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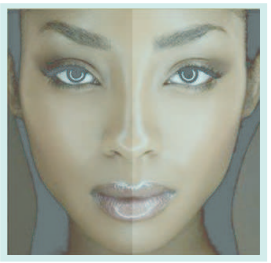
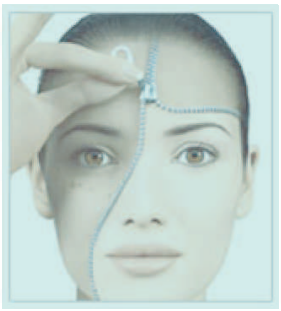
WOMEN'S HEALTH

Vol-5 No-3 July-Sept 2012





Editorial Note:

Dear Doctor,

It's our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on skin lightening producsts and the effects of chronic use.

Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

Complications of chronic use of skin lightening cosmetics

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WOMEN'S HEALTH

Complications of chronic use of skin lightening cosmetics

A middle-aged Nigerian lady was recently brought home to die from a Western European country because she developed an uncontrollable diabetes mellitus and evidence of hypothalamicituitary-adrenal axis suppression. On clinical examination, the lady had dense stigmatas of chronic use of skin lightening creams, which was confirmed through history. Majority of medical practitioners outside subsaharan Africa may not be familiar with this habit of bleaching the skin nor the cutaneous and extra-cutaneous complications of this widespread cosmetic habit of black Africans. Furthermore, these cosmetics and toiletries are not sold in the regular departmental stores nor pharmacy shops in Europe and North America. They are either manufactured purely for export to Africa or are exported from Africa to Europe and N. America so that they are sold only in local shops in ghettos patronized by the black Africans.

This paper sets out to give a brief review of this problem so that practitioners worldwide would be aware of these complications which may at times be fatal.

Literature review

The use of skin bleaching agents or lighteners has been reported in many parts of the world, such as Kenya, Ghana, South Africa, Zimbabwe, USA, Great Britain, and Saudi-Arabia. Various chemicals have been used with consequent undesirable side-effects. While phenols were reported to have been associated with ochronosis the mercurials were implicated in nephropathy. Addo in Ghana has also reported squamous cell carcinoma associated with prolonged bleaching.

A survey done in Mali reported that 25% of two hundred and ten women developed 74 different side-effects from the use of bleaching creams. Similarly, in a refugee camp in Balkan, 22.3% of the inhabitants including children were found to have high concentrations of urinary mercury, which was traced to the use of mercury containing bleaching ointments, supplied.

Exogenous ochronosis was first reported in 1906. It commonly presents as asymptomatic blue-black macules on the malar areas, temples, inferior cheeks and neck. This condition resembles endogenous ochronosis in the skin histologically, but does not exhibit any systemic complications or the urinary abnormality. Hydroquinones are by far the most common offending agents, but phenol, quinine injection and resorcinol have also been implicated.

In South Africa, where the first reports of complications of hydroquinone abuse was reported, the government was prevailed upon in 1980 to set an upper limit of 2% hydroquinone content in cosmetic products. Britain and the United States of America also limit the concentration of hydroquinone in cosmetic products to a maximum of 2%, and in dermatological preparations to 4%. Although it was originally believed that only high concentrations of hydroquinone were causal there have been reports of ochronosis after use of 2% hydroquinone preparations. It has also been suggested that the percentage of hydroquinone quoted by a manufacturer may not represent the true concentration of hydroquinone in a product. It may be that it is not the high concentration of hydroquinone, but rather, extended use of this substance, which causes the disease. An analysis of 41 bleaching creams available over the counter in the UK in 1986 by Boyle and Kennedy revealed that eight contained more than 2% hydroquinone.

The scenario in Nigeria

The use of skin lightening creams has become a serious phenomenon widely practiced by both men and women in Nigeria. In a study of four hundred and fifty Nigerians who confessed the use of bleaching creams, 73.3% were

Table 1 A list of some of the bleaching creams used by patients in Nigeria and ingredients as labeled

Cream	Ingredients
Movate	Betamethasone dipropionate
Crusader	Vitamed B3 toner 2%, Escalol UV 507, Vit E Allantoin
Looking Good	2% hydroquinone, Allantoin, Sunscreen, Vit E
Peauclair	Hydroquinone, Clobetasol propionate
Mic	Hydroquinone, Dimethicone, D-methyl-PABA
Tura	Octyl-Dimethyl PABA, Dimethicone,
Aqua	glyceryl, propylene glycol mubbery
A3	A-hydroxyl acids, methyl p-ben
Ultra	Vitamed B3 toner 2%, Escalol UV 507, Vit E Allantoin
Venus	Benzophone 3-Dimethicone, Cyclomethicone
Swiss	collagen Triethanolamine, Carbomer, Dimethicone
Fashion	Fair Betamethasone dipropionate
IKB	Triethanolamine
Shirley	Natural Essences from botany
Ambi	2% hydroquinone padimate
Skin Success	2% hydroquinone Octisalate
Sivoclaire	2% hydroquinone, Vit E 1.0
Fashoin Fair	Clobetasol propionate 0.05
Tony Montana	Stearic Acid, MPG, Sorbitol Jelly, Fragrance

women and 27.6% were men. The use of bleaching creams cuts across all sociodemographic characteristics. People of all religious groups, single or married, rich and poor, literate and illiterate, low, middle and upper class use the products.

Various reasons were given for using the products. Some of these are to look more attractive; to go with existing fashion trend; to treat skin blemishes like acne or melasma; to cleanse or "tone" the face and body; or to satisfy the taste of ones spouse. Although the men also use the products for the above reasons, some of them claimed they use the creams because their wives use them; and some male marketers of female cosmetics and toiletries claim they use the products to advertise their wares. Some of the men are homosexuals. The habit of bleaching the skin is most rampant among commercial sex workers who camouflage their occupation in the clinic data as "fashion designer" because of the opprobium attached to prostitution.

It is noteworthy that even some people who are naturally fair in complexion, still use the bleaching creams to "maintain" the light skin color and prevent tanning or blotches from sunlight. As a result of both medical and public outcry against the damaging effects of the skin lightening creams, the National Food and Drug Agency of Nigeria (NAFDAC) had initially allowed a maximum of 2% hydroquinone in bleaching creams. However, due to the adverse side-effects associated with long-term hydroquinone use and also lack of compliance with content and labeling requirements, all forms of bleaching agents were prohibited in cosmetics and toiletries. However, in spite of the ban on these products, both the importation and manufacture of the products have continued unabated.

This situation has been fostered largely by the vulnerability of the consumers, the inexpensive nature of some of these products, and the advertising agencies, who use light complexioned ladies to advertise most consumer products (e.g. alcoholic and nonalcoholic beverages, toiletries, cosmetics, textiles, telephone handsets, etc.) both on the electronic and print media. Hence, the dominant signal being sent to an undiscerning mind is that light complexioned people are the beautiful ones.

In regard to ingredient labeling of cosmetics and toiletries in Nigeria, most products are not registered by NAFDAC, and bear no ingredient labeling nor address of manufacturers. Some are even misbranded, e.g. a product which was labeled as "Betnovate-N" was found to contain Mercury. Furthermore, the concentrations of chemicals on the labeled products were largely found to be inaccurate on analysis as most products exceeded the concentrations displayed on the products. Since hydroquinone and mercury in cosmetics and toiletries have been prohibited and have gained some notoriety, manufacturers have now resorted to using synonyms of hydroquinone to camouflage the products. Some of these synonyms include 1, 4-Benzenediol, Quinol, Benzene-1, 4-diol, p-Diphenol, p-Dihydroxyl benzene, Hydrochinone, p-hydroxylphenol, Hydrochinonium, Hydroquinol, and Tequino l. All corticosteroid preparations can be purchased over-the-counter in Nigeria. Hence, these products are readily available not only in the pharmacy shops but also among drug vendors in the open market place.

Table 2 Contents of some creams analyzed

Cream	Hydroquinone (mg%)	Mercury (mg/kg)
Looking Good	1.36	0.17
Movate	5.10	0.20
Crusader	3.45	0.26
Sivoclaire	0.06	0.22
Peauclaire	0.06	0.21
Mercury	1.68	0.82
Mic	0.06	0.22
Tura	1.45	0.23
A3	0.42	0.18

Chemicals often used and methods of use

The list of some of the bleaching creams used are given in Table 1, and the contents of some analyzed products are on Table 2. The same products are largely available in the African countries mentioned above because of easy cross country trade links. The active ingredients commonly used are hydroquinone, mercury, and a broad spectrum of the very potent corticosteroid preparations containing, e.g. Betamethasone valerate and Clobetasol propionate.

Furthermore, the products are hardly used as marketed and various additives are used to "enhance" the bleaching effect. Some of the additives (concoction) are lemon juice, potash, tooth paste, liquid milk, pulverized Naphthalene (camphor) balls – a mothproofing agent, Vitamin C, peroxides and chlorates used in hair dyes. At times detergents are added to the concoction. Some of the creams have equivalent soaps with same chemicals incorporated. Indeed, the above listed additives are not exhaustive.

At the initiation of the bleaching habit, a total body surface immersion "bath" is often used for maximum effect. The bleaching is then maintained with daily applications of the creams. Most of the creams are very cheap so it is possible to spend as little as 2 US dollars (about 300 Nigerian Naira) a month on the bleaching creams to maintain the light complexion. Continuous use of the chemical is mandatory so that the skin does not repigment. Even when the complications appear, the bleachers often intensify the use of the chemicals with the

hope that the skin complications would eventually be bleached away. Multiple products containing different chemicals may be used concurrently or sequentially.

The duration of use of the bleaching creams before the onset of complications vary from 6 to 60 months. However, history from patients is often inaccurate, and some even deny use of the bleaching creams, or pretend not to know their functions due to a guilt complex, because various religious groups and the press continue to condemn the practice of changing the color of the natural skin.

Pathogenesis and complications

Hydroquinone

Hydroquinone is a dihydric phenol that has two important derivatives viz monobenzyl and monomethyl ether of hydroquinone. Hydroquinone is known to competitively inhibit melanin production by inhibiting sulfhydryl groups and acting as a substrate for tyrosinase. The melanosomes and ultimately the melanocytes are damaged by semiquinone free radicals released during the above reaction.

With prolonged application and sun stimulation, the melanocytes recover from the damaging effect of the hydroquinone which passes down into the papillary dermis of the skin. Hence they are actively taken up by fibroblasts and lead to altered elastic fiber production and excretion of abnormal material into new fiber bundles. Furthermore, benzoquinone acetic acid formed during the oxidative processes in which hydroquinone is involved, bind and cross link collagen fibers leading to degenerative changes due to altered physico-chemical bonds.

Histologic examination of exogenous ochronotic lesions reveals yellow-brown banana-shaped fibers in the papillary dermis. Homogenization and swelling of the collagen bundles is noted and a moderate histiocytic infiltrate may be present. Sarcoid-like granulomas with multinucleated giant cells engulfing ochronotic particles have been noted. Transfollicular elimination of ochronotic fibers has also been described. Fibers stain black with Fontana stain and blue-black with methylene blue stain. Ultrastructural examination reveals homogenous electron-dense, irregular structures embedded in an amorphous granular material infiltrating adjacent collagen fibril bundles. The source of these ochronotic fibers is not clear. Topical hydroquinones may inhibit homogentisic acid oxidase in the skin, resulting in the local accumulation of homogentisic acid that then polymerizes to form ochronotic pigment. Pigmented particles may be elastic or collagen fibers. Melanocytes may be involved; most cases involve sun-exposed sites and one case is reported of ochronosis that avoided areas of vitiligo. The changes in the collagen bundles may be responsible for the loss of elasticity and poor wound healing.

Complications of hydroquinone use that have been reported are dermatitis, exogenous ochronosis, cataract, pigmented colloid milia, scleral and nail pigmentation and patchy depigmentation. The pigmented exogenous ochronotic lesions are most marked on sun-exposed areas of the body namely, face, upper chest and upper back. Dogliotte described 3 stages of this condition: (1) Erythema and mild pigmentation; (2) hyperpigmentation, black colloid milia and scanty atrophy; and (3) papulonodules with or without surrounding inflammation- exogenous ochronosis. Since most commercial sex workers use these skin lightening creams, some of them are HIV positive; and in an attempt to bleach away the pruritic papular eruption (PPE) commonly seen in HIV/AIDS patients, the skin of the extremities appear scruffy with the excoriated papules on a background of ochronotic pigmentation on bleached skin. A

Figure: Exogenous ochronosis

patient developed squamous cell carcinoma on the site of chronic exogenous ochronosis. It is not clear if this is a chance finding or an expected sequelae of hydroquinone induced exogenous ochronosis with superimposed chronic sun damage on the vulnerable skin. Coalescence of multiple colloid milia may give rise to big nodular lesions particularly on the upper back. The fawn colored pigmentation of all 20 nails may mimic the yellow nail syndrome – hence the authors call the phenomenon " pseudo yellow–nail syndrome." Abnormal repigmentation of depigmented skin has also been reported on discontinuing therapy. This abnormal repigmentation has been attributed to the Meirowsky effect of long wavelengths of ultraviolet light darkening melanin already present in the skin and leading to a skin color darker than that prior to bleaching. Because of this repigmentation, users find it compelling to continue to use the bleaching creams to maintain the newly acquired light colored skin. Hence, the inevitable complications from prolonged use. A more serious complication is loss of elasticity of the skin and impaired wound healing. When cutting through the skin, either for incisional biopsy or other surgical procedures, it is as if one was cutting through the skin of a cadaver. There is difficulty in apposing the edges of the wounds when stitching, hence the skin often tears through the suture material. Furthermore, there is often delayed wound healing. After major abdominal surgeries like Caesarian section, myomectomy, hysterectomy, etc., there may be catastrophic wound dehiscence, burst abdomen, and death from overwhelming infection.

The chronic bleachers also exude an offensive fish odor in the sweat like the "fish odor syndrome." The "fish odor syndrome", also known as trimethylaminuria, is characterized by body odor of rotten fish. This is due to excretion of a chemical, trimethylamine in the breath, urine, sweat, saliva, and vaginal secretions.

Trimethylamine (TMA) is produced in the gut mainly by bacterial degradation of choline and lecithin-rich foods, such as salt water fish, eggs, offals (such as intestines, liver, and kidney), and leguminous vegetables such as soya beans. Normally, this compound is converted by TMA oxidase into a stable nonodorous trimethylamine N-oxide (TMA-oxide) that is then excreted in the urine. In the presence of a defective TMA oxidase activity, the accumulated TMA is eliminated as a volatile product in the urine, sweat, and breath, giving the affected individual the characteristic fishy smell.

The TMA oxidase activity may be defective because of a congenital, inherited impairment of N-oxidation (primary trimethylaminuria) or for other acquired reasons that interfere with the action of the enzyme (secondary trimethylaminurias). Some of these causes are: (1) overload with TMA precursors, such as choline and lecithin, leading to the formation of an increased burden of TMA through enterobacterial degradation; (2) intake of inhibitors of TMA oxidase, both dietary (e.g. Brussels sprouts) and pharmacologic (e.g. thiourea), and (3) liver and kidney diseases. In all these cases, the causative agent may act rather as an inducing, precipitating factor in predisposed subjects, who are carriers of the potential defect as heterozygotes. Other causes of fish odor are bacterial vaginosis, and pemphigus vulgaris or foliaceus due to muco-cutaneous bacterial degradation of body fluids.

Hydroquinone is an antioxidant, it may cause the fish odor by reducing the ability to oxidize trimethylamine in chronic bleachers, or hydroquinone may act rather as an inducing, precipitating factor in predisposed subjects, who are carriers of the potential defect as heterozygotes.

Treatment of exogenous ochronosis has been disappointing. Tretinoin gel, cryotherapy, and trichloroacetic acid have been tried without benefit. Cases of exogenous ochronosis successfully treated with dermabrasion and CO_2 laser and Q-switched ruby laser have been reported.

Mercury

Mercury exists in three forms: organic, inorganic and elemental. Mercury is a protoplasmic poison, which can be absorbed by the respiratory tract as vapor or through the skin and gastrointestinal tract as finely dispersed granules, and excreted through the kidneys and colon. Cole observed that the amount of mercury excreted by the kidneys was proportional to the quantity applied on the skin. Until some decades ago, mercury was ubiquitous in medicinal products such as those used for treating syphilis, psoriasis, ringworm, ophthalmic solutions, teething powders, and diuretics. Though it is no longer commonly used in medications. Mercury toxicity after topical applications was noted in 1923.

Mercury toxicity may manifest in an acute or chronic form. Acute toxicity usually manifests as a pneumonitis and gastric discomfort. Chronic toxicity may be evidenced by neurological manifestations and nephrotoxicity. Both organic and inorganic preparations of mercury have been associated with acute and chronic toxicity. Nephrotic syndrome due to topical or systemic use of mercury has been well documented. Both membranous glomerulonephritis and proliferative glomerulonephritis were found in patients who had used mercury containing skin lightening creams.

Mercurious chloride, oxide and ammoniated mercury were first introduced into the market during the first decade of the 20th century as the active ingredient in cosmetics and toiletries. They eventually became popular as skin lighteners. Following studies with electron microscope, mercury bleaches the skin by probably inactivating the

sulfhydryl enzymes. These enzymes, which are called mercaptans due to their ability to capture mercurial ions, then replace copper by competitive inhibition leading to inactivation of the tyrosinase molecule and interrupting melanin production. Paradoxically, chronic use of mercury can also lead to increased pigmentation, due to accumulation of mercury granules in the dermis. These granules are absorbed via the skin appendages such as the hair follicles and sebaceous glands into the dermis. Deposition of mercury in keratin also leads to discoloration and brittleness of the nails. Goeckermann noted that a brown-gray discoloration of the face and neck (especially the skin folds and eyelids) was associated with prolonged use of mercury containing creams.

Corticosteroids

Corticosteroids bleach the skin. It is believed that they lighten the skin due to inhibition of endogenous steroid production and thus a decrease in precursor hormone levels. This precursor hormone, propiocortin is also the precursor for melanocyte stimulating hormone and thus, such negative feedback will lead to decreased amounts of the hormone. Topical steroids are also cytostatic to the epidermis. When used over a prolonged period, they decrease the rate of epidermal turnover, with fewer, abnormal, and less pigmented melanocytes on histology. The skin lightening properties of these preparations have been found to be directly proportional to their vasoconstrictor (blanching) effect.

Fluocinonide (Topsyn gel), Betamethasone dipropionate and Clobetasol propionate rate as some of the strongest topical corticoids, and are among the commonly used bleaching agents in Nigeria. They are readily available in the market place among the battery of bleaching creams. When used as cosmetics, they are applied over a large surface area for prolonged periods – several months to years. This factor, coupled with the occlusive effect of environmental heat and humidity, promote percutaneous absorption, and hence, complications. The possible complications of chronic corticosteroid use are shown in Table 3. All these complications have been observed among chronic bleachers in Nigeria. Overt features of Cushing's syndrome – "mooning" of the face and truncal obesity are frequently seen. Some of them, at the time of presentation, have already developed systemic manifestations like glucose intolerance and hypertension.

Table 3: Complications of topical steroids

Cutaneous
- Atrophy of the skin (thinning and fine wrinkling)
- Telangiectasia, purpura, persistent erythema
- Skin fragility
- Hypertrichosis
- Perioral dermatitis
- Pustular acneiform eruption (face) – steroid rosacea
- Folliculitis
- Striae
- Hypopigmentation
- Steroid addiction syndrome
- Predisposition and masking of cutaneous infection (e.g. Tinea incognito, multiple filiform warts)
- Allergic contact dermatitis

Ophthalmologic
- Glaucoma
- Cataracts

Endocrinologic
- Cushingoid syndrome with moon facies, buffalo humps, supraclavicular fat pads
- Hyperglycaemia and diabetes mellitus
- Suppression of hypothalamic-pituitary-adrenal axis
- Suppression of growth in children
- Menstrual irregularities
- Edema
- Electrolyte imbalance
- Hypertension
- Pseudotumor cerebri

Others
- Aseptic necrosis of the head of femur
- Predisposition to infection
- Protein catabolism with negative nitrogen balance
- Weakness, vertigo
- Thrombophlebitis
- Osteoporosis

Steroid addiction syndrome

The steroid addiction syndrome is the result of chronic daily application for greater than a 1-month period of a potent or moderately potent glucocorticosteroid preparation to the facial skin, neck, scrotum or vulva. These tissues become "addicted" to the topical steroid, so that withdrawing the topical steroid results in severe burning which is only relieved by further steroid applications. As application continues, the patient experiences a rebound vasodilatation. Permanent redness of the facial skin eventuates, with thinning and fine wrinkling of the skin. Indeed the redness is so striking that the authors call the phenomenon "L'homme rouge." For unexplainable reason, this permanent redness is more pronounced on male bleachers. Furthermore, the thinning and wrinkling of the skin on the neck gives a rippling pattern like the neck of a plucked chicken, rather reminiscent of pseudoxanthoma elasticum – hence, the authors code this complication of steroid as "pseudo - pseudoxanthoma elasticum." Some bleachers claim that they developed the habit of chronic steroid use while trying to treat acne. They experienced good response initially due to the anti-inflammatory effect of the steroids. Abruptly stopping the topical steroids preparation will result in increased numbers of papules and pustules over the subsequent days – a "rebound phenomenon." The patient

soon finds it difficult to stop the steroid and the facial skin then develops persistent redness, and acneiform papules and pustules located on the nose, chin, cheeks, and lower eyelids – acne rosacea.

Predisposition to infections

A very common observed complication of steroid on chronic bleachers is dermatophyte infection. Tinea faciei (Fig. 11) is common in these patients and may mimic cutaneous lupus erythematosus or rosacea. Very bizarre and extensive Tinea corposis and cruris (Fig. 12) are often seen, which are readily transmitted to the spouse and baby. Hence, it is common to find the trio of wife, husband and baby with Tinea incognito. Older children are not part of this phenomenon. The wife often transmits the fungal infection to husband and baby because of close body contact. Figure 13 shows a child with Tinea incognito on the forehead, acquired from the infected skin of the mother while feeding on her breast. The clinical presentation of these steroid induced dermatophyte infections are often atypical – hence the term Tinea incognito. Tinea versicolor could also be very extensive, and is usually pigmented with dirty brown scales.

Figure: Tinea faciei

Also, multiple histologically proven viral warts are frequently found on these chronic bleachers. They often appear in an eruptive manner – rather reminiscent of eruptive seborrheic keratosis (Leser-Trélat sign). Hence the authors call this complication " pseudo -Leser-Trelat sign." They are multiple tiny filiform warts, common on the neck and upper trunk. Paradoxically, topical corticosteroid preparations may induce allergic contact dermatitis. This complication should be considered in any patient with an eczematous dermatitis who becomes worse or is refractory to topical steroid treatment.

Figure: Tinea incognito in a child

Ref: Complications of chronic use of skin lightening cosmetics. Yetunde M. Olumide,,MD, Ayesha O. Akinkugbe MD, Dan Altraide MD et al.. International Journal of Dermatology 2008, 47, 344–353.

Congratulations !

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