THE COLOR OF HAIR

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Abstract : The color of hair has always been one of the main characteristics of human beings used to describe and identify people among others. In this article we describe the melanin biochemistry and synthesis, hair color genetics, molecular basis of congenital hypopigmentary disorders, natural hair color variety, racial and ethnic variation, heterochromia, red hair (riutilism), green hair, grey hair and premature greying, poliosis, hair color changes due to natural and local factors and pathological reasons and syndromes related to hair color changes, hereditary disorders and hair color alterations due to systemic and to external or local use of drugs and other elements and the presence of minerals, chemicals, trace elements and drugs in hair according to the color.

…,ηλθε δ' Αθηνη
ουρανοθεν ' προ γαρ ηκε θεα λευκολενος 'Ηρη
'αμφω ομως θυμω φηλεουσα τε κυδομενη τε '
στη δ' οπισθεν, ξανθης δε κομης ελε Πηλειωνα
οιω φαινομενη: των δ' αλλων ου τις ορατο:
θαμβησεν δ' Αχηλευς, μετα δ' ετραπετ', αυτικα δ' εγνω…

….êlthe d' Athênê
ouranothen: pro gar hêke thea leukôlenos Hêrê
amphô homôs thumôi phileousa te kêdomenê te:
stê d' opithen, xanthês de komês hele Pêleïôna
oiôi phainomenê: tôn d' allôn ou tis horato:
thambêsen d' Achileus, meta d' etrapet', autika d' egnô…

…..Minerva came down from heaven (for Juno had sent her in the love she bore to them both), and seized the son of Peleus by his yellow hair, visible to him alone, for of the others no man could see her…….
(Homer's ILIAD book I; 194-199).

…ενθα μεσαιπολιος περ εων Δαναοισι κελευσας
Ιδομενευς Τρωεσσι μεταλμενος εν φοβον ωρσε.
Πεφνε γαρ Οθρυονηα Καβησοθεν ενδον εοντα,
ος ρα νεον πολεμοιο μετα κλεος ειληλουθει,…

….entha mesaipolios per eôn Danaoisi keleusas
Idomeneus Trôessi metalmenos en phobon ôrse.
pephne gar Othruonêa Kabêsothen endon eonta,
hos rha neon polemoio meta kleos eilêlouthei,….

……And now Idomeneus, though his hair was already flecked with grey,called loud on the Danaans and spread panic among the Trojans as he leaped in among them……
(Homer's ILIAD book XIII; 360-365).

……CLEOPATRA
For the most part, too, they are foolish that are so.
Her hair, what color?

Messenger
Brown, madam: and her forehead
As low as she would wish it……

(William Shakespeare's ANTONY AND CLEOPATRA
Act 3, Scene 3)

INTRODUCTION

The color of human hair seems only to be decorative with no biological or physical significance. Lanugo hair that is present in utero is unpigmented, while Vellous hair is mostly unpigmented presenting a slight pigmentation in some fibers, especially in men after puberty. The differences noted in various races and ethnic groups are probably related to skin color and are not affected within sunlight protection[1]. In most people hair color slightly varies in different sites of the body individually[1,2]. Eyelashes represent the darkest area of hair on the human body whereas the genital area hair is normally darker than the scalp taking a reddish color in individuals with brown hair.

The range of hair is seen as getting darker with age in both sexes. During the period of intensified growth, girls show a slight tendency to darker hair than boys do at the same age due to their rapid development[3].

The whole color spectrum of the human hair is due to two types of melanin polymers: (1) the eumelanins that are mainly present in black and brown hair and (2) the phaeomelanins (yellow or red), presented in auburn and blonde hair [1].

Melanin has a brown color and gives a dark brown solution in aqueous alkaline hydrogen peroxide[4].

The proportions in which two eumelanin monomers, mainly being 5,6-dihydroxyindole-2-carboxylic acid (DHICA) and 5,6-dihydroxyindole (DHI), are believed to determine properties of the pigment including its color. Other investigators sustain that there is no significant relationship between proportion of DHICA-derived units in eumelanin and hair color, which is mostly determined by the ratio of pheo- to eumelanin syntheses[5]. Serum iron also is important in the kinetics of melanogenesis within the follicular melanocytes[6].

Eumelanin is photoprotective, whereas phaeomelanin, may contribute to UV-induced skin damage due of potentiality to generate free radicals in response to UVR, (people with red hair fail to tan), and become mutagenic after exposure to long wave-length

UV-light; a hypothesis for the origin of freckles and the high susceptibility of redheads and blonds to sunlight-induced skin cancers[7].

In mammals, the relative proportions of phaeomelanin and eumelanin are regulated by the melanocyte stimulating hormone (MSH), which acts via its receptor (MC1R), on melanocytes, to increase the synthesis of eumelanin and the product of the agouti locus which antagonises this action[8].

Melanin is an irregular light-absorbing polymer containing indoles, cysteine residues[9] and other intermediate products derived from the oxidation of tyrosine. It is the major pigment present in the surface structures of vertebrates. Melanin has many biological functions. The reactive quinone intermediates in the melanin biosynthetic pathway exhibiting antibiotic properties, with the polymer as an important strengthening element of plant cell walls and insect cuticle. Light absorption by melanin has several biological functions, such as photo-receptor shielding, thermo-regulation, photo-protection, camouflage and display. Melanin is a powerful cation chelator and may act as a free radical sink. It is used commercially as a component of photoprotective creams, mainly for its free radical scavenging rather than its light absorption properties. The pigment is also a potential target for anti-melanoma therapy[10].

There are considerable difference in growth rates of pigmented and white anagen beard hair (0.47 mm/day vs 1.12 mm/day, on average) was measured in three individuals over a 3-year period[11].

The melanin polymers synthesized from tyrosine by a complex series of reactions. Tyrosine is uptaken initially by hairbulbs, with a different speed according to the color of hair. This procedure, that appears to be a metabolic process, can be reduced, in vitro, with the inhibition of tyrosinase activity, by low temperatures (4^0 and 21^0 C) and with the addition of unlabeled tyrosine to the incubation[12].

At least seven membrane glycoproteins, including the enzyme tyrosinase, participate in melanin synthesis. Alpha-Melanocyte stimulating hormone (alpha-MSH) regulates skin and hair pigmentation by modulating the activity of MSH receptor (MC1R).

Researchers identified Arg151Cys variant of human MC1R in genomic DNA isolated from an individual with red hair and light skin (type I). The Arg151Cys variant of MC1R binds to radio-labelled analogue of alpha-MSH with identical affinity as the wild type MC1R but cannot be stimulated to produce cyclic AMP (cAMP), thus rendering human MC1R completely nonfunctional; this explains the red hair, light skin and poor tanning ability (skin type I)[13]. Tyrosinase synthesis and activity appears to be greater in hair follicles of red heads than dark heads and is not increased by the alpha-MSH. On the other hand, the 8-Bromo-cyclic AMP, on the other hand, increases tyrosinase synthesis but only in the hair follicles from dark heads[14].

Melanins are synthesized within melanocytes in a specialized organelle, the melanosome, and are deposited on filaments within it.

The four stages in the biogenesis of the melanosome, are defined by electron microscopy. Premelanosomes (stage 1) appear to derive from smooth membranous saccules, possibly the smooth endoplasmic reticulum (ER) and as an internal matrix structure develops, the melanosomes fuse with Golgi-derived (G) coated vesicles (V) containing tyrosinase (T) and other members of its gene family. This fusion initiates the onset of melanin synthesis and deposition within the melanosome[15] ***(FIG 1)***. Hair follicle melanocytes are located at the edge of the follicular papilla with their main body in contact with the basement membrane. Dendritic processes of the melanocytes are phagocytized by differentiating matrix cells incorporated into the hair cortex and medulla, followed by the release of melanin granules into the cytoplasm[16]. In black color, hair follicles deposition of melanin in melanosomes is uniformly dense. Lighter colored hair shows that melanosomes are with less melanin deposition than in blonde colored hair follicles, which shows melanosomes with a moth-eaten appearance. Black and brown hair follicles have ellipsoidal melanosomes, while red and blonde hair spherical ones. The distribution of the melanin granules in the hair cortex is elevated in the periphery, presenting numerical, structural and physical differences in black and blond hair[17,18].

Melanins are natural black high-polymers that are completely insoluble, and therefore not amenable to ordinary purification procedures and structure investigation.

Recent researches sustain that contrary to what had been believed the natural and synthetic black pigments are complex materials in the solid state and it is not possible to write their formulas or to determine their molecular weight. These materials show stable unpaired electrons (EPR) with electroactivity. All black pigments are conductors or candidates to conductivity. The "color" (black, red, yellow) depends to electronic transitions in band materials and change with the amplitude (expressed in eV) of the Fermi band. The melanins are melanoproteins (protein/melanin ratio about 1 : 10) Many of those black pigments are formed by a, non enzymatic, radicalic process sensitive to oxygen, peroxides, light, pH, concentration etc, occuring in the presence or absence of oxygen, are probably controlled by metals, and are toxic for the cell. A structural approach in the study of the intermediate oligomers, is not possible, due to its enormous theoretic number. Only DHI and DHICA melanin monomers are well known. The natural known black pigments (melanins) are *eumelanin, pheomelanin, allomelanin, neuromelanin, humic acid, fullerenes, graphite* whilst synthetic black pigments are *pyrrole-black, indole-black* and *benzene-black*[19,20,21] ***(FIG 3).***

GENETICS

Hair color and the control mechanisms of the process of melanin pigmentation are under genetic influence[22,23,24,25]. Responsible are, at least four, gene loci which are probably allelic[26] and changes in pigmentation are important markers of genetic aberrations. Melanin pigmentation is related to four biologic processes: (1) formation of melanosomes in melanocytes; (2) melanization of melanosomes in melanocytes; (3) secretion of melanosomes into keratinocytes and (4) transport by keratinocytes of melanosomes within lysosome-like organelles[27,28,29,30].

Dominance may play a small role in the case of hair color, while it seems to be absent in the eye-color. There are no sufficient indications of X-linked factors for both characters[31].

The follicular melanocytes' mitosis, melanosome production and transfer occur only during the anagen phase of the hair cycle and respond to the Melanocyte Stimulating Hormone (MSH)[1,10]. Three different types of MSH have been identify : *alpha, beta* and *gamma* where there are small peptides consisting of 12-18 aminoacids, produced from the intermediate lobe of the pituitary gland and deriving from a common precursor peptide, the pro-opiomelanocortin[1].

Alpha-MSH binds to melanocytes in binding sites that seem to be present only on melanin synthesizing melanocytes and is thought to stimulate melanogenesis through a cyclic-AMP-dependent mechanism. The follicles of senile white hair, which do not contain active melanocytes, are short of binding sites[32].

The switch of melanogenesis would be significantly controlled by structural and functional availability of vesiculoglobular bodies which are encoded or associated with HMSA-5 (69 kDa) glycoprotein. This HMSA-5 protein shares a significant homology with gp75 "b-locus" protein. However, because of the hypothesis that vesiculoglobular bodies carry post- (and pre-) tyrosinase regulatory factors involving in both pheo- and eumelanogenesis, the term "b-protein" which focuses only on eumelanogenesis may not be applied to HMSA-5[33].

NATURAL COLOR VARIETY

RACIAL-ETHNIC VARIATION

The racial and ethnic differences are obvious amongst dissimilar races and ethnic groups. In residents of Asia, Africa and Latin America, the volumic density of pigment in the human hair is differentiated in hair samples from the head, chest, armpits, and pubis area, from those hair samples taken from residents in the regions of the former Soviet Union[34]. This samples show that hair color and shape are separately inherited[35].

RED HAIR (rutilism)

Red hair color is due to pheuemalanin and the incidence among the general population varies from 0.3% in Northern Germany to 11% in some regions of Scotland.

The MSHR gene cannot be solely responsible for the red hair phenotype and variances in the MSHR gene are necessary but not always sufficient, for red hair production. Three alleles are associated with the red hair color expression[36], since red hair often darkens with age[1,7].

High UV sensitivity is associated with high phaeomelanin and low eumelanin levels that point to the eumelanin/phaeomelanin ratio, as a novel chemical parameter that could be used for predicting individuals at high risk for skin cancer and melanoma [28].

In humans, melanocortin 1 receptor variants are associated with red hair and fair skin. In addition, melanocortin 1 receptor variants are a risk factor, possibly independent of skin type, for melanoma susceptibility[22].

A number of authors[37] suggest an association between the occurrence of natural red hair and those factors that lead to the development of endometriosis. The red haired man is considered as unattractive compared to other hair colored men[38]. A distinct esthetic/sexual preference exists among men for blondes over brunettes[39].

HETEROCHROMIA

The heterochromia of hair is the presence of more than one distinct color of hair in the same individual. The color difference between scalp hair, the mustache or side burns is not uncommon. Pubic, axillary hair and eyebrows and eyelashes are often darker than scalp hair in a fair haired person. There is a rare occurrence of a circumscribed patch of hair to appear of different colors. However, diffuse heterochromia of black and red scalp hair, has been reported in appearance of a father and son[40]. Generally, scalp hair darkens with age. A circumscribed patch of hair rarely occurs of different color due to pathological reasons, (irregularly alternating segmentation of hair into dark and light bands, in some cases of iron

deficiency anaemia[6]) or due to genetic predisposition of several types: very dark hair growing from a melanocytic naevus or white hair from naevus depigmentosus[41]. It can also be of heredity reasons, usually autosomal dominant heterochromia, as a result of somatic mosaicism, of the white forelock of piebaldism, of the “flag sign” forelock in Kwashiorkor[42], or as a finding of protein deficiency[1,43]. The white forelock has also been reported in Down's syndrome[44].

MINERALS, CHEMICALS, TRACE ELEMENTS AND DRUGS IN HAIR

Hair analyses comprises the determination of minerals, trace elements and drugs. Besides its number of advantages, hair analysis is impaired with the difficulty to distinguish between endogenous and exogenous sources of metals. Except for methylmercury, there are no available critical limit values for trace elements in hair. Aluminium in hair is of no value in environmental medicine. For assessment of cadmium and inorganic arsenic exposure, hair analysis is only suitable as a screening method, based on large populations. The monitoring of lead in hair is also a valuable screening method for small groups, especially for children. Based on toxicokinetics and under the consideration of practicability, the optimal biomarker of methylmercury exposure, is the hair concentration. For other mercury compounds, hair analysis is of lower significance. Nicotine and cotinine measurements provide a practical and proper method for estimating environmental tobacco smoke exposure and validating the smoker’s status in epidemiological studies[45].

Whistle the testing of hair has been used for two hundred years in cases of arsenic determination, today, the development of new methods, such as gas chromatography/mass spectrometry, has permitted numerous applications based on the analysis of organic substances trapped in hair. Useful conclusions can be taken by means of hair analysis and used in several fields, such as : screening procedure of psychiatric patients; management of epileptic patients in monitoring neuroleptics; in the process of evidence of gestational drug exposure; hair nicotine as a marker of passive exposure to tobacco; detection and clinical survey of the heroin addict;

evaluation of pharmaceutical exposure; a tool of clinical diagnosis and for compliance monitoring[46].

More than one mechanism is used to propose and explain the incorporation of drugs into hair. Drugs enter hair only by passive diffusion from the blood stream into the growing cells at the base of the hair follicle, according to one of them. More recent experimental findings suggest that drugs probably enter the hair from multiple sites via multiple mechanisms at various times during the hair growth cycle. A more complex model which is proposed, is that drugs and metabolites are incorporated into hair (a) during formation of the hair shaft - via diffusion from blood to the actively growing follicle - (b) after formation - via secretions of the apocrine and sebaceous glands - and (c) after hair has emerged from the skin - from the external environment. Furthermore, drugs can be transferred to hair from multiple body compartments, or pools, that are located in tissues surrounding the hair follicle. These mechanisms can also be drug-specific[47]. The incorporation of some drugs from sweat into elder hair regions and the slow removal by means of washing, are also discussed[48].

Human scalp hair retains the past of dosage history over a rather long period of time, acting as a 'tape-recorder'. In hair, the length of 1-cm, is successively cut from the scalp end, it will contain the drug that approximately corresponded to the amount ingested over a one month time period. Nevertheless, the rate of hair growth is variable both within and between subjects, due to its own growth cycle[49] and having the ability of radioligand binding with cocaine. Melanin was considered the most likely binding site for cocaine in hair, taking into account that the concentration of melanin is much greater in dark than in light hair; scatchard analysis indicated that dark hair had a 5 to 43 fold greater binding capacity than light hair. Differences in radioligand binding between hair types appeared to be due to differences in the density of binding sites formed by melanin in hair[50]. Other drugs, or their metabolites can also be identified in hair fibers, and the natural hair color is an important parameter in the evaluation of drug concentration pertaining to hair. Hair samples were taken from

patients with grizzled hair and on permanent medical treatment by amitriptyline, carbamazepine, chlorprothixene, diclofenac, doxepine, indomethacine, maprotiline or metoclopramide, haloperidol[51], and also with chronic heroin and cocaine abuse; these hair samples were separated into white and pigmented fibers and both fractions were independently investigated by GC-MS. The concentrations in the white fibers were smaller than in the pigmented ones for the most of the samples investigated[52].The method can be useful in investigating deaths due to an overdose and also in the previous history of drug use and abuse; even more, a "first" or the occasional intake of heroin, can also be determined, which could be a contributing factor to the death related overdose cases, due to lack of tolerance[53,54]. In continuation, cannabis concentration was found to be higher in pubic hair than in scalp hair[55].

Hair would also be a good specimen for disclosure on drug history of fenethylline (FNT) and for the discrimination between FNT use and amphetamine (AP) abuse[56]. Detection in hair of other drugs or their metabolites is also possible : phencyclidine (PCP) and its two major metabolites, 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (PCHP) and trans-1-(1-phenyl-4-hydroxycyclohexyl)-4'-hydroxypiperidine (t-PCPdiol)[57], benzodiazepines and other psychotropic drugs[58].

The synthetic opioid methadone[59] and stanozolol, an anabolic androgenic steroid occasionally abused by athletes[60], can also be traced in hair.

Measuring uric acid in hair can be available for the metabolic control in hyperuricemia[61,62]. It has been found that antimicrobial quinolones (ofloxacinone[49] and temafloxacin[63]), are detectable in hair even after their short exposure. Fentanyl (head hair samples were taken from surgery patients who received the medicine during anesthesia[64]), the antimycotic triazole, fluconazole, during and after administration[65], and chlorpromazine (CPZ) resulted being in white hairs much lower (< 10%) than in black hairs, suggesting that the strong affinity of CPZ for hair melanin may explain the accumulation in black hair[66]. Phencyclidine (PCP)[67], lysergic acid

diethylamide (LSD)[68], ecstasis[69] and their metabolites, can also be detected in human hair.

After multiple and single doses of codeine administration the medicine can be revealed in hair[70,71]. The in vitro incorporation of benzoylecgonine is proportional to melanin content in hair[72]. Arsenic can also be traced in hair after a long term of drinking arsenic contaminated water[73]. Uranium concentrations in hair of non-exposed and occupationally exposed persons, shows some promise as an indicator of exposure[74]. Mercury has also been traced in human hair, sometimes related with the occupational use (in dentists exposed to mercury used in dental restorations)[75] yet not always related to environmental mercury concentrations[76]. The content of antimony in human scalp hair does not seem to represent an indicator of the external absorption from soil. The rate of transfer of antimony from the soil to humans, in the exposure case, seemed to be very low[77].

In both sexes, total and organic mercury concentrations were significantly higher in gray hair than in dark hair, yet no difference was observed between dark hair and gray hair for the concentration of inorganic mercury[78]. Manganese dioxide, in dust, is trapped in hair and reduced by the components of sweat. It then follows the diffusion of manganese into the hair shaft. A population of high exposure to manganese can be affected by the neurological condition of Groote Eylandt Syndrome[79]. The differences in hair metal contents of: mercury (Hg), lead (Pb), cadmium (Cd) , copper (Cu), calcium (Ca), magnesium (Mg), sodium (Na) and potassium (K), iron (Fe), manganese (Mn), aluminum (Al), barium (Ba), calcium (Ca), selenium (Se), boron (B), titanium (Ti), arsenic (As), chromium (Cr), tin (Sn), strontium (Sr)[80], in hair samples, are due to the differences in community lifestyle (dietary, environmental or occupational intake)[81,82]. Zinc (Zn) levels in hair increased and then decreased with age within the puberty group to the elderly group (61-70 year-old). The hair lead (Pb) levels are the lowest in newborns, increased with age from newborn to infant (1-2 year-old), and then decreased with age from infant to elderly. The hair Pb and Zn

levels are inversely related in various age groups that suggest there is possibly antagonism between Pb and Zn, in the human body. The hair Pb levels of subjects living in urban areas, except for newborns, are higher than those of subjects residing in the rural areas, whereas no difference was revealed in the hair Zn contents in populations residing in urban and rural areas[83].

Hair color influences Cu concentrations in both males and females. In males, white hair contains less Cu than black hair; in females, white hair's Cu levels are significantly lower than those of dark blond, red, light brown, and brown hair. There are no significant differences in Zn concentrations with respect to different hair colors, in either males or females[84]. Some researchers believe that hair color, in young boys, shows no significant differences in Zn and Cu concentrations but a significantly higher concentration for Zn:Cu is revealed in boys with black hair than in the other color groups. Correlation between mineral content (Zn and Cu) and melanin is low and non-significant, except for Zn in hair color ranging from 0-100 melanin units ($r = -0.34$, P less than 0.05). Hair color change in children may be important in estimation of mineral nutritional status[85,86].

In female hair, the content of zinc, copper, nickel, manganese and lead, is higher than in male hair independently of color. Blond hair has the lowest concentration values of the elements studied independently of sex. The maximum amount of these metals is found generally in black hair, followed by red and brown. Age seems to have a different influence upon the copper element, decreasing appreciably in brown and blond female hair, as the age of the subjects increased[87].

The hair segment analysis of nicotine indicates that environmental nicotine is the dominating contributor to the overall nicotine found in hair both from smokers and non-smokers[88]. In hair samples obtained from 36 smokers, who had smoked > or = 3 years, there was a significant positive correlation between the concentration of nicotine and the number of cigarettes consumed daily. The nicotine content of white hair was much less than that of black hair collected from the same subjects with

grizzled hair[89]. The nicotine content in hair is proportional to the number of cigarettes consumed daily[49]. The determination of caffeine concentration in the plasma and hair of subjects consuming normal daily amounts of caffeine-containing beverages provides a practical assessment of individual liver metabolic capacity[90].

The diabetics' hair is more heavily glycosylated than normal and there is a correlation between hair glycosylation and the concentration of glycosylated haemoglobin in the diabetics[91].

HAIR COLOR ALTERATIONS DUE TO SYSTEMIC USE OF DRUGS

A wide variety of drugs have been implicated in causing hair color changes but very few have data to support a true relationship[92].

Some systemic drugs alter hair color by interfering with the eumelanin or phaeomelanin pathway. In others, the mechanism is not known[1].

Chloroquine and cancer chemotherapeutic agents have the best evidence to support an association. Chloroquine interferes with phaeomelanin synthesis, and affects only blonde and red-haired individuals where the changes are completely reversible[1]. Hypopigmentation, of hair and freckles, occurred in a patient receiving chloroquine sulfate therapy suffering from severe congenital renal failure, that presumably increased plasma and tissue levels of the drug[93]. Long term therapy with chloroquine and hydroxychloroquine can turn the hair color in white in blonde and red-haired men[94]. Hyperpigmentation of hair has also been reported after chemotherapy[95] and Cyclosporine-A administration[96].

Horizontal pigmented bands developing within the hair of a patient on intermittent high dose methotrexate chemotherapy, is presented in a case report[97].

Tamoxifen has also been reported to induce hair color changes[98].

In the case of a 45-year-old woman who at the age of 34 and for a period of 25 months, was taking a silver-containing pharmacological product (colloidal silicon with 0.5 percent of silver) in order to treat an intestinal dyspepsia with diarrheic episodes.

After few months she developed a cutaneous greyish-blue irreversible pigmentation extending over the whole body, nails, hair, and the oral and gingival mucosae[99].

Yet, other drugs, such as p-aminobenzoic acid, calcium pantothenate, anthralin, chinoform, mephenesin, minoxidil, propofol, valproic acid, and verapamil their direct association in the changing of color, is not yet confirmed. Drug-induced causes should be considered in any patient with unexplained hair color changes[92].

HAIR COLOR ALTERATIONS DUE TO EXTERNAL OR TOPICAL USE OF DRUGS OR OTHER ELEMENTS

Dithranol and chrysarobin (anthrone derivative), anti-psoriatic drugs, can stain light colored or gray hair in mahogany brown, probably due to an increase in plasma of the 5-S-cysteinyldopa (5-S-CD)[100]. Resorcin, formerly used in a variety of skin diseases, turns black or white hair color in yellow or yellowish-brown. Resorcin has the tendency to stain selectively elastic fibres in several human tissues[48]. Today, it is used (combined with other elements) as biological adhesive (GRF) glue in cardiovascular operations[101]. Increasing brown discoloration of all nails and previously fair hair, in short period, was found in patients using water with a high iron content for washing. A high iron content was detected in the discolored parts of the hair[102].

Mephenesin, a glycerol ether used for diseases with muscle spasms, causes pigmentary loss in dark-haired people[92].

Triparanol, (an anticholesterolaemic drug) and fluorobutyrophenone, (an antipsychotic drug) both interfere with keratinization and cause hypopigmentation and sparse hair. Minoxidil and diazoxide, are two potent anti-hypertensive agents, both cause hypertrichosis and darkening of the hair. The color produced by diazoxide is reddish. Minoxidil darkens hair mainly converting vellus hair to terminal hair. Hydroquinone and phenylthiourea interfere with tyrosine activity, causing hypopigmentation of skin and hair[1,92].

GREEN HAIR

An unusual dermatologic condition, usually due to the deposition of copper in the hair, from exogenous sources, has mostly been reported in patients with blond hair, as a consequence of increased concentrations of copper in domestic or swimming pool water. Other predisposing factors include previous hair damage (mechanical, sun exposure, bleaching, dyeing, waving), frequent contact with chlorinated water (swimming pools), or use of alkaline shampoos[103,104]. Green hair discoloration can also be provoked by selenium sulfide[105], and can disappear after the use of penicillamine containing shampoo[106].

COLOR CHANGES DUE TO NATURAL AND TOPICAL FACTORS

Natural hair color changes may occur during lifetime due to biochemical changes and is no longer believed that an individual is producing only one type of melanin, eumelanins or phaeomelanins throughout life[107].

The terminal part of the hair, along its shaft, appears lighter than the rest (the normal "weathering") due to the many interfaces deriving of cortex disruption and followed from internal reflection and refraction of light. The color white, seen when melanin is absent is an optical effect due to reflection and refraction of the incident light from various interfaces at which zones of different refractive index are in contact in the hair shaft[1,9].

Skin whitening, has been associated with the application of hair rinses and permanent and semipermanent hair colors, but their effect on hair color is not yet clear[108].

Irreversible hair matting, is a rare acquired hair disorder, created during hair shampooing. Light and electron microscopy showed dramatic permanent twisting and bending of the hairs through 180 degrees. This bending and entanglement of hairs of varying widths (felting) seemed to be the main reason for the hairs becoming so dramatically knotted together[109].

Cobalt workers get bright blue hair where a deep blue tint may be seen in indigo handlers. Yellowish hair color can be noticed in white or gray haired heavy smokers

due to tar in cigarette smoke. This yellow hair staining may also occur from picric acid and dithranol, whereas trinitrotoluene (TNT) workers, sometimes develop yellow skin and reddish brown hair[1]. Ormones like estrogenes and progesterone, probably increase the hair color[1].

Bleaching of hair has been reported after use of carbamide perhydrate[110], benzoyl peroxide acne lotions[111] and valproic acid[112] and red hair staining after application of chinoform[113].

GREY HAIR

Graying of hair (canities), is the most notable of manifestations of the aging process. This also represents a main characteristic of individual's description. The age of onset is primarily genetically predisposed, being dissimilar in different races, ethnic groups and sexes. It appears earlier in men than women, and in Caucasians than in Negroes and Japanese people. The beard and moustache areas commonly become grayer before scalp and body hair. And the scalp temples usually start graying first[1]. Age estimation, by appearance of grey hair in pubic area is proposed by researchers[114].

The greying of hair, is due to progressive loss of melanocytes from the hair follicles[115] and a decline in the number of melanosomes, synthesized, leading to reduced pigmentation[116].

The larger medullary spaces of older people, may contribute to the process decrease, and eventually cessation of tyrosinase activity in the lower bulb[117]. Autoimmunity has been suggested in participating of the pathogenesis of graying; gray hair certainly has an association with autoimmune diseases, anemias and metabolic disorders[118,119,120]. In human mitochondrial DNA (mtDNA), in hair follicles, deletions occur and accumulate during human ageing[121].

Temporal concentration variations of the short-lived, isotope-producing elements Br, Ca, Cl, Cu, I, Mg, Mn, Na, S, and Zn over time in pigmented and white hair, is also established[122].

Grey hair may temporarily darken after inflammatory processes, after electron-beam induced alopecia, and also after some chemotherapy regimens[123]. Pertaining to a patient with long-standing Parkinson's disease, the white color of his hair turned grey and darkened 8 months after the addition of carbidopa to the established levodopa (L-dopa) therapy and 4 months after the introduction of bromocriptine[124]. Another example is the re-appearance of black hair, after the period of 40 years, that was reported following erosive candidiasis of the scalp[125].

Familial grey hair appeared to be higher than expected in frequency, which is one of a clinical and metabolic characteristic of Parkinsonian patients whose illness started before the age of 40 years[118].

Premature grey hair, associated with anemia, hyperpigmented skin, paresthesia, recurrent aphthous ulcers and epistaxis is reported in literature[121], and eventually proved to be a case of vitamin B_{12} deficiency. However, due to its rarity, the diagnosis may be overlooked. Therapeutic response to vitamin B_{12} was dramatic[126,127].

TURNING WHITE OVERNIGHT - IS IT POSSIBLE?

The first reported episode of rapid whitening of the hair is recorded in the Talmud. Historical examples include Sir Thomas Moore and Marie Antoinette whose hair became gray over the night before their execution[1]. This process can be explained in a two-step course. The first step involves the rapid development of white hair due to vitiligo or alopecia areata[128]. The second step involves the apparent sudden whitening of the scalp hair due to either simultaneous lingering of the white hair or selective loss of the dark hair. In fact, the hair that is perceived as suddenly whitening was already white[129,130]. In the case of a patient (presenting rapid whitening of scalp hair in a three month period) with a diffuse, subtotal alopecia, an immunofluorescence microscopy of biopsy material, showed prominent deposits of IgG and IgM in a granular pattern in the epithelium of the lower portions of hair follicles. The cause of this particular patient's loss of hair color, may be different from

others that are described as having rapid whitening of scalp hair, on account of alopecia areata or vitiligo[131].

The process however, is normally[132] progressive and permanent, ongoing with aging. Repigmentation is reported in cases related with alopecia areata[128], vitiligo and metabolic disorders when the underlying disease is affronted[119,133,134]. Rapid progression of whitening and loss of hair in a 2 months period, was the first manifestation of amyloidosis in a 67-year-old male patient[135].

Premature greying

Premature greying is consider when the onset of greying is before the 20 years of age in Caucasians and 30 years of age in Negroes, and probably with a genetic predisposition which occasionally occurs as an isolated autosomal dominant condition. Premature graying of hair is associated with pathological conditions on the basis of genetic linkage[1]. This can be the early sign of pernicious anaemia, as serum iron also is important in the kinetics of melanogenesis within the follicular melanocytes[6], hyperthyroidism and less commonly, hypothyroidism. Pernicious anemia, premature graying, reversible immunodeficiency and hypoadrenalism where simultaneously presented in a case of primary hypoparathyroidism[136].

Distal lipoatrophy with canities, stunted somatic growth, painful muscle cramps and hypoplastic uterus is presented in the literature as a unique report[137].

Premature canities is an inconstant charateristic of the Rothmund - Thomson syndrome, which is a rare, autosomal recessive disorder associated with characteristic cutaneous changes, sparse hair, juvenile cataracts, short stature, skeletal defects, dystrophic teeth and nails, and hypogonadism. Mental retardation is unusual. An increased incidence of certain malignancies has been reported. Clonal or mosaic chromosome abnormalities and abnormalities in DNA repair mechanisms have been reported in some cases[138]. Correlations with gastrointestinal abnormalities have also been reported[139]. In a recent case-control study, premature graying of the hair is associated with osteopenia, suggesting that this might be a clinically useful

risk factor for osteoporosis[140]. Some researchers are suggesting that premature graying of the hair is associated with premature cardiovascular disease. It should probably be regarded as a coronary risk factor and used to identify patients at increased risk[141,142]. Other studies performed to see if early graying was associated with increased morbidity, earlier age at death, and specific cause of death, provide no such evidence to support the contention that early gray hair is a risk factor[143,144].

In one case a patient with Darier's disease presented jouvenile canities[145].

"Asymmetric gray hair" phenomenon has been suggested as a clinical sign in the diagnosis of syringomyelia[146].

Canities and vitiligo can be complicating factors in interferon therapy for hepatitis C[147].

Gray hair, is also presented in patients with *ataxia-telangiectasia (A-T)*, also called *Louis-Bar (L-B) syndrome*, with the characteristic telangiectasias and vitiligo, impetigo, recurrent herpetic gingivostomatitis, hirsutism, lipoatrophyprogeroid changes and hyper- and hypopigmented macules[148]. Cerebellar ataxia begins in infancy with a slow progressive course. In the late stages, free walking and standing are no longer possible. Progressive atactic speech disorders and cerebellar atrophy are also presented[149]. Individuals with this form of ataxia are more susceptible to sinus and lung infections and may also develop tumors (neoplasia)[123,150].

Very early graying can be a symptom in premature aging syndromes as a result of the accelerated aging procedures[151].

Hutchinson-Gilford progeria syndrome, is a very rare progressive disorder of childhood characterized by premature aging (progeria). Growth delays, occurring in the first year of life, and results in short stature and low weight, deterioration of the layer of fat beneath the skin (subcutaneous adipose tissue), and characteristic craniofacial abnormalities including an abnormally small face, underdeveloped jaw (micrognathia), unusually prominent eyes, and/or a small, "beak-like" nose. In addition, during the first year or two of life, scalp hair, eyebrows, and eyelashes may

become sparse, and veins of the scalp may become unusually prominent. Additional symptoms and physical findings may include joint stiffness, repeated nonhealing fractures, a progressive aged appearance of the skin, delays in tooth eruption (dentition), and/or malformation and crowding of the teeth. Individuals with the disorder typically have normal intelligence. In most cases, affected individuals experience premature, widespread thickening and loss of elasticity of artery walls (arteriosclerosis), potentially resulting in life-threatening complications. Hutchinson-Gilford Progeria Syndrome is thought to be due to an autosomal dominant genetic change (mutation) that occurs for unknown reasons (sporadic)[152].

It is also worthy to note *Werner's syndrome (pangeria)*, that begins in adolescence or early adulthood, and results in the appearance of old age by the age of 30 - 40. Physical characteristics associated with the disorder may include short stature, prematurely aged appearance of the skin, premature balding, cataract, and/or other abnormalities. The Werner Syndrome is thought to be inherited as an autosomal recessive genetic trait[151,152,153].

Premature greying may be also presented, as a non-constant symptom, in other, rare progeroid syndromes such as:

Wiedemann-Rautenstrauch syndrome (also known as *Neonatal Progeroid Syndrome)* is an extremely rare genetic disorder, characterized by an aged appearance at birth (neonatal progeroid appearance). Growth delays before and after birth (prenatal and postnatal growth retardation), subcutaneous lipoatrophy, causing the skin to appear abnormally thin, fragile and wrinkled. In addition, for reasons that are not understood, abnormal deposits of fat may accumulate around the buttocks, the anogenital area and flanks. Affected infants and children also have distinctive malformations of the craniofacial area including an unusually prominent forehead (frontal bossing) and sides of the skull (parietal bossing), causing the head to appear abnormally large (pseudohydrocephalus). Unusually small, hypoplastic bones of the face and abnormally small facial features, a small "beak-shaped" nose that becomes

more pronounced with advancing age, and/or sparse scalp hair, eyebrows, and/or eyelashes. Most infants and children also have unusually thin arms and legs, abnormally large hands and feet, progressive neurological and neuromuscular abnormalities, varying degrees of mental retardation and severe delays in the acquisition of skills requiring the coordination of mental and muscular activities (psychomotor retardation). Furthermore, in many cases, affected infants and children prone to repeated respiratory infections that may result in life-threatening complications. The syndrome is inherited as an autosomal recessive genetic trait[154,155].

GAPO syndrome, with white eyelashes[156]) . The onset of greying hair can be the first symptom of other pathological entities as in dystrophia myotonica[1], or in other cases a non constant symptom as in *Wolf-Hirschhorn syndrome,* an extremely rare disorder due to deletions on chromosome 4p16[157]. Major symptoms may include extremely wide-set eyes (ocular hypertelorism) with a broad or beaked nose, microcephaly, low-set malformed ears, mental and growth deficiency, cardiac defects, and seizures. In some cases antibody deficiencies are reported[158].

Cri du Chat syndrome, a rare chromosomal disorder that is apparent at birth and is characterized by a distinctive high-shrill-mewing-"kitten-like"-cry during infancy. This distinctive “cry” becomes less pronounced during late infancy. Other findings and symptoms may include low birth weight and failure to grow at the expected rate; also distinctive abnormalities of the craniofacial area including microcephaly, widely spaced eyes (ocular hypertelorism), and an unusually small jaw (micrognathia). Mental retardation exists, due to contiguous gene deletion resulting from hemizygous deletions of chromosome 5p[159].

and *Book's syndrome*[1].

Grey hair can be also be presented in rare syndromes as in :

1)Spastic paraparesis, mental retardation, and cutaneous pigmentation disorder, presented in four siblings of a family with a highly consanguineous background with

an unusual combination of muscle wasting, microcephaly, skeletal deformities, and hypopigmented and hyperpigmented lesions and graying of the hair[160].

2) In a new familial syndrome that affected young women with a very peculiar phenotype, poikilodermia and hair graying, and idiopathic nonarteriosclerotic cerebral calcifications. A marked and progressive hyalinosis involving capillaries and often arterioles and small veins of the digestive tract, kidneys, and calcified areas of the brain. Diarrhea, rectal bleeding, malabsorption, and protein-losing enteropathy were the main and lethal clinical problems. Hypertension, and mild proteinuria, peripheral retinal ischemic syndrome and chorioretinal scars and a subarachnoid hemorrhage, due to a right sylvian aneurism, also occurred in both sisters and was lethal for one of them[161].

HAIR COLOR CHANGES DUE TO PATHOLOGICAL REASONS

Changes in the shape and color of hair are mentioned in malabsorption syndromes like: acrodermatitis enteropathica, dermatitis herpetiformis, Whipple disease, Cronkhite-Canada syndrome, dermatogenic enteropathy and abnormalities that occur as complication from the surgery treatment for obesity improvement[162].

Hair color changes result from alterations in melanin production and from changes in the hair structure, altering its optical properties. A variety of genetic, metabolic, nutritional, and acquired disorders result in hair color changes. When the underlying defect can be corrected, hair color usually returns to normal. The flag sign can occur as a result of nutritional insults[86] or due to medication. Most drug-induced changes in hair color result into a lighter hair color, although PABA and some chemotherapy regimens have resulted in darkening hair[123].

Tuberous sclerosis

Is a rare genetic multi-system disorder, characterized by the appearance of characteristic benign tumors in various areas of the body, seizures, and mental retardation. Other findings and symptoms may include developmental delays; characteristic skin lesions (e.g., adenoma sebaceum), lesions in the eyes (ocular),

uncontrollable involuntary muscle spasms (myoclonic jerking), and/or learning disabilities. The range and severity of associated symptoms and findings may vary greatly from case to case. Tuberous sclerosis is inherited as an autosomal dominant genetic trait. Two genes have been identified that may cause this disorder. One disease gene, the TSC1 gene, is located on the long arm of chromosome 9 (9q34). The other, TSC2 gene, has been located on the short arm of chromosome 16 (16p13.3)[163]. Approximately 65 percent of the cases of Tuberous Sclerosis occur as a result of a spontaneous genetic change (new mutation). The disease can be bilateral and can have an early onset[164]. A tuft of white scalp hair is a useful new sign of tuberous sclerosis in the newborn and young child, whilst the hair should be examined as carefully as the skin when early 'organic' seizures are unexplained[165,166].

AIDS

Four Negroes, with the acquired immunodeficiency syndrome (AIDS) demonstrated profound alterations in hair patterns 2 to 3 years after their first symptoms appeared. The hair became longer, lighter, softer, and silky, with an occasional discoloring[167].

Segmented heterochromia

A newly recognized disorder of black scalp hair, is described as the irregular alternating segmentation of hair into dark and light bands, in 15-year-old girl who had segmented heterochromic scalp hair, in association with iron-deficiency anemia. Clinical and laboratory investigations support the view that low serum iron levels, play a critical role in reducing eumelanogenesis, and in the possible failure of melanin transfer. The segmented heterochromic hair recovered completely after iron supplementation (Canities segmentata sideropaenica)[6].

Hypopigmentation in Prader-Willi (PWS) and Angelman (AS) syndromes.

Hypopigmentation in PWS and AS syndromes, is characterized by light skin, reduced retinal pigment, low hairbulb tyrosinase activity, and incomplete melanization of melanosomes, due to interstitial deletions of the proximal long arm of one

chromosome 15 (q11-q13). PWS usually results from a paternal deletion of 15q11-q13 or maternal disomy for chromosome 15. Hypopigmentation is the result of deletion of the P gene in the context of PWS[168]. Electron microscopic examination of hairbulb melanocytes showed normal melanosome and melanocyte architecture and number, but reduced melanin formation, with many stage II and III premelanosomes but few stage IV fully melanized melanosomes[30,169,170,171].

The Angelman syndrome is an extremely rare disorder, characterized by congenital mental retardation, the absence of speech, unprovoked laughter, unusual facial features, and muscular abnormalities. Children with this disorder smile often and easily and may have episodes of excessive laughter. This syndrome was first described as the Happy Puppet Syndrome; this term is now obsolete. On the basis of molecular findings, the Angelman syndrome (AS) patients can be classified into the following 4 groups: (1) familial cases without deletion, (2) familial cases with submicroscopic deletion, (3) sporadic cases with deletion, and (4) sporadic cases without deletion. The molecular deletion, which commonly extended from D15S9 to D15S12, although not all deletions, are identical. In other groups of patients deletion involves only 2 loci, D15S10 and GABRB3. Among sporadic and familial cases without deletion, no uniparental disomy was found and most of them were shown to inherit chromosomes 15 from both parents (biparental inheritance). Most clinical manifestations, including neurological signs and facial characteristics, were not distinct in each group except for hypopigmentation of skin or hair. Familial cases with submicroscopic deletion were not associated with hypopigmentation[172].

Prader-Labhart-Willi syndrome (PLWS)

Hypopigmentation, behavioral problems, significant differences in hair color, sun sensitivity and dental abnormalities are the main characteristics of the PLWS. Individuals with the deletion frequently had lighter hair color, more sun sensitivity, and fairer complexion than did either other family members or nondeletion PLWS patients. No significant differences in biochemical findings (phenylalanine, tyrosine,

catecholamines, or beta-melanocyte-stimulating hormone) were found between deletion and nondeletion PLWS patients, or between hypopigmented and normally pigmented patients. The data suggest that a gene(s) controlling the activity of tyrosinase or other enzymes required for melanin production is located on proximal 15q[171,173].

Menkes' disease

Is a genetic disorder of copper metabolism, beginning before birth. Copper accumulates in excessive amounts in the liver, and is deficient in most other tissues of the body. Structural changes occur in the hair, brain, bones, liver and arteries. Is a sex-linked recessive disease (abnormal X chromosome)[174]. It is manifested in the first year of life with severely retarded mental and physical development, convulsions, a particular phenotype and abnormalities of the hair, bones and arteries. Diverticula of the bladder mucosa and serosa, as well as cortical atrophy and malformed cerebral vessels can also be associated with the disease[41]. Also hair abnormalities consisting of pili torti and white hair, and low levels of serum copper (Cu) and ceruloplasmin. Is also called kinky hair or steely hair syndrome, and is caused by abnormal Cu metabolism. The kinky hair formation results from low activity of sulfhydryl oxidase, which is a Cu enzyme[175].

In very bright portions of hair eumelanin's and pheomelanin's levels are only half of those to be normal. A patient's hair changed to dark brown after subcutaneous administration of copper-histidinate for 2 months[176].

Partial yellow scalp hair

Partial yellow coloration of the scalp hair has been reported, due to decreament of eumelanin content, in the yellow hair, whereas the pheomelanin content was normal. As an example, the patient suffers of congenital hypomelanosis with a segmental pattern on the left abdomen, whorl-like pattern on the back; mosaic pattern on the chest, right abdomen, and proximal extremities. (Nevus depigmentosus systematicus with partial yellow scalp hair)[177].

ANEMIAS

Serum iron also is important in the kinetics of melanogenesis within the follicular melanocytes[6].

Two Latin-American patients, one with congenital and one with acquired pernicious anemia, had reddish hair while they were cobalamin deficient. With the appropriate treatment, the new hair growth assumed its normal premorbid dark brown color[178].

Hair depigmentation has also been reported in patients with pernicious anaemia, from Africa[179].

Cross syndrome

Cross syndrome has autosomal recessive inheritance[180] and is characterized by oculocerebral syndrome and cutaneous hypopigmentation as first delineated by Cross in 1967 in three siblings of an inbred Amish family. The mixed pattern of hair pigmentation is an important diagnostic sign [181]. The cases can be sporadic or with familial recurrence presenting deep mental retardation and spastic tetraplegia with athetoid movements[180,182].

Uveitis, poliosis, hypomelanosis, and alopecia in a patient with malignant melanoma.

The spontaneous development of bilateral uveitis, poliosis, hypomelanosis, and alopecia (Vogt-Koyanagi-Harada syndrome) was found in a 57-year-old woman following operation for metastatic malignant melanoma[183].

A case resembling the 'fleck retina of Kandori' with ectodermal peculiarities and macula degeneration.

The case of a 36-year-old woman followed-up for nine years is reported presenting unique, sharply-defined, irregular, yellow, large flecks of the retina combined with bilateral macula degeneration. The patient's rusty-red hair, enamel dysplasia, and ashen-gray skin color were also noted. It is the first case reported outside Japan[184].

Riyadh chromosome breakage syndrome : mental retardation with depigmentation of the skin and hair.

A recently described entity in 20-month-old infant with "silvery-blond" hair color, widespread confetti-like depigmentation of the skin, and mental retardation. in lymphocytes and fibroblast cultures, increased spontaneous chromosome breaks and breaks induced by both mitomycin and gamma-irradiation. The sister chromatid exchange frequency was normal. This child probably represents a new chromosome breakage syndrome[185].

Ataxia-deafness-retardation syndrome

First described in three brothers by Berman et al (1973), followed by a case of three sisters aged 16, 12 and 8 years from a consanguineous family. They present progressive spinocerebellar ataxia combined with moderate mental retardation, progressive sensorineural hearing loss and signs of both upper and lower motor neuron disease. In the described family, the transmission of the disease appears to be linked with occurrence of red hair color[186].

Waardenburg syndrome (WS)

Waardenburg syndrome (WS) is a hereditary disorder that causes hypopigmentation and hearing impairment. Depending on additional symptoms, WS is classified into four types: WS1, WS2, WS3 and WS4. Mutations in MITF (microphthalmia-associated transcription factor) and PAX3, encoding transcription factors, are responsible for WS2 and WS1/WS3, respectively. MITF transactivates the gene for tyrosinase, and is critically involved in melanocyte differentiation. Absence of melanocytes affects pigmentation of the skin, hair and eyes, and hearing function in the cochlea.

Hypopigmentation and hearing loss in WS2 are results of an anomaly of melanocyte differentiation caused by MITF mutations. PAX3 directly regulates MITF and the failure of this regulation due to PAX3 mutations causes the pigmentary and auditory symptoms in at least some individuals with WS1. The molecular mechanism by which PAX3 mutations cause the pigmentary and auditory disorders in WS1/WS3 is not yet clear[187].

Waardenburg syndrome type 1 (WS1)

Type 1 Waardenburg syndrome (WS1) is an autosomal dominant disorder characterized by dystopia canthorum, sensorineural deafness, and pigmentary disturbances[188]. 17%-58% of the patients present a white forelock[189,190] .

Waardenburg syndrome type 2 (WS2)

Type 2 Waardenburg syndrome (WS2), is a dominantly inherited syndrome of hearing loss, with no dystopia canthorum and pigmentary disturbances of reduced hair pigmentation, due to mutations affecting splice sites in the MITF gene located in the chromosome 3p12.3-p14.1[191]. Broad nasal root, heterochromic or hypochromic irides and synophrys are also presented in both types of the syndrome.

Woolf's Syndrome

Can present with pigmentary changes that are similar to Waardenburg syndrome. Woolf's syndrome also includes deafness. However, the distinguishing structural ophthomologic abnormalities of dystopia canthorum, broad nasal root, and synophrys are not found in Woolf's syndrome[189].

Reversible Hypopigmentation in Homocystinuria

Deficiency of cystathionine beta-synthase (CBS) is a genetic disorder of transsulfuration resulting in elevated plasma homocyst(e)ine and methionine and decreased cysteine. Homocyst(e)ine inhibits tyrosinase, the major pigment enzyme and where the probable mechanism of this inhibition is the interaction of homocyst(e)ine with copper at the active site of tyrosinase. Affected patients have multisystem involvement, which may include light skin and hair[192].

Endocrine disorders resulting in severe early-onset obesity, adrenal insufficiency and red hair pigmentation in two patients.

The central role of alpha-MSH in the regulation of food intake by activation of the brain melanocortin-4-receptor (MC4-R; refs 3-5) and the linkage of human obesity to chromosome 2 in close proximity to the precursor protein pre-pro-opiomelanocortin (POMC) (that generates the melanocortin peptides adrenocorticotrophin (ACTH),

melanocyte-stimulating hormones (MSH) alpha, beta and gamma as well as the opioid-receptor ligand beta-endorphin) locus, lead to the proposal of an association of POMC with human obesity. Patients with a defect in POMC function present early-onset obesity, adrenal insufficiency and red hair pigmentation[193].

Disordered pigmentation, spastic paraparesis and peripheral neuropathy

Three siblings of a Jordanian family presented with a distinctive syndrome consisting of disordered skin and hair pigmentation, progressive spastic paraparesis and peripheral neuropathy. Sural nerve biopsy revealed axonal degeneration and skin biopsy showed abnormal epidermal pigmentation. No underlying biochemical defect has been found in this previously undescribed neurocutaneous syndrome[194].

Spastic paraparesis, mental retardation, and cutaneous pigmentation disorder

The unusual combination of spastic paraparesis, muscle wasting, microcephaly, mental retardation, skeletal deformities, and cutaneous manifestations of hypopigmented and hyperpigmented lesions and graying of the hair, is reported in four siblings in a family with a highly consanguineous background. An autosomal recessive inheritance is probable[195].

Neuroectodermal melanolysosomal disease.

The syndrome was identified in three consanguineous families, who had common ancestors, and is characterized by profound dysfunction of the central nervous system, silver-leaden colored hair, abnormal melanosomes and melanocytes, and abnormal inclusion bodies in fibroblasts, bone marrow histiocytes and lymphocytes which appear to represent abnormal lysosomal bodies[196].

Chediak-Higashi syndrome

Chediak-Higashi syndrome is a rare recessive autosomal disease, a form of albinism, caused by mutations in a single gene encoding a protein of unknown function, called lysosomal-trafficking regulator[197]. It is characterized by a decreased pigmentation and visual difficulties. Leukocyte abnormalities associated with Chediak-Higashi

syndrome result in immune deficiencies. Affected individuals may have an increased susceptibility to infections and certain cancers[198].

An African Kenyan female infant was born with very light skin and ashen grey, scanty hair. At 18 months she was presented with a bluish skin pigmentation, hepatosplenomegaly, generalised lymphadenopathy and non-responsive fever. A bone marrow aspirate and peripheral blood examination done revealed characteristic features of the Chıdiak-Higashi Syndrome. This is a rare disorder, not previously described in Africans[199].

Griscelli syndrome

The Griscelli syndrome is a rare autosomal recessive disorder on chromosome 15q21 and is associated with mutations in the myosin-Va gene leading to disorders in organelle-transport machinery[200].

Partial albinism with immunodeficiency defines this uncommon disorder characterized by pigmentary dilution (relatively light skin color) and variable immunodeficiency, presented with a silvery-gray sheen to the hair, large clumped melanosomes in hair shafts, and prominent mature melanosomes in cutaneous melanocytes with sparse pigmentation of adjacent keratinocytes. Immunologic abnormalities include impaired natural killer cell activity, absent delayed-type hypersensitivity, and impaired responses to mitogens and hypogammaglobulinemia. Acute phases of uncontrolled lymphocyte and macrophage activation, leads to death in the absence of bone-marrow transplantation[200]. Recurrent infections may be present and neurological involvement varying from mild cognitive delay with a convulsive disorder to a fatal degenerative course, is reported[201].

The syndrome can be differentiated from the Chediak-Higashi syndrome by pathognomonic features in light and electron microscopy in skin and hair, and the absence of consistent granulocyte abnormalities. Symptoms may start in the newborn period[202]. Cerebral involvement. hypotonia and motor retardation with increasing hepatosplenomegaly, have also been reported in a case[203,204].

The Griscelli-Prunieras syndrome

The case report of a six-year-old girl, with silvered hair syndrome, of Griscelli-Prunieras variety, is presented. A hereditary sickness with regressive autosomic and distinguished by partial albinism and leukocytic alterations. The patient presented the acute phase of the sickness defined by: hepatosplenomegaly, thrombocytopenia, generalized lymphadenopathy, and systematic infection; the giant inclusions in bone marrow leukocyte and peripheric blood, that are feature of Chediak-Higashi syndrome, were not present in this case. The distribution of mote of melanin on the hair that in the Griscelli-Prunieras syndrome are six times bigger in the Chediak-Higashi syndrome[205].

Marfan's syndrome

Marfan syndrome is an inherited disorder that affects the connective tissues of the heart and blood vessels (cardiovascular system). The musculoskeletal system (ligaments and muscles) is also affected. Major symptoms also include unusual height, large hands and feet, and involvement of the lungs and the eyes. The anatomical substrate of Marfan's syndrome is a degeneration of elastic fibres and disorganization of the collagen, due to mutation of genes localized on chromosome 15. The first (FBN1) codes for the main constitutive protein of the elastic tissue: fibrillin 1, are present mainly in structures which must resist load and stress (aortic adventitia, the suspending ligament of the lens and skin); the second (FBN2) codes for fibrillin 2 : responsible for the orientation of the elastin and mainly present in cartilage, the aortic media, the bronchi, and all tissues rich in elastin[206].

The cutaneous expression of Marfan's syndrome is generally limited to striae distensae and a number of uncommon associations with other dermatologic disorders. It is reported a patient with Marfan's syndrome who presented with an acquired white forelock[207].

Hypohidrotic ectodermal dysplasia (HED)

Hypohidrotic ectodermal dysplasia (HED) can be distinguished in two types the X-linked form of HED (XLHED) autosomal recessive disorder (ARHED)[208]. The disease involves abnormalities of tissues of ectodermal origin due to developing mental disturbances in the embryonal state, including trichodysplasia, dental defects, onychodysplasia, and dyshidrosis, eczemas, thin, dry skin, typical facial features such as saddle-nose, unusually thick lips, and/or a large chin, deformity and periorbital wrinkling and pigmentation. It is primarily characterized by partial or complete absence of certain sweat glands (eccrine glands), causing lack of/or diminished sweating (anhidrosis or hypohidrosis), heat intolerance, and fever. Also underdevelopment (hypoplasia) or absence (aplasia) of mucous glands within the respiratory and gastrointestinal (GI) tracts and, in some cases, decreased function of certain components of the immune system (e.g., depressed lymphocyte function, cellular immune hypofunction). There can also be present otolaryngologic problems, respiratory diseases and mild mental retardation. Diagnosis of the syndrome can be suspected at an early stage in a child with recurrent fever of unknown etiology, thin blond hair, and anodontia. Patients with the syndrome have a life expectancy similar to that of the general population. Direct mutation detection would enable carrier detection in female relatives of sporadic cases, as well as to help distinguish the X-linked form of HED (XLHED) from the rarer and clinically indistinguishable, autosomal recessive disorder (ARHED)[208].

The X-linked recessive form of HED, also known as Christ-Siemens-Touraine syndrome, is the most frequent and widely documented form that is caused by mutation in a novel transmembrane protein[209,210]. Only a small minority of affected males can be diagnosed by direct mutation analysis and linkage analysis, in informative situations, which is the only practical diagnostic option available[211]. In autosomal dominant hypohidrotic ectodermal dysplasia (ADHED) by genetic linkage analysis, researchers have mapped a gene for ADHED (EDA3) to the proximal long arm of chromosome 2 (q11-q13)[212].

Obstructive cardiomyopathy in a male dwarf with cryptorchidism

A case of a male dwarf with bilateral un-descended testes and biventricular obstructive cardiomyopathy, is reported. The clinical symptoms were choreoathetoid movements, chorioretinitis, bilateral nystagmus, and unusual red color of the hair, associated with some features of Turner phenotype. The patient presented the lack of thyrotrophic stimulating hormone (TSH). Obstructive cardiomyopathy has been reported in cases of male and female Turner phenotype with normal chromosomes[213].

Familial defect in cellular chemotaxis associated with redheadedness and recurrent infection

The familial defect in polymorphonuclear leukocyte chemotaxis associated with red-headedness and recurrent infection, was found in two of six siblings, not associated with a concurrent defect in leukocyte bactericidal activity. These children experience recurrent infections, although immunoglobulin levels (IgG, IgA, IgM, and IgE) and complement components (total hemolytic complement, Clq, C3 and C3PA) were all within normal limits; mobility and phytohemagglutinin-stimulated lymphocyte transformation were also within normal limits. These studies demonstrate a familial PMN defect limited to leukocyte chemotaxis and associated with recurrent infection and possibly red-headedness[214].

Osteopathia striata associated with familial dermopathy and white forelock

A case was reported of a white Caucasian woman and her two daughters who developed osteopathia striata and a macular, hyperpigmented dermopathy. The skin lesions were not those most often associated with osteopathia striata, but appeared to be a unique dermatosis, which also included a hypopigmented forelock, probably inherited with X-linked or autosomal dominant transmission[215].

Syndrome of brittle cornea, blue sclera, and joint hyperextensibility

This rare autosomal recessive syndrome has variable expressivity. In some of the patients affected with the syndrome of brittle cornea, blue sclera, and joint

hyperextensibility (brittle cornea syndrome), two different groups may be distinguished: one includes 5 families, all of Tunisian Jewish origin and where patients in this group also have red hair. In the second group, 9 families are from various ethnic origins where the affected patients in this group have a normal distribution of hair color. A possible explanation for the existence of these two different groups of patients is that the locus of the gene is responsible for the syndrome and is closely linked to the locus for a gene responsible in hair color with linkage disequilibrium in Tunisian Jews (Sepharadim)[216].

Acquired ichthyosis, alopecia and loss of hair pigment associated with leiomyosarcoma

A case is presented of a 70-year-old woman with acquired ichthyosis and leiomyosarcoma, one of the less frequently associated malignancies. An additional unusual finding was generalized thinning and loss of pigment, affecting her hair. Scalp biopsy showed histological evidence of ichthyosis. Following resection of the tumour, the ichthyosis resolved, and there was re-growth of darker hair[217].

Nevoid hypertrichosis

The case of a 23-month-old Caucasian girl, with congenital circumscribed areas, of deeply pigmented terminal hairs that gradually lost their pigment over the next two years, is presented in the literature. Physical examination revealed no other abnormalities[218].

Nevus depigmentosus systematicus with partial yellow scalp hair

A Japanese patient with congenital hypomelanosis, showed a segmental pattern on the left abdomen, whorl-like pattern on the back; mosaic pattern on the chest, right abdomen and proximal extremities, and with yellow hair on a portion of the scalp. Chemical analysis of the yellow hair revealed decreased eumelanin content, whereas the pheomelanin content was normal[219].

Yellow forelock--a new neuro-ophthalmological sign.

A middle-aged man with a prominent yellow forelock, complained of loss of vision in both eyes. He smoked his pipe avidly and drank a little Bourbon whisky, daily. The nicotine content of the forelock (21.7 ng/mg) was 10 times that of the hair on his occiput (2.23 ng/mg). A yellow forelock when associated with isolated painless visual loss suggests tobacco amblyopia[220].

Progressive spastic paraparesis, vitiligo, premature greying, and distinct facial appearance

Is described progressive spastic paraparesis of the lower limbs in the presence of generalized vitiligo, premature graying of body hair, and distinct facial appearance was reported in 3 patients, whose parents were first cousins and considered as autosomal recessive trait. This neurocutaneous disorder is of unknown pathogenesis[221].

Albinism

Albinism connotes a large group of genetic disorders that are characterized by diminished ocular and oftentimes cutaneous pigmentation. These disorders are generally sub-classified as oculocutaneous albinism (OCA) or ocular albinism (OA), based on the extent of their effects on the pigmentation of the skin and hair. Sometimes, different mutations in the same gene can cause OCA or OA [220]. The pathologic gene mutations causing OCA can be divided according to the phenotype disorders manifesting. When a mutated tyrosinase gene produces inactive, less active, or temperature-sensitive tyrosinase, its phenotype is tyrosinase-negative (type I-A), yellow-mutant (type I-B), or temperature-sensitive (type I-TS) OCA, respectively. Mutation of the P gene encoding the tyrosine-transporting membrane protein probably occurs in tyrosinase-positive OCA (type II)[222]. *According to other researchers five types of oculocutaneous albinism (OCA) can be determined. Type IA (tyrosinase-negative) and type IB (yellow mutant) individuals had low or no measurable tyrosinase activity, and heterozygotes for these two types are detectable. Type II (tyrosinase-positive) individuals have moderate to high activity, and the*

heterozygotes for this type are not detectable. Type III (minimal pigment) individuals have low activity, and heterozygote levels are useful in detecting this type of OCA. Type VI (Hermansky-Pudlak syndrome) individuals have moderate to no measurable activity, and heterozygotes for this type cannot be detected[223].

Hermansky-Pudlak Syndrome is a rare, hereditary disorder, that consists of four characteristics: lack of skin pigmentation (albinism), blood platelet dysfunction with prolonged bleeding, visual impairment, and abnormal storage of a fatty-like substance (ceroid lipofuscin) in various tissues of the body.

Oculocutaneous albinism, consist of hereditary disorders, in which there is a congenital absence or reduction of melanin in the skin, hair and eyes, with nystagmus, photophobia and reduced visual acuity. The body is unable to make melanin, due to the functional absence of the enzyme tyrosinase. The disease is transmitted as an autosomal recessive character. Some writers suggest six conditions distinguishable in relation to their frequency, and their clinical, biochemical, ultrastructural, and genetic characteristics. The attempt to identify the heterozygote has led to contradictory results. Abnormal transparency of the iris has only been observed in some heterozygotes, and this feature cannot be used to recognise carriers. The main problems are sensitivity to sunlight, with concomitant susceptibility to skin tumors, and collateral vision disturbances. Patients should avoid direct sunlight[224,225].

Sometimes normally pigmented people who do not look like albinos can in fact be albinos. It appears that patients with autosomal recessive albinism can be normally pigmented, and patients with X-linked albinism can be severely hypopigmented. The prevalence for all forms of albinism is at least 1:15,000 and about 10% of the albinos have X-linked albinism[226].

Autosomal recessive ocular albinism (AROA), is a disorder characterized by reduced pigmentation of the retina and iris, hypoplastic fovea, variably reduced visual acuity and nystagmus. Pigmentation of the skin and hair is normal, but is usually slightly

lighter than in unaffected sibs related with abnormalities of the tyrosinase (TYR) gene[227].

Clear ethnic differences are observed in the major form of tyrosinase-negative oculocutaneous albinism as well as in other forms of oculocutaneous albinism, cutaneous albinism and the very rare ocular albinism. Most interesting is the borderline between normal variation and abnormal forms, especially illuminated in rutilism or red headedness in Negroids, and high frequencies of pigmentation anomalies without appreciable disadvantages for the carrier, e.g., the reddish skin of geographically isolated Papuans. The very differential frequencies of the occurrence of pigmentation anomalies in some populations are influenced as well by population genetic factors (isolation/inbreeding, founder-effect, heterosis) as also by socio-cultural factors (albinism as a marriage barrier, infanticide), and in some areas perhaps some kind of “negative selection” in which individuals with the character in question, fail to reach reproductive age[228].

By some writers, it was proposed to modify the albino definition as a hereditary and congenital inborn error of metabolism related to the pigment cell, characterized by anomalies of eyes, and hypopigmentation in most cases or absence of pigment in skin, hair, and eyes, and the characteristic neuro-anatomical consequences. Also to abandon the terms oculo-cutaneous albinism (OCA), and X-linked ocular albinism (XOA), and use the terms autosomal recessive albinism, and X-linked albinism instead[226].

Pseudoalbinism due to selenium deficiency.

Selenium levels were low in four children receiving long-term total parenteral nutrition (TPN) who developed erythrocyte macrocytosis (3/4), loss of pigmentation of hair and skin (2/4), elevated transaminase and creatine kinase levels (2/4), and profound muscle weakness (1/4). After 6 to 12 months of intravenous selenium supplementation, the two children with decreased pigmentation became darker skinned and their hair color changed from blonde to dark brown; a third child's hair,

which had been blonde, also became darker. Transaminase and creatine kinase levels returned to near normal in those affected and, in the one child with severe myopathy, muscle weakness improved[229].

Red or rufous albinism

Red or rufous albinism is a rare type of oculocutaneous albinism described, but not as yet fully investigated, in Africa and New Guinea. The combination of the unusual red skin color, ginger to reddish hair, low sensitivity to sun damage, and minimal visual problems, in affected individuals, suggested that they form a group which is distinct from the brown and other types of albinism[230]. The mode of inheritance was found to be recessive. Tyrosinase assays showed that rufous albinos are tyrosinase positive and on electron microscopy studies normal melanosomes and melanocytes were observed in hair bulbs and skin. Visual evoked potential testing did not show the gross decussation abnormalities of the optic pathway detected in other types of albinism. Rufous albinism might be at one end of the spectrum of types of oculocutaneous albinism[231].

Phenylketonuria

This is an autosomal recessive disorder, in which the tissues are unable to metabolize phenylalanine to tyrosine because of phenylalanine hydroxylase deficiency, due to base substitutions in exon 12 of the phenylalanine hydroxylase (PAH) gene[232]. Mental retardation fits and decreased pigmentation of the skin, eyes and hair occurs with eczema and dermographism. Black hair may become brown, reddish[233], or in older phenylketonurias may have pale blonde or gray hair. Tyrosine treatment causes darkening towards normal color within 12 months[1].

Poliosis

This is called the presence of a localized patch of white hair due to the absence or deficiency of melanin in a group of neighboring follicles.

Etiology

Molecular basis of congenital hypopigmentary disorders

The melanocytes are of neural crest embryonic origin, migrate into specific target sites, synthesizing melanin(s) within a specialized organelle, transfers pigment granules to neighboring cells, and responds to various exogenous stimuli. The process of melanogenesis can be interrupted by mutations in many of the respective encoding genes and can result in hypopigmentary disorders of skin and hair. The specific transcription factors PAX3 and MITF (microphthalmia transcription factor) appear to play a regulatory role in early embryonic development of the pigment system and in associated diseases (Waardenburg syndromes). During the subsequent development and commitment of the melanoblast, concomitant expression of the receptors for fibroblasts growth factor (FGFR2), endothelin-B (EDNRB), and steel factor (cKIT) also appears essential for the continued survival of migrating melanoblasts. Lack or dysfunction of these receptors result in :

Apert syndrome (acrocephalosyndactyly)[234], a rare inherited disorder characterized by premature closure of the bones of the skull (craniosynostosis) causing the head to appear long and pointed at the top (acrocephaly). Other features of this disorder include fusion or webbing (syndactyly) of the fingers and/or toes and unusual facial features such as widely spaced, protruding eyes and dental crowding. May be inherited as an autosomal dominant genetic trait, or sporadic.

Hirschsprung syndrome (Aganglionosis involving the rectum or rectosigmoid or the left colon, the proximal colon or total colonic aganglionosis. Enterocolitis occurres in some cases[77]. Aganglionosis is due to loss of neural cell adhesion molecule inhibits neurocytes to migrate to aganglionic regions, and loss of nitric oxide can well explain the spasticity associated with the aganglionic region)[235] and

Piebaldism, respectively. Once the melanocyte resides in its target tissue, a plethora of melanocyte specific enzymes and structural proteins are coordinately expressed to

form the melanosome and to convert tyrosine to melanin within it. Mutations in the genes encoding these proteins results in a family of congenital hypopigmentary diseases called oculocutaneous albinism (OCA). The tyrosinase gene family of proteins (tyrosinase, TRP1, and TRP2) regulate the type of eumelanin synthesized and mutations affecting them result in OCA1, OCA3, and slaty (in the murine system), respectively. The P protein, with 12 transmembrane domains localized to the melanosome, has no assigned function as of yet but is responsible for OCA2 when dysfunctional. There are other genetically based syndromes, phenotypically resembling albinism, in which the synthesis of pigmented melanosomes, as well as specialized organelles of other cell types, is compromised. The Hermansky-Pudlak syndrome (HPS) and the Chediak-Higashi syndrome (CHS) are two such disorders. Eventually, the functional melanocyte must be maintained in the tissue throughout life. In some cases it is lost either normally or prematurely. White hair results in the absence of melanocytes repopulating the germinative hair follicle during subsequent anagen stages. Vitiligo, in contrast, results from the destruction and removal of the melanocyte in the epidermis and mucous membranes[198].

Hereditary defects

Piebaldism (white spotting or partial albinism) is an autosomal dominant genetic disorder[23] of pigmentation characterized by congenital white patches of skin and hair totally depigmented, which remain unchanged throughout life. The frontal white patch - the white forelock - may be the only sign[1]. Melanocytes are lacking or are dramatically decreased in number, with abnormal shape and contain normal nonmelanized premelanosomes, and also premelanosomes and melanosomes of abnormal appearance[178]. It is suggested that piebaldism-affected skin is immunologically different from normal skin[236].

These hypopigmented regions can be the result of mutations of the KIT-gene (c-kit gene), which encodes the cell surface receptor transmembrane tyrosine kinase for an embryonic growth factor, the steel factor (SLF)[237]. Several pathologic mutations of

the KIT-gene have been identified in different patients with piebaldism and the correlation of these mutations with the associated piebald phenotypes has led to the recognition of a hierarchy of three classes of mutations that result in a graded series of piebald phenotypes[238]. An heterozygous mutation of the c-kit gene encoding mast cell-stem cell growth factor receptor also contributes in inducing piebaldism[223].

Sometimes it is characterized by a white forelock and freckled depigmentation of the forehead, chin, ventral trunk and extremities. Normal pigmentation is found on the back, hands and feet. Within the non-pigmented areas may be present patches of hyperpigmentation[237]. The melanin pigmentary abnormalities of the hair and skin in piebaldism, Waardenburg's syndrome, piebaldism with deafness, and piebaldism or Waardenburg's syndrome with aganglionosis of the gut were suggested as disorders belonging to the same category, considering them the results of defective development of the neural crest[240]. These disorders of pigment cell development represent a subgroup of the neurocristopathies, involving defects of various neural crest cell lineage's that include melanocytes, and many other tissues derived from the neural crest[241]. Piebaldism can also be associated with other diseases like neurofibromatosis 1 (NF-1)[242].

Successful repigmentation was achieved 6 to 8 months in 6 patients with three types of hypomelanosis (vitiligo, piebaldism, and albinism) by transplantation of fresh, autologous cultured epithelium with melanocytes, The autologous cultured epithelial grafting procedure, is a promising treatment for patients with hypomelanosis[243].

Cartilage-hair hypoplasia

Cartilage-hair hypoplasia is an autosomal recessive metaphyseal chondrodysplasia with short-limbed short stature, hypoplastic hair and defective immunity and erythrogenesis. Is manifested with increased ligamentous laxity, limited extension of the elbows, increased lumbar lordosis, thoracal deformity, genu varum, scoliosis, defective cellular immunity and increased susceptibility to infections and childhood anaemia. Hirschsprung disease can be associated with this entity[244].

ABCD syndrome

The case of a macrosomic newborn girl with albinism, a black lock at the right temporo-occipital region, and retinal depigmentation, bilateral deafness and a severe defect of intestinal innervation. Biopsy showed aganglionosis of the large intestine and total absence of neurocytes and nerve fibers in the small intestine, indicating a total lack of sympathetic and parasympathetic innervation. The infant died of intestinal dysfunction at 5 weeks. She was the 14th child of consanguineous Kurdish parents. Four sibs of our patient had the same syndrome and died a few days after birth. The other 9 sibs are well, with an unremarkable phenotype. It represents a new neural crest syndrome with autosomal-recessive inheritance[245].

Tiez's syndrome

Tiez's syndrome is generalized as a 'white spot' loss of skin and hair pigment, complete deafness, mutism and eyebrow hypoplasia. Whether or not melanocytes are present in the affected areas remains controversial[1].

Vogt-Koyanagi-Harada syndrome

This is a rare disease of unknown origin that affects many body systems such as the eyes, ears, skin, and the meninges. The most noticeable symptom is a rapid loss of vision. There may also be neurological signs such as severe headache, vertigo, nausea, and drowsiness. Loss of hearing, alopecia and skin color may occur along with whitening of the hair and eyelashes (poliosis). Is also presented with uveitis, dysacousia, madarosis[246], although uncommon, Vogt-Koyanagi-Harada may also affect young children, and may be severe[164].

A new white forelock (poliosis) syndrome with multiple congenital malformations in two siblings.

Two Jewish Ashkenazi male patients are reported as having a new syndrome consisting of a white forelock, distinct facial features associated with congenital malformations involving the eye, cardio-pulmonary and skeletal systems. The etiology

of this disorder is probably genetic and transmitted either as an autosomal recessive or X-linked recessive conditions[247].

Branchio-oculo-facial syndrome associated with a white forelock

A father and his daughter are presented with branchio-oculo-facial syndrome. Since birth the father, and to a lesser extent his daughter, demonstrated a white forelock which has not been reported before as associated with this syndrome. The analysis of the second to the eighth exon of PAX3 genes did not reveal any abnormality in these cases. By the authors is proposed the analysis of the EYA1 gene[248].

Elejalde syndrome--a melanolysosomal neurocutaneous syndrome in 7 patients

This rare autosomal recessive disease is characterize by silvery hair and severe dysfunction of the central nervous system (neuroectodermal melanolysosomal disease or Elejalde syndrome) The main clinical features include silver-leaden hair, bronze skin after sun exposure, and neurologic involvement (seizures, severe hypotonia, and mental retardation). Large granules of melanin unevenly distributed in the hair shaft and abnormal melanocytes and melanosomes and abnormal inclusion bodies in fibroblasts may be present. The differential diagnosis must be done with Chıdiak-Higashi syndrome and Griscelli syndrome. The age of onset of neurologic signs ranged from 1 month to 11 years including severe muscular hypotonia, ocular alterations, and seizures. Mental retardation since the first months of life was noted in 4 cases. Psychomotor development was normal in 3 cases, but suddenly the patients presented with a regressive neurologic process. Four patients died between 6 months and 3 years after the onset of neurologic dysfunction. One patient showed characteristic ultrastructural findings of Elejalde syndrome. Psychomotor impairment may have two forms of presentation: congenital or infantile. Although Elejalde syndrome and Griscelli syndrome are similar, the possibility that they are two different diseases, although probably allelic related, is suggested[249].

Epidermal melanocytes in different hypopigmentary disorders, from skin specimens from patients with piebaldism, naevus depigmentosus, and vitiligo, were examined by immunohistochemistry (cryosections), using monoclonal antibodies against the c-kit protein (YB5.B8) and melanosomes (TA99). In piebaldism, hypomelanotic epidermis contained only a few TA99-positive epidermal melanocytes and no detectable c-kit protein, in naevus depigmentosus the expression of c-kit protein was strong, and TA99 immunoreactivity was faint. In vitiligo lesions, no epidermal immunoreactivity for melanosomes or c-kit protein was found[236].

Physical hair changes

The new-formed unpigmented hair has yellowish color due to its dense keratine.

Hairs on exposed parts may be bleached by sunlight [9].

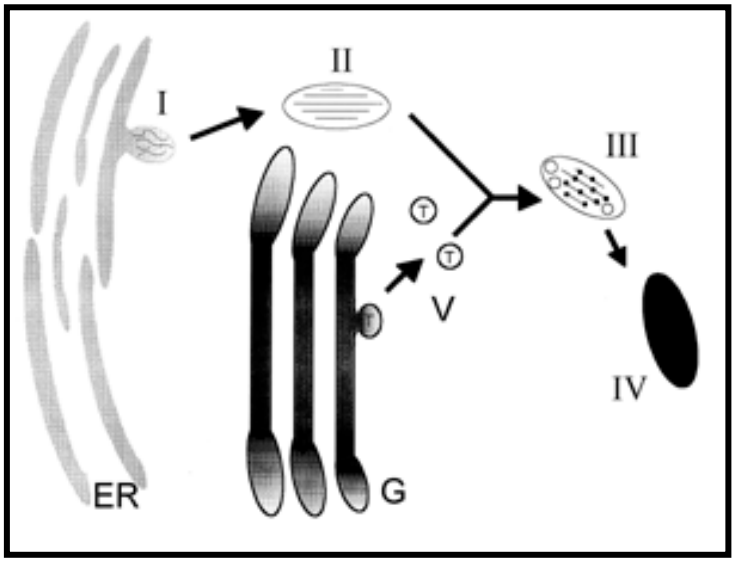
I
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FIG 1

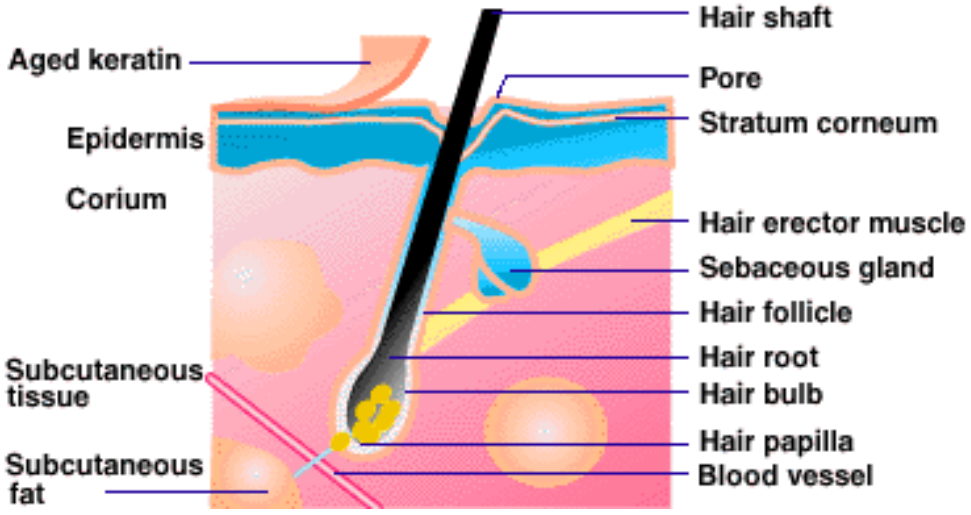
Aged keratin
Epidermis
Corium
Subcutaneous tissue
Subcutaneous fat
Hair shaft
Pore
Stratum corneum
Hair erector muscle
Sebaceous gland
Hair follicle
Hair root
Hair bulb
Hair papilla
Blood vessel

FIG 2

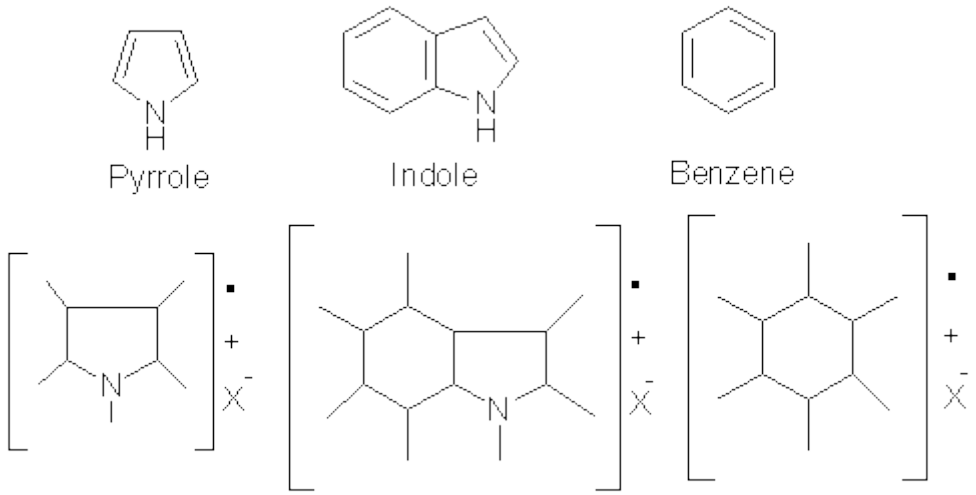

FIG 3

FIG 4

Von Luschan's Chromatic Scale

The equipment necessary for classification is: Von Luschan's chromatic scale for classifying the color of the skin. There are 36 opaque glass tiles for confronting the subject's skin-color. Martin's color grading scale for the color of the eyes. It consists of 16 glass eyes used to compare the color of the subject's eyes. Fisher's hair color chart consisting of 30 tufts of cellulose hair. (Museo di Storia Naturale.UNIVERSITÀ DEGLI STUDI DI FIRENZE, ITALY).

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