconsciously, by recognizing localization, distribution, and appearance of the primary or secondary skin lesions. Other less obvious parameters, like immunologic, molecular, genetic, or other background parameters, also could serve as a grid for classification of dermatoses.

Concerning color as a major criterion for differentiating various afflictions of the skin, there are many variations, which would be even broader if people could perceive electromagnetic waves beyond (x-rays) and above (infrared and radio waves) the visible wavelengths. The reasons for the various colors of dermatoses are due to the structure and functions of the various morphologic elements of the skin:

- the thickness of the horny layer
- the distribution of the melanin in the epidermis
- the dense or loose (edematous) texture of the connective tissue
- the superficial network of capillaries
- the type and density of cellular infiltrate
- the extravasation of fluid (edema) and red blood cells
- the granulomatous infiltrates
- the deposits of foreign bodies (ie, iron, fat, pigment, plus several physical and optical effects, which result in blue, brown, white, red, yellow, gray, or black dermatoses: a “cutaneous rainbow”)

The color of the skin may change over time, locally or generally, due to various diseases:

- Primary: Skin diseases with extracutaneous involvement.
- Secondary: Systemic diseases with skin involvement.

Fortunately, or unfortunately, classifying dermatoses on the basis of their color may be an interesting exercise; unfortunately, it often has little practical diagnostic impact.

The various colors

Red

The most frequent discoloration of the skin seen in conjunction with several systemic diseases (Figure 1):

- Atopic dermatitis.¹⁻³
- Lupus erythematosus (LE): An autoimmune disease attacking several organs, preferentially kidney and heart.
- Amyloidosis: Bluish-red discoloration around the eyes.^{4,5}
- Vasculitis: Presentation of petechiae or bluish-red patches and involving also the kidney, gut, and other organs.
- Erythromelalgia: A rare inherited neurovascular disease, showing paroxysmal painful swelling and erythema of the extremities and ears.⁶⁻⁸



Fig. 1 Red skin lesions. Erythropoietic protoporphyria (upper left); specific skin infiltrates in myelomonocytic leukemia (upper right); Amyloidosis (lower left); Blastic plasmacytoid dendritic cell neoplasm (CD4 ++; CD54 ++) (lower right).



Fig. 2 Yellow skin lesions: Psoriasis (upper left), linear tendinous xanthomas (upper right), xanthelasma (lower left), necrobiotic xanthogranuloma (lower right).

- Erythropoietic protoporphyria: Induction of non-blistering burning and redness in UV(A) exposed areas. Even though the basic defect lies in the porphyrin–metabolism–cascade of red blood cells, it also may secondarily affect the liver.⁹
- Palmar erythema: Found in rheumatoid arthritis, hemochromatosis, diabetes mellitus (rubeosis diabetorum of the palms and cheeks), primary or metastatic brain neoplasms, and alcoholics (ie, hepatic cirrhosis, pancreatitis, generalized lipomatosis, neuropathy, and malum performance).^{10,11}
- Red cheeks: Patients with mitral valve stenosis showing redness of the cheeks and resembling systemic lupus erythematosus or rubeosis diabetorum.
- Red man syndrome: Erythroderma due to a vancomycin drug reaction.
- Erythroderma: Found in Sézary’s syndrome and sometimes in other disease, including atopic dermatitis or pityriasis rubra pilaris. Whereas in Sézary’s syndrome the involvement of lymph nodes and peripheral blood is an integral part of the disease, additional systemic involvement is not necessarily present in other “red men” syndromes.¹² Some hematopoietic disorders show a very distinct red color. Specific skin infiltrates in myelomonocytic leukemia display very typical rusty-brown papules.^{13,14} Blastic plasmacytoid dendritic cell neoplasm (CD4+; CD54+) due to the extravasation of erythrocytes in the upper portion of the dermis presents as widespread confluent contusiform red-brown patches and plaques.^{15,16}

Yellow

The color is due to the thickening and apposition of the horny layer, involving lipids deposition, deposition of pigment (melanin or iron), or changes in the dermal texture as in solar elastosis (Figure 2):

- Psoriasis: Thick hyperkeratosis of the untreated plaques appearing yellow or light-gray.^{17,18}
- Yellow nail syndrome: Association with such pulmonary disease as bronchiectasis and pericarditis.^{19–22}
- Xanthomas and xanthelasma.
- Necrobiotic xanthogranuloma: Belongs to the non-Langerhans cell histiocytoses. It shows periorbital lesions in most cases and is frequently associated with hematopoietic disorders, monoclonal gammopathy, and involvement of the liver, brain, and other organs.^{23–25}
- Jaundice: Underlying disorders in the bilirubin metabolism, hepatocellular dysfunction, or biliary obstruction, when the serum bilirubin level exceeds 2.5 to 3 mg/dL.
- Carotenemia: Excess uptake of carotenoids in vegetables or drugs, where, in contrast to jaundice, conjunctivae are spared in carotenosis.²⁶

Blue appearance

This is due to distinct vascular structures or deposits of dense and densely packed dermal pigment, as found in the blue nevus of Jadassohn (Figure 3):



Fig. 3 Blue and brown: tuberculoid lepra (left); pellagra in an alcoholic (right).

- Cyanosis of acral regions of fingers, toes, nose, and ears: A leading sign in progressive systemic sclerosis (Raynaud syndrome) that also involves the gastrointestinal tract, lungs, kidney, heart, and other organs.²⁷
- Blue rubber bleb nevus syndrome: A sporadic or inherited venous malformation with ectatic venous-like channels, predominantly on the palms and soles and associated with malformations of other organs, such as in



Fig. 4 Silver-gray skin color: diffuse amyloidosis (left); ashy dermatosis (right).

the gastrointestinal tract, causing bleeding and anemia.^{28,29}

- Lupus vulgaris or tuberculous leprosy: Deep-seated granulomas that may have a bluish appearance.
- Amiodarone: Phototoxic blue-gray skin discoloration.
- Patent blue: Used for detecting sentinel lymph nodes in neoplasms, causing prolonged skin discoloration at the site of the injection or even systemically due to accidental arterial injection.³⁰

Brown appearance

(Figure 3):

- Most nevi.
- Fixed drug reaction.
- Neurocutaneous melanosis: Characterized by the involvement of the skin and the central nervous system. It is associated with a high risk for melanoma, seizures, and hydrocephalus.^{31,32}
- Pellagra: A primary or secondary phenomenon involving depletion of niacin, a component of the vitamin B complex, due to abnormal nutrition (primary pellagra) or the malabsorption seen, for example, in alcoholics (secondary pellagra). Besides systemic disturbances, like diarrhea and bleeding, the skin in sun-exposed areas shows typical eczematous brown-red mahogany discoloration.³³

Silver, “dirty,” ash-gray

(Figure 4):

- Erythema dyschromicum perstans (“ashy dermatosis”) without any systemic involvement.
- Amyloidosis: Diffuse silver-gray patches due to deposition of amyloid in the papillary dermis in patients with plasmacytoma.³⁴
- Medication containing silver compounds.
- Occupational hazard with long-term contact with silver at the working place with cysteine-bound silver transported into the skin.³⁵ A photochemical reaction induces the deposition of tiny silver grains, especially to elastic fibers and basement membranes around blood vessels, adnexal structures, and preferentially in the sclera.
- Ocular argyrosis: A mimic of conjunctival melanoma.³⁶ “Black tears” are due to ocular argyrosis.³⁷ Differential diagnosis includes chrysiasis, cyanosis, and alkaptonuria.

Green appearance

- Chemical reaction of nails or hair after external contact with copper sulfate used for reducing algae in swimming pools or from washing hair with water running through old copper pipes³⁸ and without systemic clinical manifestations.
- Green nails: Due to local *Pseudomonas aeruginosa* infection.³⁹



Fig. 5 Black skin color: lingua villosa nigra (left); ochronosis (right)



Fig. 6 White spots in pseudoleukoderma angiospasticum in a patient with Waldenströms macroglobulinemia

Black discoloration

(Figure 5):

- Compact hyperkeratosis or deposition of pigment in the dermis, as in tattoos or melasma.
- Ichthyoses: Diffuse compact thickening of the horny layer, giving the skin a dirty-black appearance.
- Acanthosis nigricans: Strip-like hyperkeratosis with pigmentation in the basal layer with a malignant variant associated with paraneoplasia.^{40,41}
- Oral discoloration: Associated with minocycline, sometimes present in younger patients with minocycline. Also with tetracycline and its compounds in 5% of patients under 12 where the incorporation of the insoluble chelation of iron and melanin into teeth, the mucogingival junction, sclera, skin, nails, and bone result in black-brown discoloration, which may be temporary or permanent, depending on the doses and duration of exposure.^{42,43}
- Lingua villosa nigra (black hair tongue): Due to filiform hyperkeratosis in the proximal part of the tongue. This also is not directly linked to a systemic disorder but indirectly through the indication for taking or sucking antibiotics, chemotherapeutic drugs or disinfectious mouthwash. A predilection for smokers.^{44,45}
- Ochronosis: Circumscribed black discoloration of the skin, occurring more often in darker pigmented people exposed to phenol, trinitrophenol, resorcinol, mercury,

picric acid, benzene, hydroquinone, quinine, or other antimalarial drugs.^{46,47} Also found in alkaptonuria, an autosomal recessive metabolic disorder (endogenous ochronosis), leading to generalized deposits of homogentisic acid in soft tissues, preferentially in cartilage, joints, sclerae, and skin.⁴⁸

White spots or patches

(Figure 6):

- Vitiligo: Not always a skin disease, it may be associated with various syndromes, such as Vogt-Koyanagi-Harada disease and Alezzandrini, Kabuki, and MELAS syndromes.⁴⁹ There is a long list of comorbidities of vitiligo. Autoimmune diseases are found in about 20% of patients,⁵⁰ comprising autoimmune thyroiditis, alopecia areata, diabetes mellitus, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, Addison's disease, inflammatory bowel disease, Sjogren's syndrome, dermatomyositis, scleroderma, ocular and audiological abnormalities, and atopic dermatitis.⁵¹
- Albinism: Association with several syndromes, including Chediak-Higashi syndrome, Hermansky-Pudlack syndrome, Griscelli syndrome, Elejalde syndrome, and Cross-McKusick-Breen syndrome.⁵²
- Hypopigmented ("white"): An important hint for infectious diseases such as leukoderma syphiliticum or leprosum.

- Pseudoleucoderma angiospaticum: White-checked patches over the palms, soles, buttocks, and flexural areas of the arms and legs, resulting from central arteriolar spasm with peripheral vasodilatation and not linked to any systemic disorder.
- Waldenström's macroglobulinemia: Exposed acral areas to low external temperature and expressing patchy leukoderma, due to small intravascular emboli in the draining arterioles and vasculitis, blocking blood flow in the dermal capillaries (Figure 6).⁵³

The pathophysiology background of the varying skin colors largely depends on one or mostly multiple morphologic components, in which all structural levels of the skin are involved:

- Horny layer: thickness and structure
- Epidermis: thickness and pigment
- Dermis: thickness, vascularization, edema, structure, and pigment
- Cellular infiltrate: composition and structure (granulomatous), depth of infiltrate, and density
- Deposits: melanin and other endogenous (lipids, iron) or external pigments, pus, serum, and blood
- Filtering effects due to the Tyndall phenomenon

Conclusions

Making a correct diagnosis involves observing not only the local and gross morphology but also the color of the skin. Apart from ethnic factors, the color due to various physicochemical parameters provides additional information related to the histopathologic substrate underlying the skin lesions. Changes in the structure and pigmentation of the epidermis, dermis, dermal constituents, and subcutis may provide a rainbow, which extends from the most common red to yellow, blue, brown, silver, green, black, and white. Observing these changes in color may help in determining the comorbidities or extracutaneous involvement of many skin diseases and the extent of accompanying systemic diseases.

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