A New Formula for Depigmenting Human Skin

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Complete depigmentation of the normal skin of adult male blacks was procured by the daily application for five to seven weeks of a formula consisting of 0.1% tretinoin, 5.0% hydroquinone, 0.1% dexamethasone, and hydrophilic ointment. Depigmentation was not attainable when any one of the components was omitted.

The formula was therapeutically effective in treatment of melasma, ephelides, and postinflammatory hyperpigmentation. Senile lentigines were resistant to this therapy.

Pigmentary changes are an important source of human misery. They immediately set one apart and consequently threaten psychosocial and psychosexual identity. Pigmentary nonconformists are never praised and are generally viewed as odd and unattractive. The lack of

to pigmentary abnormalities as "cosmetic." One untoward effect of such cavalier "put-downs" is to divert individuals with pigmentary problems to beauticians rather than physicians. Dermatologists, happy to say, generally accord these patients the sympathy they need and are well schooled in the utilization of available remedies.

The current therapy for hyperpigmentation is unsatisfactory. Although a great deal is known about

nin synthesis, an acceptable means of reducing excessive melanization is not at hand.

HISTORICAL BACKGROUND

The ancients showed great enterprise in the search for agents that would lighten hyperpigmented skin. The fact that many of their methods are still with us today eloquently de-

period began when Oettel produced grey hair in black cats by feeding them hydroquinone.[1] Since that time the capacity of this agent to produce depigmentation has been demonstrated in fish, rodents, and man.[2,3,4]

An occupational accident in 1939 triggered a tremendous interest in the possible therapeutic applications of hydroquinone derivatives.[5] Black workers in a tannery experienced depigmentation of the hands under the

responsible agent proved to be the anti-oxidant, monobenzylether of hydroquinone (MBEH). Lerner and Fitzpatrick then showed that this chemical could depigment the normal skin of blacks and was indeed useful for alleviating pathologic hyperpigmentation.[6] Creams containing up to 20% MBEH became available by prescription. Hope, however, soon gave

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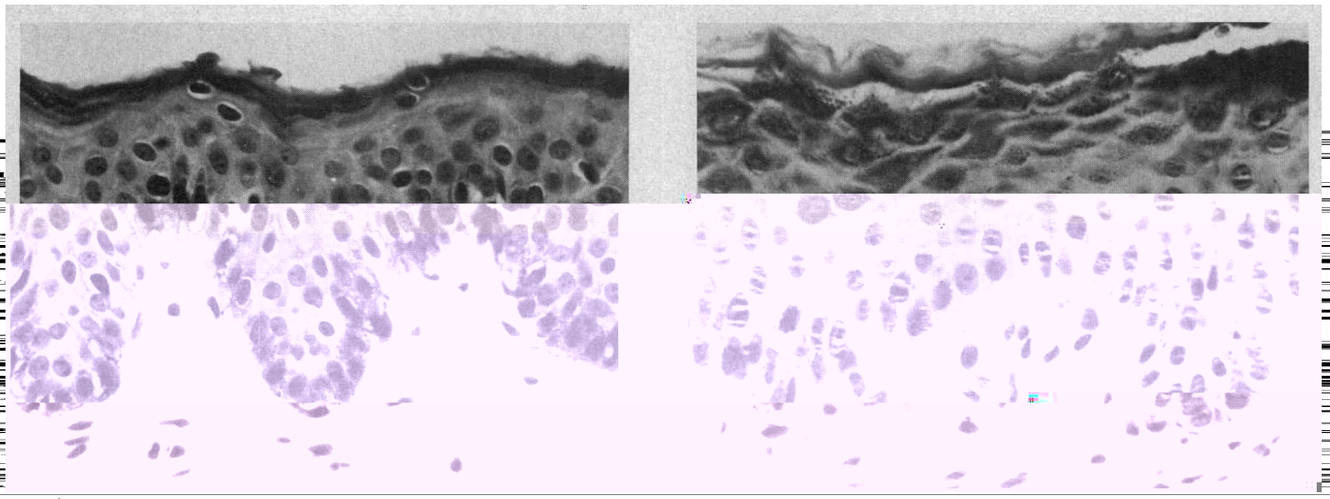

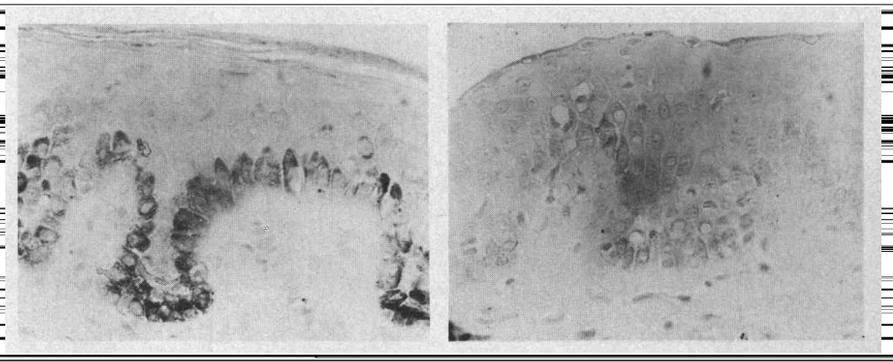

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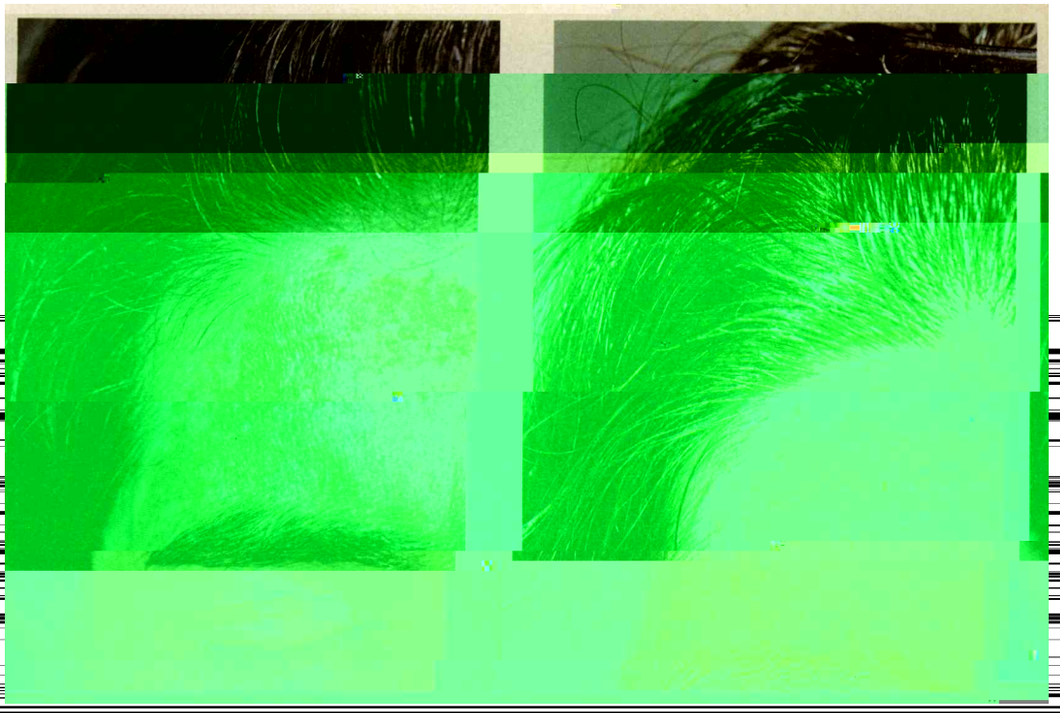

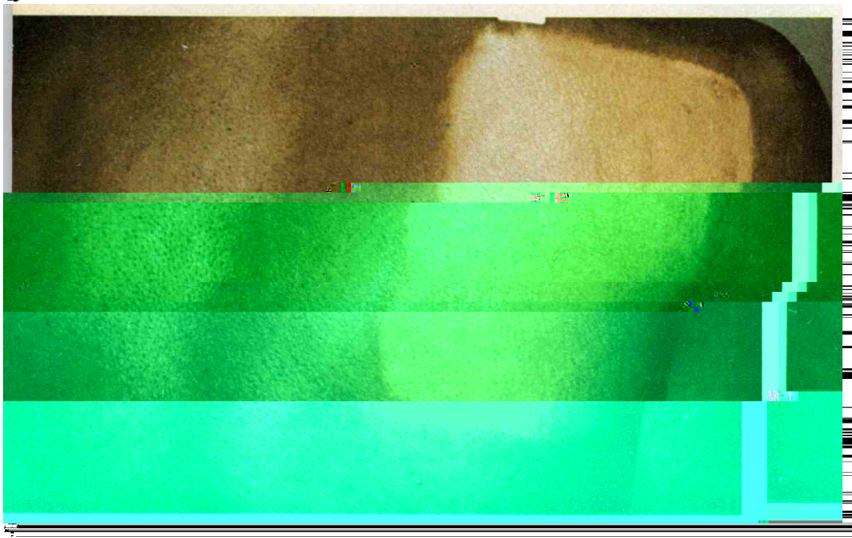

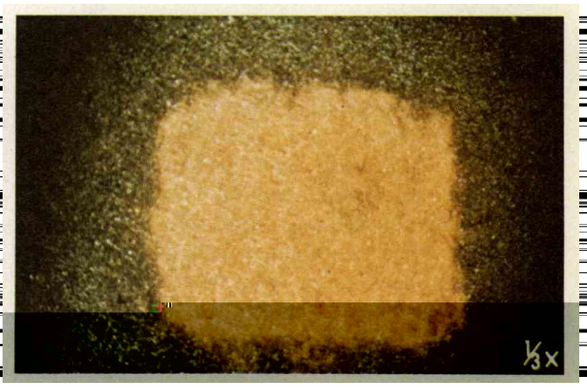

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notes, is not a substituted phenol. Earlier, Denton et al were able to show that most of these compounds could block the hydroxylation of tyrosine to dopa in vitro and thus might inhibit the first step in melanin synthesis.[3]

Spencer noted that hydroquinone

sistent hyperpigmentation. Extensive patch testing of black volunteers with various irritating and allergenic chemicals awakened our sensibilities to the problem of hyperpigmentation in blacks.

Two observations led us to suppose that a way might yet be found to en-

chemical destination. It would serve no purpose to chronicle our experimental wanderings. The formula that eventuated has the following composition: tretinoin, 0.1%; hydroquinone, 5.0%; and dexamethasone, 0.1%.

The vehicle was either hydrophilic ointment or a solution consisting of equal parts

[redacted]

itself was apparently free of the deleterious effects of MBEH. With the use of 2%, 3%, and 5% concentrations of hydroquinone, depigmentation of senile lentigines in more than 75% of white males was obtained.[18] Repigmentation occurred promptly after cessation of treatment and depigmentation of distant sites was absent. As shown by light microscopy, melanin granules were decreased in depigmented skin but the number of melanocytes was about the same. In this way the use of hydroquinone in a low concentration was introduced into practice.

In a study of 56 patients with various pigmentary disturbances, Arndt and Fitzpatrick found 2% and 5% hydroquinone creams to be moderately effective depigmenting agents in 80%

hance the pharmacologic effectiveness of hydroquinone. First, in treating hundreds of acne patients with topically applied tretinoin, we became aware that the skin sometimes became lighter after many months of use. The degree of hypopigmentation was slight. Second, the intradermal injection of corticosteroids into the skin of blacks in connection with assays of anti-inflammatory activity quite commonly resulted in striking loss of pigment at the injection site. Cahn noticed this phenomenon after injection of corticosteroids into lesions of black patients.[20] We too have observed this, so far only in blacks. In time the pigment returns. The application of tape containing corticosteroids may also result in lightening.[21]

were considerably less effective included petrolatum, lanolin, and polyethylene glycol. Dexamethasone was selected as the test steroid because it was economically available to us in a pure form. Other steroids may be substituted.

The cream and solution were never more than 30 days old. The addition of anti-oxidants did not enhance activity.

Method of Application

The agents were applied twice daily to squares of back skin outlined by a cardboard stencil. We came to appreciate that a moderate degree of irritation (peeling and erythema) promoted earlier and greater depigmentation. The amount applied was therefore regulated to achieve this effect.

Histologic Studies

Biopsy specimens fixed in formaldehyde solution were stained with hematoxylin-

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mentation.

Peeling and sometimes redness usually preceded depigmentation. Tenderness and burning were frequent complaints but inflammation was never severe enough to discontinue treatment. After about one month of treatment, the skin became hardened; thereafter, liberal applications produced little or no irritation.

It should be emphasized that irritation is not a prerequisite for depigmentation; it does, however, accelerate the process. When depigmentation was complete, applications were reduced to once daily. The sites stayed depigmented as long as treatment continued. We observed at least a dozen individuals who were treated daily without mishap for about six months. The only visible skin change was loss of pigment. Depigmentation did not spread beyond the borders of the treated areas.

Repigmentation started within one to two weeks after treatment ceased. This followed the course so well known in vitíligo—inward spread from the borders and centrifugally from the follicular orifices. The pigment was not only restored by about a month but sometimes was increased in relation to normal skin. Generally there was sufficient color blending by three to four months after cessation of treatment to render the treated sites invisible.

Effect of Ultraviolet Radiation

The biweekly application of two minimum erythema doses (MEDs) (determined individually on normal skin) during the period of application was extremely antagonistic to the depigmenting effect. The most that could be achieved was moderate lightening after two months of use. The application of two MEDs of erythemic radiation in depigmented subjects immediately after stopping treatment, with one additional exposure five days later, resulted in complete repigmentation by 10 to 14 days. Irradiated depigmented sites always become hyperpigmented with relation to untreated sites.

Occlusive vs Open Applications

Application twice daily to one side of the back of four individuals was compared to once daily application under a continuous occlusive seal of polyethylene film.

Occlusion increased irritation in each case. It also enhanced the onset and rate of depigmentation. In three of these four subjects hypopigmentation was evident in a week and was maximal by three to four weeks after the start of treatment.

Variations in the Concentration of Components

The concentration of one ingredient at a time was varied in a group of five subjects.

Hydroquinone.—A hydroquinone concentration of 10% brought about depigmentation more rapidly than that of 5%. Irritancy increased and the cream was more likely to undergo brownish discoloration. This had been noted by Spencer too.[19]

Reducing the concentration of the drug to 2% decreased its irritativeness but diminished its potency. Complete depigmentation could be achieved but at the expense of time, maximal effects requiring three months or so. Applications thrice daily almost overcame this.

Tretinoin.—Increasing the concentration of tretinoin to 0.2% accentuated irritation without a corresponding gain in effectiveness. With a concentration of 0.05%, irritancy decreased but a few weeks longer were required for complete depigmentation. Depigmentation was not achieved when the concentration was reduced to 0.01%.

Dexamethasone.—Increasing the concentration of dexamethasone to 0.2% did not lessen irritancy but did enhance effectiveness in a very clear-cut manner. With a 0.05% concentration there appeared to be only a slight loss of effectiveness.

In sum, lowering the concentration of each component by about one half decreases potency, but depigmentation is still obtainable.

Omission of One Ingredient

Omitting one component always results in loss of therapeutic effectiveness; it was not possible to obtain complete depigmentation after three months of twice daily applications in groups of three to four subjects. Lightening was visible but, on the whole, slight. While every ingredient was crucial to attain our established end-point, we could form a crude estimation of the relative

sides, Kahn had come to the conclusion that practically any phenolic substance could induce hypopigmentation with sufficiently intense exposure.14 He even observed loss of pigment with occlusively applied hexachlorophene.

We tested this possibility by substituting the following substances in place of tretinoin in the basic formula: (1) 2.5% to 5.0% sodium lauryl sulfate (this denatures the horny layer barrier and greatly potentiates penetration); (2) 5% to 10% phenol; (3) 10% resorcinol; (4) 5.0% trichloroacetic acid; (5) 2.5% benzalkonium chloride 3500 (Hyamine 3500) (a cationic quaternary salt); (6) 5% sodium salt of tetrachlorphenol; and (7) 5% salicylic acid.

These studies were conducted on different groups of four to five subjects and always the basic formula was used as a control.

The irritant reactions produced by this group of substances was as great, and in some instances greater, than that produced by the basic formula. In no case, however, was the depigmenting effect comparable. Sodium lauryl sulfate came closest to being an effective replacement, that is to say, the depigmentation was greater than could be achieved with the combination of hydroquinone and the corticosteroid. Phenol was also partially effective. Neither compound can be given serious consideration. Trichloroacetic acid, the quaternary salt, and tetrachlorphenol seemed to nullify the depigmenting effect.

Racial Influence

At first, light- and dark-skinned blacks were used indiscriminately. We gradually came to appreciate that deeply pigmented individuals were more susceptible to the depigmenting effect.

This finding was evaluated in a parallel study in which twice daily applications of the basic formula were made for eight weeks in three groups consisting of five subjects each: (1) very dark blacks, (2) lightly pigmented blacks, and (3) whites of average complexion.

In regard to the onset and final effect after eight weeks of treatment, there were important

group. Again normal skin was only slightly lightened.

More difficulty was experienced with color blending in patients with postinflammatory hyperpigmentation. These patients were blacks in whom patch tests with irritants and allergens had provoked intensified pigmentation, usually on the forearm or back. Without exception, pigment-loss was first noted in the hyperpigmented square and was regularly well under way by the third week of treatment. Needless to say, in this group one seeks only to reduce pigmentation to the background level.

Two individuals with postinflammatory hyperpigmentation responded only moderately; their cases were highly instructive and revealed a limitation that cannot be overcome. In both patients, the skin had become intensely hyperpigmented following intensive allergic contact dermatitis. The reason for resistance was seen in the biopsy specimen: in addition to increased epidermal melanin, there were many dermal histiocytes with large aggregates of melanin granules. This change might be regarded as a dermal tattoo and is inaccessible to the pharmacologie actions of the depigmenting formula.

Two black patients with extensive long standing vitíligo were treated by the obverse technique, that is, by depigmenting the unaffected areas. The course of depigmentation followed the pattern we had learned to expect in normal blacks. Depigmentation was complete in 9 and 11 weeks respectively. Both seemed pleased. Inexplicably, both defected from treatment; neither could be located for follow-up.

The patients with lentigines were elderly whites, more than 65 years old, with the usual stigmata of actinically damaged skin. It was more difficult to induce peeling on the backs of the hands; nonetheless, even with three and four applications daily, only slight depigmentation was achieved.

COMMENT

The depigmenting ability of this combination of drugs is impressive (Fig 4). In our estimation, hydroquinone—no matter how formulated—is not effective enough to satisfy the needs of most patients with hyperpigmentation disorders. Claims such as Spencer's are utterly baffling to us and completely alien to our experience.18 He achieved depigmentation of senile lentigines on the backs of the hands of older white men in 28 of 41 patients by applying hydroquinone. We found those particular lesions quite resistant.

Spencer also found that 2% hydroquinone would depigment the normal skin of light-skinned blacks in about 50% of the cases. We would emphasize that our inability to achieve anything like that result with the available commercial formulations or with extemporaneous preparations containing 2% to 5% hydroquinone cannot be ascribed to inadequate usage. Our subjects were largely institutionalized volunteers, applications were two to three times daily, and the test period rarely less than three months.

Arndt and Fitzpatrick were careful to state that a concentration of 2% to 5% of hydroquinone was "a moderately effective depigmenting agent" in the treatment of 80% of various disorders of hyperpigmentation. Our value judgments evidently differ from those of other investigators.

As regards the mechanism by which each component contributes to pigment loss, knowledge is sketchy and incomplete. We offer the following tentative analysis:

1. In respect to hydroquinone, Denton et al have demonstrated in vitro inhibition of the enzymic oxidation of tyrosine to dopa, the first step in the synthesis of melanin.3 According to Iijima and Watanaba, hydroquinone blocks the dopa-reaction in human skin.22 It is a likelihood that hydroquinone interrupts one or more steps in the tyrosine-tyrosinase pathway of melanin synthesis.

Unlike the substituted phenols, hydroquinone is not melanocidal. Indeed, the density of dopa-positive melanocytes was increased.

2. How corticosteroids promote depigmentation is pure conjecture. The general effect of steroids on many cell systems is antimetabolic. Steroids are cytotoxic or at least cytostatic for the epidermis; they decrease epidermal turnover and eventually produce atrophy.23 Perhaps the secretory product of the melanocyte is suppressed in the same fashion as collagen synthesis is suppressed by fibroblasts.24

We studied specimens of black skin in which epidermal atrophy had been induced by prolonged topical application of a corticosteroid. There was only slight hypopigmentation at the time of biopsy. The quantity of pigment did not seem to be altered. With the dopa stain, however, melanocytes were fewer and often shrunken, with short attenuated dendrites. The intensity of the stain was also diminished. One would normally expect such changes to be accompanied by clinically apparent pigment loss. The probable explanation for this paradox is decreased epidermal turnover. Keratinocytes move outward at a slowed rate and can thus acquire pigment over a longer time. Production is less, but so is the loss.

3. Tretinoin acts in a different manner. Khaidbey and Kligman have recently made histologie observations of human skin that had become hardened to tretinoin after vigorous topical use. (K. Khaidbey, MD, A.M. Kligman, MD, PhD, unpublished data). Tretinoin by itself caused a dispersion of pigment granules in keratinocytes, with notable loss of supranuclear caps in the basal layer. This alone would tend to cause l5aqTl[Gd5causeqTBngzBL2

a few days, speeding up the loss of pigment.

It is important to note that there is some balancing-out of the individual effects when the three agents are combined. Clearly, tretinoin overrides the atrophy-producing and antimitotic effect of the corticosteroid. The cor-

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use of other potentially irritating substances; washing with soap should be limited to one or two times daily.

Hyperpigmentation rarely begins before three weeks. Do not promise rapid results and urge patience. If hypopigmentation is not under way by two months, the case may be regarded as a treatment failure.

After the desired degree of lightening is obtained, it may be possible to maintain the effect by treatment with low-strength preparations. We are encouraged to think that in some conditions 5% hydroquinone alone will sustain the effect.

Finally, we perforce must mention one potentially nightmarish outcome of this work, namely, the use of this formula to lighten the skin of normal blacks. We fervently pray that improving social relationships will restrain any dignified black person from that demoralizing practice. Depigmenting normal skin is ethically acceptable only in extensive vitíligo.

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