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The actions of melanin and melanocyte stimulating hormone (MSH)

Natalie Rasmussen, Francine Nelson, Piyarat Govitrapong & Manuchair Ebadi
Department of Pharmacology, Physiology, and Therapeutics, University of North Dakota School of Medicine and Health Sciences, Grand Forks, North Dakota, 58203, USA.

Correspondence to: Manuchair Ebadi, Ph.D., Professor and Chairman,
Department of Pharmacology, Physiology, and Therapeutics,
University of North Dakota School of Medicine and Health Sciences,
501 North Columbia Road, Grand Forks, ND 58203, USA.
TEL: +1 701 777 2284; FAX: +1 701 777 6124;
E-mail: mebadi@medicine.nodak.edu

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Abstract

The skin, the largest organ of the body, plays an important role in the total metabolism of several hormones. **Melanin**, the major product of the **melanocyte**, is largely responsible for the coloring of skin. Melanin is a complex of insoluble, polyquinone, brown or red pigment and protein, formed by the oxidation of tyrosine and 3,4-dihydroxyphenylalanine in the presence of **tyrosinase**. There exists two main groups of melanin: the black to dark-brown insoluble **eumelanins** and the yellow to reddish brown, alkali-soluble **pheomelanins**. MSH, ACTH and β-lipoprotein are able to influence skin pigmentation. The functions attributed to melanins are acting as a barrier against ionizing radiation; participating in developmental processes, serving as a cosmetic entity, and scavenging cytotoxic radicals and intermediates. Melanocytes express numerous receptors that allow interaction with other cells in their microenvironment, including **keratinocytes** and the immune component of the skin **Langerhans cells**. **Albinism** represents a group of inherited abnormalities that present with congenital hypopigmentation that can involve the skin, hair, and eyes (**oculocutaneous albinism**) or be limited primarily to the eyes (**ocular albinism**). The inherited disorders of keratin include **epidermolysis bullosu simplex** causing cell degeneration within the basal layer. Sunlight and ultraviolet radiation from artificial light sources could be tonic or toxic to human skin. The harmful effects of solar radiation are skin cancer, photosensitivity diseases, sunburn, photoallergy, photoimmunologic alterations, cataracts, mutations, skin aging and phototoxicity. Sunscreen chemicals protect the skin against ultraviolet radiation.

Introduction

The skin, the largest organ of the body, plays an important role in the total metabolism of several hormones. The skin is unusually heterogeneous in its cellular composition, comprising of proliferating, keratinizing, epidermal and hair follicle cells, lipid-synthesizing sebaceous glands, pigment-producing melanocytes, and dermal connective tissue cells responsible for the production of fibrous tissue and ground substances. Each cell type has its own unique metabolic pattern, and therefore the integument is capable of a wide variety of biochemical activities (see Fig. 2).

The metabolic activities of skin are under hormonal regulation. The control of cutaneous pigmentation by **melanocyte-stimulating hormone (MSH)** is well known, as are the stimulatory effects of **androgens** on sebaceous glands and certain hair follicles. The hormonal regulation of constitutive and facultative melanin pigmentation in humans may best be summarized as one of a gradual shift from that of a central control predominantly by hormones disseminated from the pituitary gland toward one of a local (peripheral) control by regulatory factors synthesized within the skin. Snell [1] summarized the prevailing consensus about the action of hormones on mammalian melanocytes, particularly on those of human subjects. Injection of human subjects with the melanotropins α-MSH and β-MSH elicits a darkening of skin that results from elevated melanogenesis within epidermal melanocytes and increased transport of melanocyte-derived melanosomes within keratinocytes. Cutaneous hyperpigmentation is also observed when human subjects are injected with high doses of adrenocorticotropic hormone (ACTH). The influence of the exogenous melanotropins and ACTH is most evident in dark-skinned individuals of African descent.

Hydrocortisone of adrenal origin was considered to inhibit melanogenesis indirectly by inhibiting the release of the melanotropins and ACTH from the pituitary gland. Female sex hormones (estrogen and progesterone) circulating at high titers in the blood were thought to be important agents in producing the characteristic hypermelanization of the nipples and areolae and more variable darkening of the facial skin, abdominal midline, and genitalia. It was speculated that the melanotropins assisted the sex hormones in darkening skin during pregnancy, but a major role was doubted. Snell [1] concluded that "surprisingly little is known about the hormone control of pigmentation in mammals." Although our knowledge of endocrinology has mushroomed since 1967, almost inconceivably, our understanding of the hormonal regulation of human pigmentation has become less clear.

At present, it is generally agreed that the adult human pituitary produces significant quantities of only two hormones ACTH and β-lipotropin (LPH), with potential melanotropic activity [2, 3]. They do not appear to influence melanin pigmentation in normal humans. This reassessment of pituitary function was stimulated by the demonstration that melanotropins, lipotropins, and corticotropins are derived from a single prohormone designated as **pro-opiomelanocortin** [4].

The various hormones are released from the prohormone by a selective enzymatic cleavage of the molecule and certain of its cleavage products. α-MSH, β-MSH, α-LPH, and β-LPH as well as endorphin are produced in this way. In vertebrates, the intermediate lobe of the pituitary is the site where ACTH, cleaved from pro-opiomelanocortin, is further divided into α-MSH and corticotropin-like protein. The absence of significant amounts of α-MSH in the adult human pituitary has been attributed to the lack of an organized intermediate lobe [2, 3].

Hadley [2] has concluded that α-MSH is not produced in significant amounts within the human pituitary. In addition, it was stated that there is no evidence that β-MSH serves any peripheral physiological function other than as a necessary secretory by-product of other hormones derived from the melanotrophs and corticotrophs. He also maintains that γ-MSH released from pro-opiomelanocortin has very little melanocyte-stimulating capacity. However, it must be recognized that disagreement exists over what quantities of α-MSH may be synthesized by the pituitary and whether or not measurable amounts of it circulate in the blood of adult humans [5]. Furthermore, it appears that ACTH and β-LPH of pituitary origin can influence skin pigmentation, but only at blood titers considerably higher than those maintained by the normal pituitary, making it unlikely that these hormones modulate constitutive skin color.

In contrast to the adult, an intermediate lobe is present in the pituitary of the human fetus and has been demonstrated to contain measurable α-MSH, suggesting that pituitary-derived α-MSH may influence the developing melanocyte system. α-MSH has been reported to be produced by normal human skin and, in pregnant women, by the mother's pituitary gland, the placenta, and the fetal pituitary gland. Therefore, circulating α-MSH may augment estrogen and progesterone in stimulating the region-specific darkening of maternal facial skin, nipples, genitalia, and midline of the abdomen observed during pregnancy. The darkening of facial skin in pregnant

women may require exposure to UVR in addition to sex hormones possibly augmented by α-MSH. Apart from pregnancy, sex hormones appear to have little influence on the constitutive color of the skin of humans at any age. However, change in melanin pigmentation is observed during the menstrual cycle in females or following castration of males.

Hormonal control of constitutive- and facultative melanin pigmentation of human skin

Marked regional variation exists in the sensitivity of certain melanocytes to specific hormones. For example, during pregnancy estrogens and progesterones stimulate melanogenesis in melanocytes of the areolae and nipples and to a lesser extent in those on the face, midline of the anterior abdominal wall, and genitals [6]. Three pituitary hormones, **ACTH, α-MSH,** and **β-MSH**, are capable of causing generalized hyperpigmentation in humans. A 13 amino-acid polypeptide, α-MSH has the same sequence as the first 13 amino acids of ACTH, while human β-MSH consists of 22 amino acids whose arrangement is almost identical to the first one-third of the ACTH polypeptide. The skin of humans given injections of MSH begins to darken in 24 hours, and continued daily doses increase the general darkening until the hormone is discontinued, following which normal color returns in 3-5 weeks. The pigmentation in these subjects is most pronounced over the face and mucous membranes and within nevi. Similar pigmentation occurs following ACTH administration, but massive doses (2,400 units/day) must be used.Normal human pituitary glands contain α-MSH and β-MSH as identified and quantitated by radioimmunoassay. β-MSH accounts for 98% of the MSH activity, while α-MSH contributes 2%. In view of the predominance of β-MSH in the human pituitary and the somewhat unphysiologic amounts of ACTH required to cause hyperpigmentation, it is generally accepted that β-MSH plays the major role in maintaining human pigmentation.

Patients with adrenal cortical insufficiency develop diffuse darkening of the exposed parts, such as face, neck, arms, and dorsum of the hands, as well as the axillae, palmar creases, anogenital region, and buccal mucosa. Nevi darken, new ones may appear, and occasionally darkening of nevi occurs several years before any other pigmentary changes. Scars that develop after the onset of adrenal insufficiency become hyperpigmented as well. Hair becomes darker and longitudinal pigmented bands are observed on the nails. The pigmentary changes are brought on by increased levels of MSH and ACTH in the plasma. Diminution of plasma levels of cortisol provokes a compensatory increased release of pituitary MSH and ACTH, probably mediated through the activation of the respective hypothalamic releasing factor(s) (see Fig. 1).

The importance of skin in metabolism

The epidermis is capable of metabolizing carbohydrate by the same pathways as do other tissues, in order to provide not only energy (ATP) for the synthetic, and energy-requiring processes, but also for the synthesis of various intermediate substances utilized by epidermal cells. Biochemical studies on human and experimental animal epidermis have verified the presence of the anaerobic glycolytic pathway, the oxidative phosphorylative hexose monophosphate shunt, and tricarboxylic acid cycle.

The epidermis is also an active site of sterol, fatty acid, and polar lipid synthesis, utilizing pyruvate, some amino acids, acetate, and glucose as substrates. Glucose, however, seems to be the major precursor of lipogenesis, being the only compound that stimulates this process *in vitro*. Glucose also appears to regulate lipogenesis *in vivo*, since glucose feeding accelerates cutaneous lipid synthesis, while fasting produces the opposite effect [6].

Replacement therapy with corticosteroid produces a gradual diminution of the hyperpigmentation. In the treated Addisonian patients, a waxing and waning in the intensity of pigmentary change may be one of the most sensitive indices of changing requirements in the maintenance dose of steroids and so provides an objective criterion for increasing medication.

Generalized hyperpigmentation like that seen in **Addison's disease** also occurs in some patients with **Cushing's disease** who undergo bilateral adrenalectomy and in the ectopic ACTH syndrome caused by various neoplasms, such as carcinomas of the lung, liver, pancreas, and thymus. In each of these instances, plasma ACTH, α-MSH, and β-MSH have been characteristically elevated. The pigmentary changes are due to β-MSH, because the quantity of ACTH and α-MSH is too small to account for the amount of melanocyte-stimulating activity. Pituitary tumors emerging after adrenalectomy are associated with marked hyperpigmentation, amenorrhea, and local pressure signs of an expanding pituitary lesion.

The hyperpigmentation in pituitary tumors exceeds that found in any other condition and is also associated with the highest blood levels of ACTH and MSH. Radioimmunoassays of tumors taken from hyperpigmented patients with the ectopic ACTH syndrome show large concentrations of

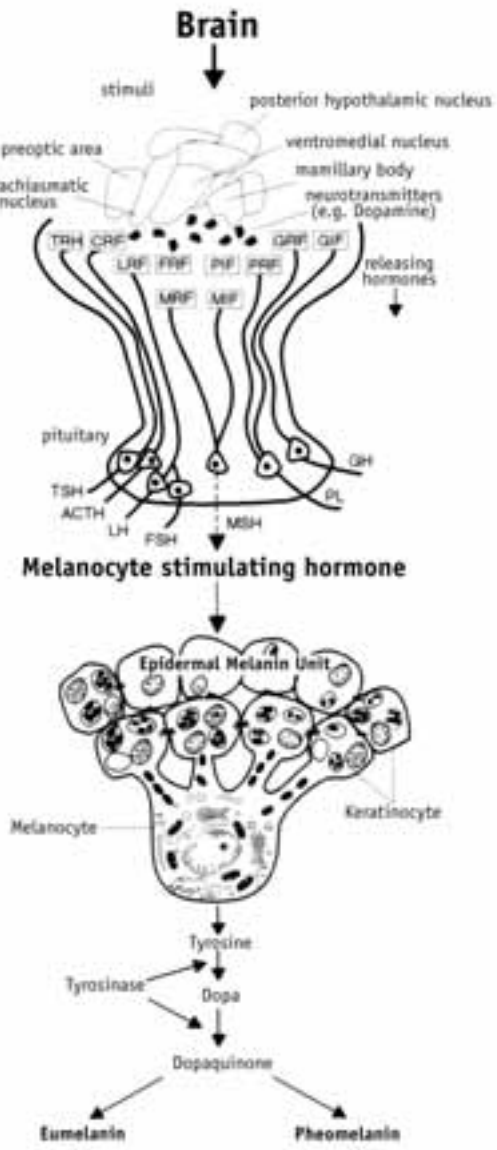


Fig. 1. The involvement of melanocyte stimulating hormone in pigmentation. Hypothalamic peptides are released into the hypothalamic-hypophyseal portal circulation, and this provides the means by which the central nervous system (CNS) communicates with the anterior pituitary and the peripheral endocrine organs. Releasing and trophic hormones in modulating endocrine functions are: TRH = thyrotropin-releasing hormone; CRF = corticotropin-releasing factor; LRF = luteinizing hormone-releasing factor; FRF = follicle-stimulating hormone-releasing factor; MRF = melanocyte stimulating hormone-releasing factor; PIF = prolactin-inhibiting factor; MIF = migration-inhibitory factor; PRF = prolactin-releasing factor; GRF = growth hormone-releasing factor; GIF = growth hormone-inhibitory factor; TSH = thyroid-stimulating hormone; ACTH = adrenocorticotropic hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; MSH = melanocyte-stimulating hormone; PL = prolactin; GH = growth hormone.

β-MSH, suggesting that these nonpituitary neoplasms are capable of synthesizing this hormone. Such observations clearly account for the raised plasma levels of this polypeptide and the associated cutaneous pigmentation. In some patients, surgical removal of the tumor has resulted in reversal of cutaneous pigmentation.

The close biologic relationship among α-MSH, β-MSH, and ACTH can be appreciated from consideration of the fact that all these hormones are found to accompany each other not only in pituitary tissue but also in tumors associated with the **ectopic ACTH syndrome**, even though the tumors themselves arise from a variety of tissues. One could speculate, therefore, that the synthesis and secretion of these three polypeptides may be controlled by some common mechanism.

Chronic **hyperthyroidism** can be complicated by generalized hyperpigmentation similar to that seen in Addison's disease. This pigmentation is caused by increased MSH secretion by the pituitary.

Sex hormones have long been known to play an important role in the development of secondary sexual characteristics by influencing hair growth and sebaceous gland activity, but the skin has also been noted to participate actively in the metabolism of several hormones including testosterone, progesterone, estrogens, and cortisol. Several examples can be cited to demonstrate how hormones may affect cutaneous glucose and lipid metabolism. Glucose uptake and utilization and cutaneous lipogenesis are severely impaired in both diabetic humans and experimental animals. **Thyrotoxicosis** in animals has been shown to stimulate cutaneous respiration as well as to augment glucose assimilation and aerobic metabolism. **Testosterone** and **progesterone** significantly accelerate sterol ester synthesis via the Kandutsch-Russell pathway. **Estrogen** inhibits steroidogenesis and concomitantly causes thinning of the epidermis. This decrease in epidermal thickness in relation to alterations in sterol metabolism emphasizes the critical role sterols and their esterification play in the process of epidermal maturation and keratinization.

In view of the fact that the skin constitutes 15% of the total body weight, its role in overall body hormone homeostasis and metabolism may be more important than has been assumed. The skin is capable of both activation and inactivation of steroid hormones. Several pairs of steroids are known to be reversibly transformed in the skin, including cortisol and cortisone, testosterone and androstenedione, and estradiol and estrone. The equilibrium of these reversible reactions appears to favor oxidative formation of ketones which are less active hormones. Indeed, cortisone has less anti-inflammatory activity than cortisol; androstenedione is less androgenic than testosterone; and estrone is less estrogenic than estradiol. In some instances, however, the reverse reductive reactions occur in the skin or mucous membranes, transforming the steroids into more active products. This has been shown, for example, in human vaginal mucosa, where the main product of the interconversion of estrone and estradiol favors the stronger estrogenic substances, estradiol, but not in human abdominal skin and foreskin, which produce primarily estrone. Another such example is found in

Table 1: The Effects of Various Hormones on Skin Pigmentation

Hormones	Human Skin	
	Increased Pigmentation	Decreased Pigmentation
ACTH		+ (in large doses)
α-MSH	+	
β-MSH	+	
Estrogens	+	
Progesterone	+	
Thyroxine	+	
Epinephrine	No effect	No effect
Norepinephrine	No effect	No effect
Hydrocortisone	No effect	No effect

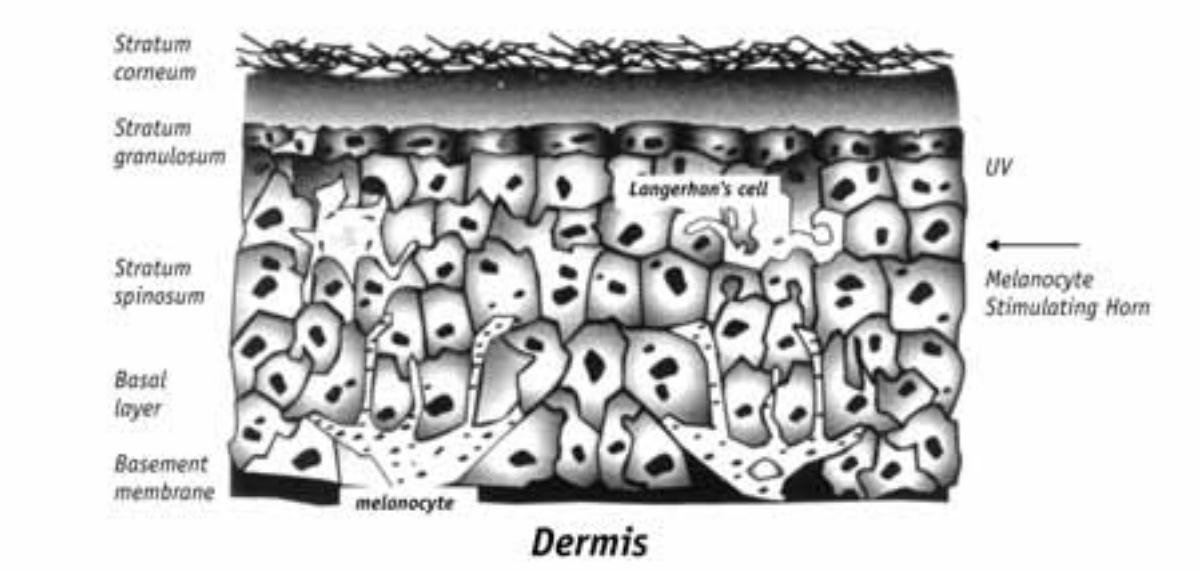
the ability of both male and female skin to form testosterone from the relatively weak androgen, 5α-dihydrotestosterone. It would appear that dihydrotestosterone is the most important androgenic metabolite in human skin, and, as in the case of the prostate gland, it may be the active form of androgenic hormone at the tissue receptor site [6].

Excessive quantities of **corticosteroid** depress proliferation of fibroblasts and inhibit the deposition of both collagen and mucopolysaccharides. Cortisol also accelerates degradation of collagen as evidenced by an increase in soluble collagen.

Excessive quantities of **growth hormone (GH)** cause fibroblastic proliferation and increased quantities of collagen and mucopolysaccharides to accumulate in the skin. In addition, hyperplasia of the epidermis and dermal appendages such as the pilosebaceous structure is seen.

Thyrotoxicosis manifests itself in the skin by its warm, moist, soft, and smooth texture related primarily to the peripheral vasodilation and increased blood flow. The changes in the skin have been linked to that of an infant's integument (see also Table 1). The skin in hypothyroidism contains large amounts of hydrophilic hyaluronic acid which is responsible for the puffy, doughy, non-pitting, edematous features of the skin [6].

In humans, increase or decrease in pigmentation initiated by the presence of too much of, or the absence of certain hormones, such as ACTH, MSH, estrogen, and progesterone, may partially be due to the movement of melanin granules, but it is more likely such changes in pigmentation are the result of alterations in the rate of melanin synthesis and melanin transfer to epidermal cells. MSH increases cAMP in experimental melanomas, and it is possible that the nucleotide is responsible for initiating tyrosinase synthesis and melanin production in human melanocytes. The administration of α-MSH to humans results in hyperpigmentation in several days, characterized histologically by increased numbers of melanin granules in the dendrites of melanocytes as well as in epidermal cells.



The interaction among melanocytes, keratinocytes, and Langerhans to synthesize melanin and cause visible pigmentation.

Fig. 2. Melanocyte functional unit. The skin is a complex system influenced by many external environmental factors. The melanocyte functional unit consists of melanocytes (M), keratinocytes, Langerhans cells (L), and other cells that produce factors regulating pigmentation, as indicated in the Figure. (See text for detailed discussion.) The melanocytes reside in the basal layer with dendritic projections into the stratum spinosum of the epidermis.

Biochemistry and melanin synthesis

Melanocytes are dendritic cells with two embryonic origins (see Fig. 2). Melanocytes originating in the neural crest during embryologic development subsequently migrate throughout the developing organism to three principal locations: the skin (at the epidermal-dermal border), the eyes (in the choroid and iris stroma), and the hair follicles. Melanocytes in the retinal pigment epithelium are derived from neuroectoderm as cells originating from the outer layer of the developing optic vesicle. Melanin is produced by melanocytes in specific subcellular organelles called "**melanosomes**," and can be of several types, with differing visible colors and, presumably, distinct functional properties. Melanin has several functions. They are:

- a barrier against ionizing radiation;
- a participant in developmental processes;
- a cosmetic entity;
- a potential scavenger of cytotoxic radicals and intermediates.

Melanocytes express numerous receptors that allow interaction with other cells in their microenvironment, including **keratinocytes** and the immune component of the skin—the **Langerhans cell**. Furthermore, in various disease conditions the skin can be infiltrated by other cell types, such as lymphocytes or macrophages, or by foreign cells penetrating a breach in the integrity of the skin. These cells can also secrete factors that bind to receptors on the melanocyte and thereby induce the melanocyte to increase or decrease its melanogenic activity. The receptors expressed on melanocytes allow these cells to respond to a wide variety of regulatory factors, including various growth factors, hormones, interferons, interleukins, prostaglandins, retinoic acid, and a host of other cytokines. Melanocytes produce some of these factors, which then function in an autocrine manner. Therefore, the melanocyte is in a highly dynamic equilibrium with different cell types in its immediate environment, all of which participate in determining its melanocyte activity.

The chemical reactions involved in the production of melanin from the amino acid tyrosine (Fig. 3) were actually described many decades ago, but only recently has the underlying complexity of the regulatory controls involved in melanin synthesis been described.

The copper-containing enzyme tyrosinase (EC 1.14.18.1) is critical to melanin formation due to its ability to catalyze the first reaction in the biosynthetic sequence—the hydroxylation of tyrosine to DOPA. This is the most critical reaction, since the spontaneous rate of tyrosine hydroxylation is negligible, and this represents the rate limiting step in the pathway. DOPA can then spontaneously autooxidize to DOPAquinone in the absence of tyrosinase, and will continue through the pathway by cyclizing to form the indole rings present in leukoDOPAchrome and DOPAchrome. Without further catalytic intervention, DOPAchrome will spontaneously decarboxylate to produce 5,6-dihydroxyindole (DHI), which in turn rapidly oxidizes to indole-5,6-qui-none. Early studies suggested that melanin consisted of a homogeneous polymer of indole-5,6-quinone, but more recent evidence suggests that melanins are much more heterogeneous in nature and probably consist of mixtures of several other intermediates in the pathway. Melanin synthesis will occur spontaneously in the test tube once DOPA is formed, but other constraints are put on these reactions in vivo. A number of additional factors that regulate the flow of this pathway have now been characterized, including other enzymes (i.e., DOPAchrome tautomerase), the availability of reactive sulfhydryls (i.e., glutathione and/or cysteine), and melanogenic inhibitors. The genes for several of these melanogenic factors have now been cloned, providing a glimpse of the complex mechanisms responsible for the production of different types of pigmentation. Perhaps more importantly, it is now possible to begin to understand the molecular lesions responsible for many abnormal pigmentation conditions, such as oculocutaneous albinism [7].

Eumelanin versus pheomelanin synthesis

There are two distinct types of melanins that can be produced in mammalian melanocytes: eumelanin (which is black and/or brown in color) and pheomelanin (which is red and/or yellow in color). The commitment to produce either type of melanin is made following the generation of DOPAquinone. If sulfhydryl groups, typically cysteine or glutathione, are available, they will stoichiometrically react with the DOPAquinone and generate cysteinylDOPA. There are actually three different cysteinylDOPAs that can be formed, including 2-S, 5-S-, and 2,5-S,S-cysteinylDOPA. The cysteinylDOPAs then undergo a series of reactions that result in the cyclization of a second ring and subsequent polymeratization into a high-molecular-weight biopolymer. Pheomelanins have properties distinct from eumelanin, including a greater solubility and distinct appearance. The pheomelanin pathway is obvi-

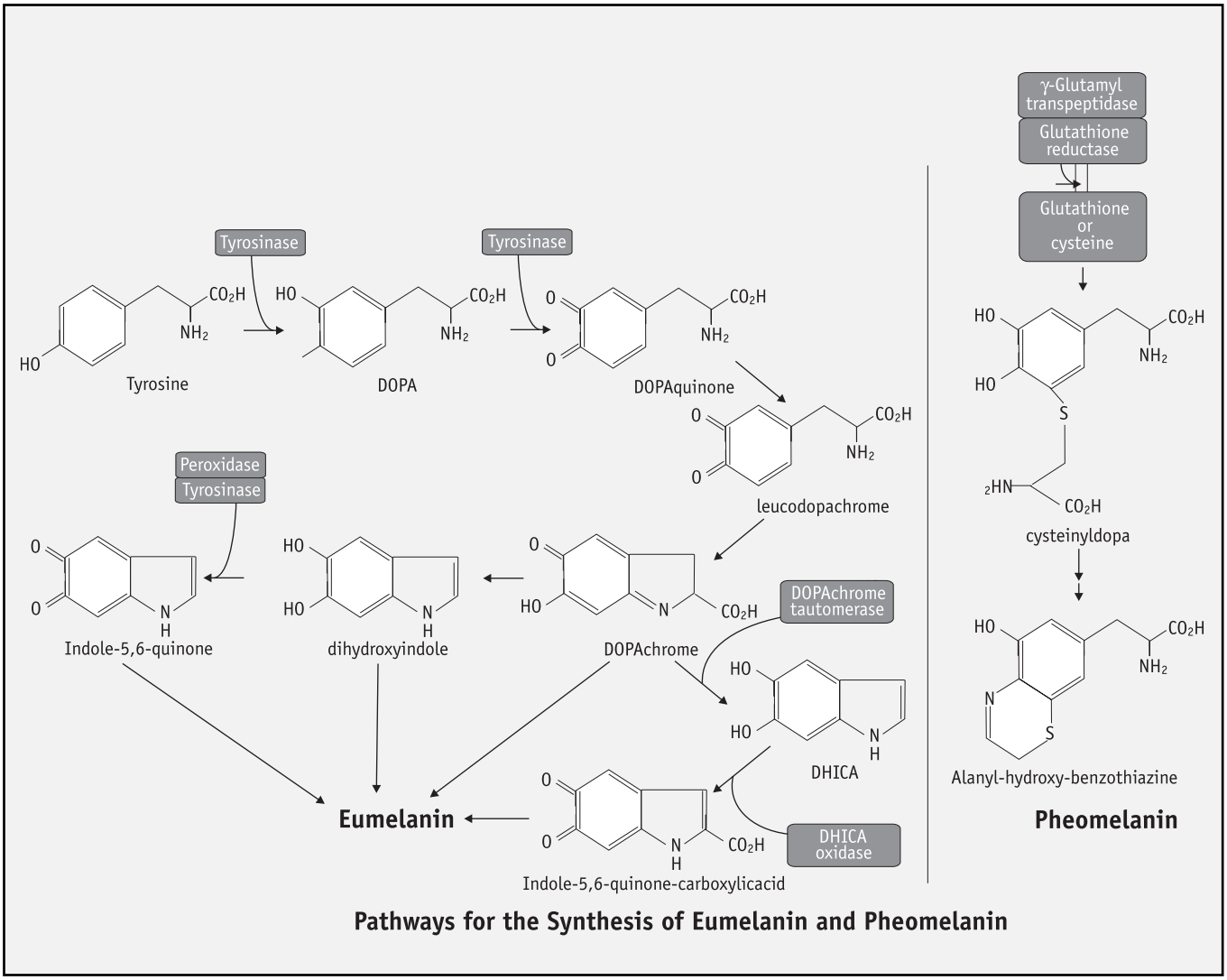


Fig. 3. The melanin pathway presents a summary of the known reactions and regulatory enzymes in eumelanogenesis and pheomelanogenesis.

ously influenced by enzymes that regulate intracellular concentrations of available sulfhydryl groups, and it is not yet known if other enzymes are involved in the further metabolism of the cysteinyl-DOPAs and their derivatives. It seems a reasonable expectation, however, that regulatory factors similar to those of eumelanogenesis will eventually be identified for pheomelanogenesis (Fig. 3).

In the absence of sulfhydryls, eumelanins will be produced. LeukoDOPAchrome forms and is quickly converted to DOPAchrome, which represents yet another key regulatory point in the pathway. DOPAchrome will quantitatively decarboxylate spontaneously to form DHI, although in the presence of certain divalent metal cations (e.g., Co^{2+}, Mg^{2+}, Fe^{2+}) and/or DOPAchrome tautomerase, the carboxylated intermediate 5,6-dihydroxyindole-2-carboxylic acid (DHICA) will be produced. Since DHI and DHICA are not interconvertible, the carboxyl content of the melanin has essentially been determined once this step has been reached. It is not yet known if there are other enzymes that function following the production of DHI and/or DHICA. Mammalian melanins contain significant levels of carboxylated and decarboxylated intermediates, although it is not known how this influences their structure and/or function [7].

The tyrosinase gene family contains three members: tyrosinase (TYR), TRP1/gp75 and TRP2/dopachrome tautomerase. The tyrosinase locus (TYR) has been mapped to chromosome 11q14-21. The gene is at least 50 kb in length and has five exons. Six polymorphic sties have been identified with TYR, and these have been used to form haplotypes for population studies. Mutations in the tyrosinase gene are responsible for tyrosinase-related oculocutaneous albinism (OCA1). The TRP1/gp75 locus has been mapped to chromosome 9p23. The role of TRP1 in pigment biosynthesis has not been conclusively determined. The dopachrome tau-

tomerase or TRP2 gene has been isolated in mice but not in humans. The three genes have similar amino acid sequences, but their gene structures are different. The protein products of these three loci are thought to be involved in the multicomponent melanogenic complex in the melanosome.

The P gene, the human homologue of the murine "pink-eyed dilution" gene, has been mapped to chromosome 15q11.2-12. The silver/pmel 17 gene is involved in premature graying in mice. This locus is thought to be related to the proliferative state of the cells and the product of this gene is produced only in cells that are growing. The melanocyte-stimulating hormone receptor (MSH-R) and the agouti gene product regulate the production of either black/brown eumelanin or red/yellow pheomelanin through their interaction. The human KIT gene, which codes for a mast/stem cell growth factor, has been mapped to chromosome 4q11-13. Mutations in the KIT gene are responsible for **piebaldism**. The PAX3 gene has been mapped to chromosome 2q35-37. Mutations of the PAX3 gene are responsible for **Waardenburg syndrome** [7].

Melanin pigmentary system in the eye, in the ear, in the central nervous system, in the hair, and in the skin

It is now accepted that the epidermal melanocytes of human skin are a product of the neural crest. Melanocytes possess the metabolic machinery for the synthesis of the melanogenic enzyme, tyrosinase, which is incorporated into melanosomes. The epidermal melanocytes are capable of transporting the fully mature melanosomes via dendrites into the neighboring keratinocytes. Any genetic or pathologic changes in the pigmentary system can now be related to changes in or absence of these cell components of the epidermal melanin unit.

On the ultrastructural level, the epidermal melanocytes reveal features typical of secretory cells with rough endoplasmic reticulum (ER), Golgi complexes, and secretory products, the melanosomes. The nuclei are either round or oval in "resting" cells or are indented after ultraviolet radiation (UVR). The internal facet of the nuclear membrane is a fibrous lamina—a feature distinguishing melanocytes from keratinocytes, which lack this structure. There are no desmosomes on the outer aspect of the plasmalemma, but condensations of some granular material of the cytoplasm can be observed on the inner leaflet of the plasmalemma facing the basal lamina. Keratinocytes do not form hemidesmosomes against melanocytes, although they are dotted by these structures on their surface, adjacent to the basal lamina [8].

Normal human skin color is produced by four skin pigments—red, yellow, brown, and blue: in the epidermis by exogenously produced carotenoids (yellow) and endogenously produced melanin (brown); in the dermis by oxygenated hemoglobin (red) in the capillaries, and reduced hemoglobin (blue) in the venules. Of these, melanin is the major determinant of differences in skin color. Normal human skin color is primarily related to size, shape, type, and color of melanosomes and their distribution in melanocytes and keratinocytes. Melanosomes are the product of specialized exocrine cells derived from the neural crest, the melanocytes, which contain arborizing nerve cells—like dendrites. Melanocytes are components of the melanin pigmentary system, which when fully developed is made up of melanocytes distributed in various sites: the eye (retinal pigment epithelium, uveal tract); the ear (in the stria vascularis); the central nervous system (in the leptomeninges); the mucous membranes; the hair (in the matrix); and the skin (at the dermal-epidermal interface) and occasionally in the dermis. Melanocytes are located in the epidermal basal layer and project their dendrites into the malpighian layer of the epidermis where they transfer melanosomes to keratinocytes.

Melanosomes are highly organized ellipsoidal organelles that contain melanin inside a unit membrane and deposit it on an internal filamentous and/or microvesicular matrix. In melanosomes of normal skin, melanin is an extremely dense, virtually insoluble polymer of high molecular matrix. In melanosomes of normal skin, melanin is an extremely dense, virtually insoluble polymer of high molecular weight and is always attached to the structural protein. In theory, mammalian melanin pigments have one of two chemical compositions: (1) **eumelanin**, a brown polymer derived from the conversion of the amino acid, tyrosine, to an alkali-insoluble brown chromophobe; or (2) **pheomelanin**, a yellow-reddish, alkali-insoluble pigment derived from tyrosine but in which one of the intermediates in the tyrosine-melanin pathway (**dopaquinone**) combines with cysteine (or glutathione) to form cysteinyl dopa; this leads to the yellow pigment, pheomelanin. The conversion of tyrosine to dopa and dopa to dopaquinone is accomplished by an aerobic copper-containing oxidase, tyrosinase. Many melanins appear to be mixtures of pheomelanic and eumelanic monomers. The ratio of the monomers varies among different samples of melanin.

Each epidermal melanocyte secretes melanosomes into a finite number of neighboring keratinocytes (approximately 36); this partnership of a melanocyte and a neighboring group of keratinocytes is called an **epidermal melanin unit** (see Fig. 2) [9]. After mela-

nosomes have been transferred to keratinocytes, they are surrounded by a membrane, becoming secondary lysosomes. In white skin, the melanosomes are relatively small and form groups within the secondary lysosomes. This is called a **melanosome complex**. However, in black skin and in the brown or black hair of all races, melanosomes are greater in length (0.7 to 10 μm) and larger in diameter (0.3 μm); when they are transferred to keratinocytes, they remain nonaggregated. Melanin is degraded during the ascent of the keratinocytes toward the outer surface of the epidermis. With the loss of the stratum corneum, the remaining melanin pigments are removed. Consequently, melanization of the epidermis is not static but requires constant renewal.

Melanocytes are cells capable of synthesizing tyrosinase, which, when incorporated within specialized organelles (the melanosomes), initiates events leading to the synthesis and deposition of melanin. Among the most important melanocytes in humans are those in the epidermis, which show a unique symbiotic relationship with the surrounding keratin-forming malpighian cells, keratinocytes. Melanocytes discharge melanosomes into the keratinocytes. Melanocytes arise not from the definitive epidermis, but from the neural crest. The melanocytes in the retinal pigment epithelium do not arise in the neural crest but from the outer layer of the optic cup. Undifferentiated precursor forms of the melanocyte first appear in human skin during the eighth week of gestation.

There are a number of apparent changes in the coloration of an individual during life. Almost all black infants are born somewhat lighter at birth and become darker during the first week of postnatal life. Freckles, originally apparent only after sun exposure, become more permanent in the first or second decade of life. The dorsal skin of the hand becomes mottled in color in old age. The most obvious change related to age is the graying of hair, starting at a genetically determined age

The melanocyte is fastidious, requiring specific factors and nutrients to maintain growth in vivo. At least two classes of mitogenic agents were found to be essential in vitro. One class contained compounds such as tumor promoters (phorbol ester, tetradecanoyl phorbol acetate), which activate protein kinase C; the other was represented by compounds such as cholera toxin and theophylline or dibutyryl cyclic AMP, which exert their effects by increasing intracellular levels of cAMP. These findings stimulated a search for the natural mitogens for use in vitro. It has been shown that **basic fibroblast growth factor** (bFGF) can be substituted for phorbol esters.

Proliferating human keratinocytes in culture contain a mitogen for human melanocytes. This mitogen, which increases six-fold after UV irradiation, has been identified as bFGF. It was proposed that bFGF is expressed on the surface of keratinocytes, allowing direct cell-cell signaling. Other factors identified as possible regulators of melanocytes and keratinocytes include transforming **growth factor** α (TGF-α), **epidermal growth factor** (EGF), **nerve growth factor** (NGF), **platelet-derived growth factor** (PDGF), and hormones such as insulin, melanocyte-stimulating hormone (MSH), and hydrocortisone.

In addition, **endothelin-1** has been shown to enhance melanocyte growth as well as to increase tyrosinase activity and melanogenesis through binding to a high-affinity surface receptor, and UVR increases keratinocyte production of endothelin-1. Endothelin-1 is a 21-amino acid peptide with vasoactive properties first isolated from endothelial cells and later found to be synthesized and secreted by keratinocytes as well [10–17]. Although melanocyte populations vary regionally in human skin, all humans, regardless of skin color, have approximately the same number of epidermal melanocytes at a particular anatomic site. Accordingly, ethnic variation in skin color results mainly from differences in the properties of melanosomes and not from differences in numbers of melanocytes [18].

Ocular albinism and oculocutaneous albinism

Albinism represents a group of inherited abnormalities that present with congenital hypopigmentation that can involve the skin, hair, and eyes (oculocutaneous albinism) or be limited primarily to the eyes (ocular albinism). The definition of albinism includes specific changes in the optic system, including nystagmus, reduced iris pigment, reduced retinal pigment with foveal hypoplasia, and misrouting of the optic fibers at the chiasm [7].

Melanin pigment in the cutaneous and ocular tissues represents one of the most visible markers of human variation. As a result, inherited disorders of melanin formation that present with hypopigmentation have long fascinated scientists and others interested in human biology. Albinism represents the extreme of these disorders—evidence by reduced amounts of melanin synthesis in all parts of the involved tissue—unlike disorders such as **piebaldism**, in which the reduction of melanin is patchy and discrete. **Albinism** itself is heterogeneous, however, and can be separated clinically into types that primarily involve the eyes [ocular albinism or (OA)] and types that involve the skin and hair as well as the eyes [oculocutaneous albinism or (OCA)]. Mela-

nocytes represent a relatively small subpopulation of the cells present in the epidermis and dermis of mammals, yet they produce the melanin that accounts for virtually all visible pigmentation

Other conditions with occurring albinism:

- **X-Linked Albinism and Deafness**

An Israeli Jewish family of Sephardic origin has been described with albinism and deaf-mutism. A similar syndrome has been described in the Hopi Indian population. The hypopigmentation was more typical of piebaldism rather than albinism, and the ocular features of albinism were absent in affected family members. The gene for this condition has now been mapped to a long arm of the X chromosome.

Oculocerebral syndrome with hypopigmentation (Cross Syndrome)

This rare syndrome presents with hypopigmentation and various neurologic changes. This syndrome is often called "Cross syndrome," but the features are quite variable and may be heterogenous in etiology. The cutaneous hypopigmentation is generalized but variable in degree, and the hair has a silver or silver-gray appearance. The ocular features of albinism have not been present in all reported cases, suggesting that this is not a true type of albinism.

Griscelli Syndrome

Griscelli et al. [19] reported two unrelated individuals with hypopigmentation characterized as silver-gray hair and scattered hypopigmented areas surrounded by hyperpigmented skin. Both had repeated pyogenic infections, neutropenia, and thrombocytopenia, and one died with sepsis. Melanocytes in the skin were congested with melanin granules and were surrounded by hypopigmented cells.

The protective role of epidermis and the keratin inherited disorders of the keratin

The epidermis and its appendages provide the protective interface between various traumas of the environment and the body [20]. The epidermis manifests its protective role by building a three-dimensional network of interconnected keratinocytes, each containing an extensive cytoskeleton of specialized 10-nm keratin filaments, encased by a membranous envelope of highly cross-linked proteins. How the epidermis produces its armor is considerably simpler than the program of differentiation carried out by its appendages. In the epidermis, the innermost, basal, layer has the capacity for DNA synthesis and mitosis. As cells commit to differentiate terminally, they begin their journey to the skin surface. In transit, they undergo a series of morphologic and biochemical changes culminating in the production of dead, flattened, enucleated squames, which are sloughed from the surface and continually replaced by inner cells differentiating outward. Keratins belong to the supergene family of >40 intermediate filament (IF) proteins, which assemble into 10 nm cytoskeletal filaments in all eukaryotic cells. Approximately 30 keratins of two distinct types are coexpressed as pairs in epithelial cells, at various stages of differentiation and development. In the epidermis, keratin (K) 5 and 14 are the major structural proteins of basal cells. As keratinocytes commit to differentiate terminally, they switch off expression of this pair and switch on expression of K1 and K10, which constitute ~85 percent of total protein in the fully differentiated squame [21].

More than 5000 type I and II keratin subunits comprise each 10-nm filament. Filaments are composed of ~4 intertwined protofibrils (4.5 nm), which in turn are composed of ~2 protofilaments (2 to 3 nm). Protofilaments can accommodate linear chains of tetramers, which for keratins, are composed of coiled-coil heterodimers arranged in antiparallel fashion. In vitro, 10-nm filament assembly relies only on type I and II keratins, and does not require auxiliary proteins or factors. In vivo, keratin filaments interact with both the nuclear envelope and desmosomes, generating an extensive cytoplasmic network imparting mechanical strength to the keratinocyte [22–27]. Many keratin genes have now been sequenced, and they have similar structures [21].

Most human type, keratin genes reside on chromosome 17 [28–31], and most human type II keratin genes are on chromosome 12 [30–33]. Most importantly, the functional genes for the epidermal keratins K14 and K10 reside at 17q12→q21 [28, 30]; and many other skin type I genes are clustered in this same region [28, 30, 32]. Similarly, the genes for the type II epidermal keratins K5 and K1 are clustered at the q11→q14 locus of chromosome 12 [30, 32, 33].

An inherited disorder of keratin includes **epidermolysis bullosu simplex** (EBS), which is a group of rare genetic skin diseases affecting 1:50,000 population. It is typified by intraepidermal blistering due to cell degeneration within the basal layer [34]. Clinical manifestations are often present at birth, with blistering associated with mild physical trauma. Blisters heal, often without scarring. Hyperpigmentation at areas of previous blisters has also been reported [35].

Additional curious features of the disease are that clinical manifestations improve with age and that the severity of blistering decreases during periods of fever but increases during warmer weather.

Epidermolysis bullosu simplex has been subdivided into three major and several minor [36, 37] subtypes (see Table 2). **Weber-Cockayne** is the mildest form of the disease. Blisters are usually confined to palmar and plantar regions of the body and, not surprisingly, the onset of the disease is often most apparent when a child begins to walk. As judged by ultrastructural analysis, basal-cell cytolysis is evident, albeit sparse, over whole body trunk regions. Cytolysis occurs in a defined zone, beneath the nucleus and above the hemidesmosomes. Keratin filaments often appear nearly normal and, as in all EBS subtypes, suprabasal layers are unperturbed, indicating a normal differentiation process.

In **EBS Koebner**, blistering is more generalized than in Weber-Cockayne. However, as in all forms of EBS, cytolysis is typically most extensive in areas susceptible to mechanical trauma, and this includes palmar and plantar epidermis. Noncutaneous involvement is rare in EBS Koebner, and when it occurs, it is usually the nails that become loosened when subjected to physical stress. Oral blistering has been reported.

Dowling-Meara is the most severe form of EBS. This disease is apparent at birth, and the incidence of neonatal death can be appreciable. Blistering is extensive, and can occur over the entire body trunk and proximal extremities, often in herpetiform clusters. In severe cases, denuding of skin can also occur. Plaque-like hyperkeratoses with extensive lamellar exfoliation also occur, particularly on the hands and feet. Nail dystrophy, loss and regrowth, oral mucosal blistering, and tooth destruction are relatively frequent. In addition, other stratified squamous epithelia, such as cornea, can also be affected, albeit to a lesser extent. In very rare cases, esophageal involvement can be affected [20].

There are a number of autosomal dominant skin diseases that involve disorganization of tonofilaments in the suprabasal layers of the epidermis. Some of these, such as **Hailey-Hailey disease** and **Darier disease**, exhibit anomalies in desmosomes or other structures as well as aberrancies in tonofilament organization [29, 38]. Other diseases, however, exhibit suprabasal alterations in tonofilament organization that are extraordinarily similar to the basal-cell-layer aberrancies that occur in EBS. Given the switch in keratin expression that takes place as epidermal cells commit to differentiate terminally, diseases involving suprabasal keratin abnormalities are prime candidates for having defects in the genes encoding the terminal differentiation-specific keratins [20].

The health-promoting and harmful effects of sunlight

Sunlight and ultraviolet radiation (UVR) from artificial light sources (290 to 400 nm) can be tonic or toxic to human skin [39]. The sun is necessary for life. We are warmed by its rays and able to see with eyes that respond to the visible light portion

Table 2. Clinical Features of the Major Subtypes of EBS

	EBS Subtype		
	Weber-Cockayne	**Koebner**	**Dowling-Meara**
Mode of inheritance	AD	AD	AD
Onset	Infancy to childhood	Birth to infancy	Birth
Distribution	Primarily palmoplantar	Generalized	Generalized
Cutaneous anomalies:			
Blisters	+	+ + +	+ + + + +
Scarring	Very rare	Rare	Rare
Pigmentation	OK	+/-	+/-
Nail dystrophy	+/-	+/-	+ + +
Mechanical fragility	+	+ +	+ + +
Oral cavity anomalies:			
Erosions	+	+	+ +
Scarring	-	-	-
Dental anodontia/hypodontia	-	-	+
Other extracutaneous involvement	-	-	Corneal, esophageal
Growth	OK	Retarded (+)	Retarded (+ +)

AD = Autosomal dominant. Concepts with permission from Fuchs, E. (20). Genetic skin disorders of keratin. In: *Fitzpatrick's Dermatology in General Medicine*, 5th edition, pp. 4421–4437. Eds. I.M. Freedberg, A.Z. Eisen, K. Wolff, K. Austen, L.A. Goldsmith, S.I. Katz, and T.B. Fitzpatrick. McGraw-Hill, New York.

of the solar spectrum (400 to 760 nm). The health-promoting qualities of sunlight (e.g., a feeling that light is good for our psyche, for the synthesis of vitamin D, for generating a healthy appearing photoprotective tan have been acknowledged since ancient times [40]. With an increase in our knowledge of cutaneous photobiology and photodermatology, however, terrestrial solar radiation and particularly UVR have become identified as major environmental factors deleterious to our health. The deleterious effects of UVR depend upon the duration and the frequency of exposures, the intensity of solar radiation based on the latitude of the location from the equator, and the reactivity of skin based on genetically determined constitutive skin color and the skin phototypes [41, 42].

The beneficial effects of solar radiation are vision and photoresponse, photosynthesis, vitamin D synthesis, warmth, killing of pathogens, phototherapy and photochemotherapy.

The harmful effects of solar radiation (see Table 3) are skin cancer, photosensitivity diseases, sunburn, photoallergy, photoimmunologic alterations, cataracts, mutations, skin aging, and phototoxicity [39]. For a normal fair-skinned healthy individual, there are at least six major concerns about the potential harmful effects of sun exposure: (1) The acute effects including sunburn, sun tanning (or increased pigmentation], and increased sensitivity to light resulting from drug-induced phototoxic or photoallergic reactions; (2) the potential long-term risk of repeated, uncontrolled sun exposures resulting in the development of actinic elastosis related to changes of photoaging or dermatoheliosis (wrinkling, irregular thinning of the epidermis, telangiectasia, hyperpigmented macules, alterations in collagen and elastin fibers]; (3) the development of premalignancies (solar keratoses] and malignancies, (basal cell and squamous cell carcinomas and melanomas]; (4) the changes of the immune responses and of the function and distribution of components of the immune system causing selective immune alterations; (5) the consequences of cumulative photochemical damage to the unprotected eyes resulting in yellow-brown discoloration of the lens and cataract formation; and (6) in certain individuals, abnormal reactions (e.g., urticaria, papules, plaques, vesicles, eczematous dermatitis] resulting from exposure to UVB (290 to 320 nm] or UVA (320 to 400 nm] radiation or occasionally visible light (400 to 760 nm]. There are nearly forty human diseases that are either caused or aggravated by sunlight (e.g., **xeroderma pigmentosum, albinism, porphyrias, polymorphous light eruptions, lupus erythematosus**] [43–49].

Melanin pigmentation of human skin occurs as a constitutive, or intrinsic, skin color and as facultative, or induced, skin color. Constitutive skin color is genetically determined level of skin pigmentation consistent with genetic programs of pigment cells in the absence of direct or indirect influences such as solar radiation, chemicals such as **psoralens**, hormones such as MSH, or other environmental factors. Facultative skin color is characterized by the increase in melanin pigmentation above the constitutive level and arises from a complex interplay of solar UVR at the DNA level in epidermis. Facultative skin color change brought about by solar radiation is commonly referred to as suntanning and involves: (1) an immediate oxidation reaction in preexisting melanin by UVA radiation (320 to 400 nm), and (2) delayed tanning reaction by UVB as well as UVA radiation that involves increased tyrosinase activity and increased production of melanin (melanosomes) by melanocytes. Thus, increased melanin pigmentation can be divided into two distinct subtypes, immediate and delayed. The immediate pigment darkening (IPD) response is induced by UVA radiation (320 to 400 nm), occurs in minutes, is prominent in more darkly pigmented individuals, appears to be an oxidation reaction in preexisting melanin or melanin precursors in skin, does not involve new melanin synthesis, and is of unclear clinical significance. Delayed melanin pigmentation (neomelanogenesis stimulated by UVB and UVA radiation) becomes prominent 48 to 72 h after UVR exposure and is the major mechanism of increased protection involving (1) absorption of radiation, (2) scattering of radiation, and (3) free radical quenching by melanin [50, 51, 17].

Drug-induced photosensitivity ultraviolet radiation

Photosensitivity induced by chemicals can be caused by exogenous or endogenous agents. Exogenous photosensitizers can be categorized into those administered systemically and agents applied topically. Based on the pathophysiology, photosensitivity induced by exogenous agents can be divided into **phototoxicity** and **photoallergy** (see also Tables 3 & 5). Phototoxicity is the result of a direct tissue injury caused by the phototoxic agent and radiation, mediated by reactive oxygen species and inflammatory mediators. It can occur in all individuals exposed to adequate doses of the phototoxic agent and the appropriate radiation. In contrast, photoallergy is a type IV delayed hypersensitivity response; it has a sensitization phase, occurs only in sensitized

Table 3. Characteristic Parameters of Phototoxicity and Photoallergy

	Phototoxicity	Photoallergy
Clinical presentation	Sunburn reaction: erythema, edema, vesicles, and bullae; frequently resolves with hyperpigmentation	Eczematous lesions, usually pruritic
Histology	Necrotic keratinocytes, epidermal degeneration; sparse dermal infiltrate of lymphocytes, macrophages, and neutrophils	Spongiotic dermatitis, dermal lymphohistiocytic infiltrate
Pathophysiology	Direct tissue injury	Type IV delayed hypersensitivity response
Occurrence after first exposure	Yes	No
Onset of eruption after exposure	Minutes to hours	24 to 48 hours
Dose of agent needed for eruption	Large	Small
Cross-reactivity with other agents	Rare	Common
Diagnosis:		
Topical agents	Clinical	Photopatch tests
Systemic agents	Clinical + phototests	Clinical + phototests; possibly photopatch tests

Concepts with permission from Lim, H.W. (52). Abnormal responses to ultraviolet radiation: Photosensitivity induced by exogenous agents. In: *Fitzpatrick's Dermatology in General Medicine*, 5th edition, pp. 1589–1598. Eds. I.M. Freedberg, A.Z. Eisen, K. Wolff, K.F. Austen, L.A. Goldsmith, S.I. Katz and T.B. Fitzpatrick. McGraw-Hill, New York.

Table 4. Topical photoxic agents are:

Agents	Exposure
Rose bengal	Ophthalmologic examination
Furocoumarins	Occur naturally in plants (especially Compositae ssp), fruits, and vegetables (lime, lemon, celery, fig, parsley, and parsnip); used in perfumes and cosmetics; used for topical photochemotherapy
Tar	Topical therapeutic agent; roofing materials

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individuals, and requires only minimal concentration of the photoallergen [52, 53].

Systemic photoxic agents (Table 4) either therapeutic or diagnostic agents, can produce exaggerated sunburn reaction. However, some may also induce the eczematous response seen in photoallergy, especially following topical exposure; phenothiazines, sulfonamides, quinine, and ketoprofen are examples of such agents [54–57]. As a rule, the action spectra are in the UVA range; exceptions include sulfonamides, vinblastine, and sulfite food additives [58, 59], whose action spectra are in the UVB range, and the porphyrins, fluorescein, and other dyes, whose action spectra are in the visible range [60] (see also Table 5).

Photoprotection of skin against ultraviolet radiation

Most of the damaging effects of solar radiation result from primary events following the absorption of UV radiation by DNA, RNA, proteins, enzymes, lipids of cell membranes, and cell organelles present in cells of the epidermis and dermis, including the vascular system (see also Table 6). These effects are dose-dependent, relating to factors such as duration

Table 5. Systemic Phototoxic Agents

Medications	Generic Name	Medications	Generic Name
Antianxiety drugs	Alprazolam (Xanax)	**Diuretics**	Furosemide (Lasix)
	Chlordiazepoxide (Librium)		Thiazides
Anticancer drugs	Dacarbazine (DTIC-Dome)		Bendroflumethiazide (Naturetin)
	Fluorouracil (Efudex, Fluoroplex)		Chlorothiazide (Diuril)
	Methotrexate (Folex)		Hydrochlorothiazide (HydroDIURIL)
	Vinblastine(Velban)	**Dye**	Fluorescein (Fluorescite)
Antidepressants	Tricyclics		Methylene blue
	Desipramine (Norpramin)	**Food additives**	Sulfites
	Imipramine (Tofranil)		
Antifungal	Griseofulvin (Fulvicin-U/F)	**Furocoumarins**	Psoralens
Antimalarials	Chloroquine (Aralen)		8-Methoxypsoralen (Oxsoralen)
	Quinine (Quinamin)		4,5,8-Trimethylpsoralen (Trisoralen)
Antimicrobials	Quinolones		
	Ciprofloxacin (Cipro)	**Hypoglycemics**	Sulfonylureas
	Enoxacin (Penetrex)		Acetohexamide (Dymelor)
	Lomefloxacin (Maxaquin)		Chlorpropamide (Diabinase)
	Nalidixic acid (NegGram)		Glyburide (Micronase)
	Norfloxacin (Noroxin)		Tolazamide (Tolinase)
	Ofloxacin (Floxin)		Tolbutamide (Orinase)
	Sulfonamides	**Hypolipidemics**	Fibric acid derivatives
	Tetracyclines		Bezafibrate
	Demeclocycline (Declomycin)		Clofibrate (Atomid-S)
	Doxycycline (Vibramycin)	**NSAIDs**	Piroxicam (Feldene)
	Minocycline (Minocin)		Propionic acid derivatives
	Tetracycline (Achromycin)		Ibuprofen (Motrin)
	Trimethoprim (Proloprim)		Ketoprofen (Orudis)
Antipsychotic drugs	Phenothiazines		Naproxen (Naprosyn)
	Chlorpromazine (Thorazine)		Tiaprofenic acid
	Perphenazine (Trilafon)	**Photodynamic therapy agents**	Hematoporphyrin derivative (Photofrin)
	Prochlorperazine (Compazine)		Hypericin
	Thioridazine (Mellaril)	**Retinoids**	Isotretinoin (Accutane)
	Trifluoperazine (Stelazine)		Etretinate (Tegison)
Cardiac medications	Amiodarone (Cordarone)		
	Quinidine (Cardioquin, Quinidex)		

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of exposure, frequency of exposures, and quality and intensity of radiation. Photoprotection and prevention of such damaging effects of UV radiation can be achieved by attenuation processes that significantly reduce the impact of UV photons impinging on the skin. Attenuation is achieved by providing to the skin certain exogenous photoprotective approaches that are governed by four biophysical principles of attenuation of solar radiation: (1) *absorption and filtration* of UV radiation at the surface of stratum corneum to prevent its further transmission (or penetration) into epidermis and dermis; (2) *scattering* of radiation; (3) *reflection* of radiation impinging on the skin by providing barriers such as molecules of titanium dioxide (TiO_2) and/or zinc oxide (ZnO) on the stratum corneum, which effectively scatter and reflect the UV radiation; and (4) *inactivation or destruction of free radicals* and reactive forms of oxygen species [e.g., singlet oxygen ($^1O_2$), superoxide anion ($O\bullet_2^-$), hydroxyl radical ($\bullet OH$)] that are produced in the skin when it is exposed to solar radiation. The formation of such UV-induced free radicals and reactive forms of oxygen occurs in the viable cells of epidermis and dermis and can be inhibited or minimized by oral administration or topical application of certain compounds that act as antioxidants or free radical quenchers (or scavengers). In addition, inflammatory mediators (e.g., histamine, prostaglan-

Table 6. Topical Photoallergens

Group	Chemical Name and/or Trade Name
Sunscreens	Benzophenone-3 (oxybenzone) Benzophenone-4 (sulisobenzone) Padimate O (octyl dimethyl PABA) Padimate A (amyl dimethyl PABA) PABA (para-aminobenzoic acid) Octyl methoxycinnamate Cinoxate (2-methoxyl-ethyl-p-methoxycinnamate) Parsol 1789 (butyl methoxydibenzoyl-methane; avobenzone) Menthyl anthranilate (cyclohexanol) Homosalate (homomenthyl salicylate)
Fragrances	Musk ambrette 6-Methylcoumarin Sandalwood oil
Antibacterials	Tetrachlorosalicyanilide (Irgasan BS200) Dibromosalicylanilide (dibromsalan, DBS) Tribromosalicylanilide (tribromsalan, TBS) Hexachlorophene (pHisoHex) Chlorhexidene (Hibiclens) Dimethylol-dimethyl hydantoin Triclosan (Irgasan DP300) Dichlorophene (G4) Bithionol (thiobisdichlorophenol)
Antifungals	Fentichlor (thiobischlorophenol) Jadit (butylchlorosalicylamide, buclosamide) Multifungin (bromochlorosalicylanilide, BCSA)
Others	Chlorpromazine (Thorazine) Promethazine (Phenergan) Thiourea (thiocarbamide) Quinidine (Cardioquin, Quinidex) Ketoprofen (Orudis) Clioquinol Olaquindox

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dins, cytokines) formed in response to UV irradiation can be effectively inhibited by specific antagonistic pharmacologic agents administered orally or topically to prevent the inflammatory response (e.g., the action of indomethacin in sunburn reaction) [61].

The methods for photoprotection include the *topical application* of chemical sunscreens in the form of creams, lotions, gels, or solutions containing a known quantity of UV-absorbing chemical or chemicals that selectively absorb, scatter, or reflect radiation and prevent the penetration of UV radiation into the skin (Table 7).

Psoralen photochemotherapy and photodynamic therapy

Psoralen photochemotherapy is a combination of psoralen (p) and long-wave ultraviolet radiation (UVA) that brings about a therapeutically beneficial result not produced by either the drug or radiation alone. This particular form of therapy is currently used in the treatment of several common and uncommon skin diseases. Psoralens can be administered orally or applied topically in the form of solutions, creams, or baths with subsequent UVA exposure [62; and Table 6). Hypotheses about the mechanism of photochemotherapy of psoriasis are based on the fact that PUVA causes photoconjugation of psoralens to

Table 7. Sunscreen Chemicals that Absorb UVA Radiation and Protect the Skin against UVA

Chemicals	Recommended Concentration, %	Protection Range (nm)	Reported Side Effects
Benzophenones			
Oxybenzone	2–6	320–360	Partially effective and irritant to few
Sulisobenzone	5–10	320–360	Partially effective and irritant to few
Dioxybenzone	3.0	320–360	Partially effective and irritant to few
Other chemicals			
Methyl anthranilate	3	300–400	Partially effective
Butylmethoxydibenzoyl	≤3	320–400	Effective up to 400 nm but may be irritant, photolabile
Red veterinary petrolatum	>30	320–370	Smarting and irritant
Titanium dioxide	2–25	300–400	Effective but may be white or occlusive
Zinc oxide	2–20	300–400	Effective but may be white or occlusive

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Table 8. Psoralen and Long-wave Ultraviolet Radiation-Responsive Diseases

Therapy of Diseases	Prevention of Diseases
Psoriasis	Polymorphous light eruption
Palmoplantar pustulosis	Hydroa vacciniforme
Mycosis fungoides (stages IA, IB)	Solar urticaria
Vitiligo	Erythropoietic protoporphyria
Atopic dermatitis	Chronic actinic dermatitis
Generalized lichen planus	
Urticaria pigmentosa	
Cutaneous graft-versus-host disease	
Generalized granuloma annulare	
Pityriasis lichenoides	
Lymphomatoid papulosis	
Pityriasis rubra pilaris	

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DNA and a subsequent suppression of mitosis, DNA synthesis, and cell proliferation. This would indeed suffice to revert increased cell proliferation rates in psoriasis to normal. On the other hand, PUVA downregulates certain lymphocyte and antigen-presenting cell functions, influences adhesion molecule expression, and diminishes Langerhans cell numbers within the epidermis. In addition, PUVA may affect specific cells such as lymphocytes or polymorphonuclear leukocytes. Since there is increasing evidence that psoriasis is caused primarily by the action of blood-derived immunocytes, it is reasonable to speculate that PUVA therapy may quite possibly act by an effect on normal or abnormal immune function involving a direct phototoxic effect on lymphocytes in skin infiltrates or on an abnormal immune function. This is in keeping with the observation that several other disorders that are not hyperproliferative in nature respond well to PUVA (Table 8).

Psoralens also stimulate melanogenesis. This involves the photoconjugation of psoralens to DNA in melanocytes, mitosis and subsequent proliferation of melanocytes, an increased formation and melanization of melanosomes, an increased transfer of melanosomes to keratinocytes, and activation and increased synthesis of tyrosine mediated by stimulation of cAMP activity [62, 63].

Conclusions

Melanin, the major product of the melanocyte, is largely responsible for the coloring of the skin. Melanocytes originate in the embryonic neural crest, from which they migrate to form a horizontal network of cells with many cytoplasmic processes or dendrites that intermesh between the basal cells of the epidermis. Melanin is a complex of insoluble, polyquinone, brown or red pigment and protein, formed by the oxidation of tyrosine and 3,4-dihydroxyphenylalanine (DOPA) in the presence of the oxidative enzyme, tyrosinase. Tyrosinase is found within distinctive ultrastructural organelles of the melanocytes, called melanosomes, which are membrane-bound ovoid structures enclosing regularly packed and coiled lamellae upon which melanin is synthesized and deposited. Eventually, when the melanosomes are filled with melanin pigment, all enzymatic activity ceases. They are then referred to as melanin granules, and the granules move out along the melanocytic dendritic processes, where they are transferred to the surrounding epidermal cells. Human skin pigmentation, therefore, depends upon not only the amount of melanin synthesized by melanocytes but also the number and dispersion of melanin granules in the adjacent basal cells.

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