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 physical impairment is but slight compensation for the mental anguish of the outcast with too little or too much melanin, especially when the changes occur in bizarre patterns.

Physicians have lagged considerably behind laymen in appreciating that these afflictions merit medical attention; even today scientists of high ability and low sensitivity refer 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 the biology and biochemistry of melanin 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 describes our therapeutic impotency. Heavy metals, especially salts of mercury, are still widely used often in combination with salicylic acid. They are partially but inconsistently effective. Enzyme inhibition is the probable mode of action. The possibility of systemic poisoning is a good reason why mercury should not be used day after day. Oxidizing agents, such as peroxides and chlorates, are more effective bleaches for hair than skin. Reducing agents, such as organic acids and lemon juice, aim to transform melanin to the colorless leukoform. These have marginal effects on the integument.

What might be called the modern 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 area covered by rubber gloves. 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 way to uncertainty; doubt then developed into despair.

Becker and Spencers' study of MBEH doomed this agent.[7] They made daily applications in vanishing cream to the normal skin of blacks for four months. They could not procure a uniform, controllable depigmentation. Approximately 25% of the subjects showed no lightening when treated with drug concentrations ranging from 1% to 20%. More seriously, about half of those patients whose skin became depigmented showed an extension of the leukoderma beyond the area of application; this continued for many months after treatment stopped. The appearance

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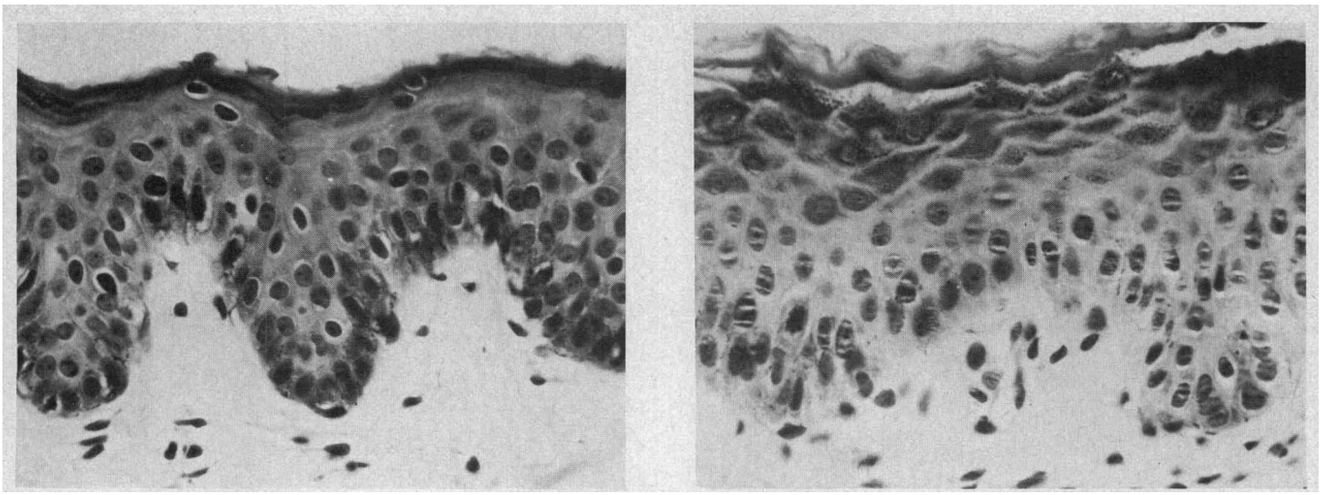

Fig 1.—Left, Transverse section of skin before treatment. Right, Specimen from depigmented skin after six weeks of treatment. Epidermis is acanthotic and keratinocytes larger; granular layer is increased, with conspicuous granules (hematoxylin-eosin, ×630).

of leukoderma at distant sites is a puzzling but rather characteristic adverse happening with this class of compounds.[8]

Moreover, MBEH proved to be a potent contact sensitizer. Worst of all, about half the subjects had leukoderma for the next two years and about a third for at least four years, presumably the longest period of follow-up. Persistent and perhaps permanent depigmentation is the spectre that caused the editorial comment that "the therapeutic use of MBEH has been responsible for a number of cosmetic disasters."[9]

Meanwhile, investigators were frenetically searching for chemicals that might be both safe and effective when they were applied topically. Brun evaluated the effect of thirty compounds applied on the pigmented nipples of guinea pigs and found that the monomethyl and monomethyl ethers of hydroquinone also were potent depigmenting agents.[10] Chavin and Schlesinger injected a number of chemicals into goldfish and added certain mercaptoamines to the list of powerful depigmentors.[2] The latter are also effective in the treatment of mammalian skin; however, they are both irritating and malodorous.[11]

Bleehen et al applied all the aforementioned compounds and many related ones, thirty-three in all, to black guinea pigs and discovered 4-isopropyl catechol to be the most effective.[12]

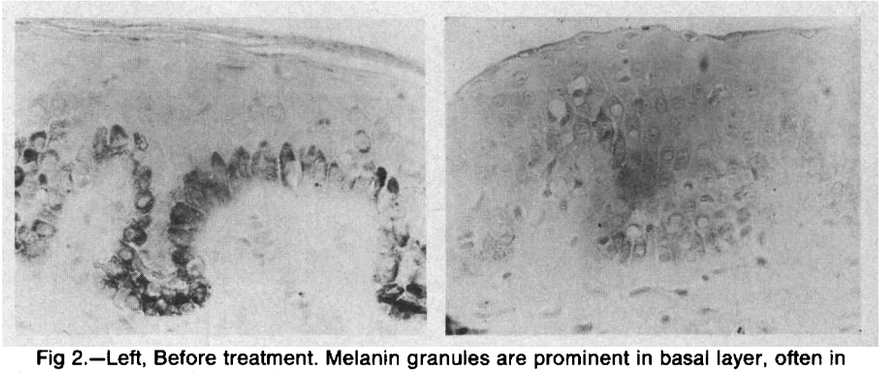

Fig 2.—Left, Before treatment. Melanin granules are prominent in basal layer, often in form of caps over the nuclei. Pigment granules are visible in horny layer of blacks. Right, After eight weeks of treatment. Pigment granules, mainly in basal cells, can barely be seen (Fontana's silver stain, ×630).

Therapeutic Effectiveness of Basic Formula

Disorder	No. of Patients Treated	No. of Patients With Satisfactory Response
Melasma	16	14
Ephelides	11	9
Postinflammatory pigmentation	18	12
Senile lentigines (hands)	7	0

This, too, is a moderately strong contact allergen.

Finally, there has recently been a spate of reports from various parts of the world concerning occupationally related depigmentation from phenolic compounds. The descriptions are startlingly similar, whether the outbreaks occurred among workers in plants producing various substituted phenols or in hospital attendants using detergent antiseptics, most notably *p*-tertiarybutyl and *p*-tertiaryamyl phenols.[13,14] The notable features are persistent depigmentation starting in areas of contact, ectopic spread to other areas, and a high incidence of allergic contact sensitization. The term "occupational vitiligo" would appear to be an apt one considering the many resemblances to vitiligo.[15]

Basic researchers have not been able to resist the lure of the intriguing problems raised by these events. Serious efforts have been

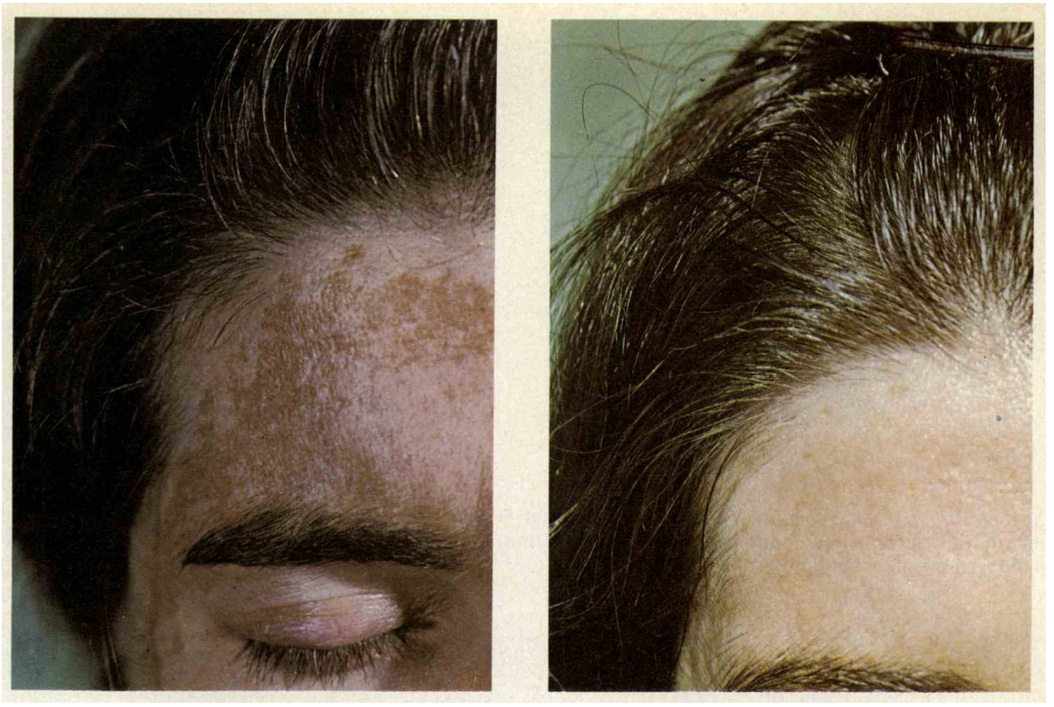

Fig 3.—Left, Melasma before treatment. Right, After eight weeks of treatment.

Fig 4.—Complete depigmentation of normal skin of blacks after six weeks of twice daily application of formulation (at left) and after nine weeks of treatment (at right).

made to find out how these various monohydroxyphenyl and dihydroxyphenyl derivatives cause depigmentation.

It is the consensus that destruction of melanocytes accounts for the depigmentation. The electron-microscopic studies of Bleehen et al in guinea pigs convincingly showed that isopropyl catechol either inactivated or destroyed melanocytes.[12] In their ultrastructural studies, Malten and his colleagues could not find melanocytes in the skin from patients depigmented by *p*-tertiarybutyl and its homologues.[15] Kahn found only occasional melanocytes in the skin of hospital attendants using phenolic germicides.[14]

But it is the work of Riley above all whose analysis has most illuminated the subject. He has shown that monomethyl ether of hydroquinone is selectively incorporated into cultured melanocytes.[16] Evidence of free radical formation has been obtained in guinea pig skin treated with this agent. Cultured melanocytes are irreversibly damaged by exposure to low concentrations.[17] Riley postulates that these compounds diffuse into the melanosomes of the pigment cell where they are oxidized by tyrosinase to produce free radicals; the latter bring about lipid peroxidation of cell membrane lipids, thus killing the cell.

It appears that all the substituted phenols so far studied in animals and man are melanocidal. Such compounds are specifically cytotoxic to melanocytes and have but little effect on keratinocytes. Hydroquinone, one

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 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% of the cases.[19]

BACKGROUND of PRESENT STUDY

Though hydroquinone seems safe enough, our experience with commercial and extemporaneously constituted creams containing 2% to 5% concentrations of hydroquinone has been disappointing. Only a fraction of melasma patients achieved enough lightening to produce a satisfying result after three months of twice daily applications. Likewise, the benefits were marginal when 2% to 10% concentrations of hydroquinone were used to depigment uninvolved skin by patients with extensive vitiligo. We have concluded that hydroquinone by itself is not sufficiently potent to accomplish the needed degree of lightening in patients with hyperpigmentary disorders.

One tends to think of hyperpigmentation as mainly a problem of whites until one begins to acquire experience with blacks. In the latter, the most trivial chemical and physical traumata, frequently unnoticed or unrecollectable, tend to produce persistent 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 enhance 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]

At last the idea was proposed that a combination of these various hypopigmenting drugs might be more effective than each alone.

MATERIALS AND METHODS

Initially, white patients with various hyperpigmentation problems were used. This proved tedious and unfeasible in view of the number of variables that had to be studied. The patient supply was too limited and too few preparations could be evaluated at a time.

We then turned to white skin artificially tanned by ultraviolet radiation. This proved feasible, but evaluation was difficult since the tan decreased spontaneously in the time required to achieve an effect.

Finally, we hit upon the idea of using the normal black skin of healthy, young, adult, black, male prisoner volunteers. This proved eminently advantageous: depigmentation was easy to appraise, and the effects were repeatable. Groups of five to ten volunteers were used per study. The formulation that resulted from these studies was finally appraised in patients with hyperpigmentary disorders.

Chemical Formulations

After many trials that led us through a maze of trails we finally arrived at our 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 of ethanol and propylene glycol. Bases that 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-eosin, PAS for glycogen, and Fontana's ammoniated silver stain for melanin. The epidermis from shave biopsy specimens was separated by 2N sodium bromide and stained by the dopa reaction for melanocytes.

RESULTS

Depigmentation of Normal Skin of Blacks

These observations pertain to more than 100 subjects who were depigmented by application of the above formulation.

As a rule, lightening was not in evidence before three weeks. Occasionally it took as long as four to five weeks for the skin of some subjects to begin depigmenting. Pigment loss was frequently blotchy at first. The follicles were generally last to depigment, creating a punctate pattern.

No individual was completely resistant, though the speed of depigmentation was variable. As a rule, maximum depigmentation was obtained in five to seven weeks and was in most cases nearly complete. We mean by this that skin color was less than that of fair skinned whites, approaching an ivory hue. The result was *depigmentation*, not hypopig-

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 vitiligo—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 importance of each. The ranking of depigmenting efficacy was (in descending order) hydroquinone, tretinoin, and the corticosteroid. Without hydroquinone, only very slight and inconsistent depigmentation could be obtained. This component has overriding importance. Without tretinoin, moderate depigmentation was usually possible. Leaving out the corticosteroid clearly lessened effectiveness but not to the extent that occurred when tretinoin was omitted.

Application of Single Components

In no instance in a group of four subjects did application of one-ingredient formulations produce substantial hypopigmentation within three months. Slight lightening was noted in two subjects treated with hydroquinone. No loss of pigment occurred when retinoic acid and the steroid were applied alone.

Variations in Steroid Component

Two percent hydrocortisone acetate was substituted for dexamethasone in the treatment of three subjects. This formulation was considerably less effective. Depigmentation required many more weeks with this drug than with fluorinated steroids.

Commercial corticosteroid creams containing 0.025 fluocinolone acetonide (Synalar) 0.1% betamethasone valerate (Valisone), and 0.1% triamcinolone acetonide (Kenalog), were compared to our formulation after each had been triturated with 5% hydroquinone and 0.1% retinoic acid. Applications were made twide daily to the backs of six subjects for a period of five weeks (a period shorter than the time generally needed for complete depigmentation).

We judged that lightening occurred earlier and was more advanced after five weeks of treatment with fluocinolone and betamethasone valerate than after treatment with the other two preparations. Results of treatment with triamcinolone and dexamethasone seemed about equivalent. The more potent anti-inflammatory agents were also more effective for depigmentation.

Replacement of Tretinoin

It seemed a possibility that the tretinoin was merely acting as an irritant, producing nonspecific effects that might be duplicated by other substances that damage the skin. Be-

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 differences among the groups. Deeply pigmented blacks were the most susceptible and whites the least. Lightly pigmented blacks were intermediately susceptible. In three of five whites, loss of pigmentation was hardly appreciable and was only modest in the other two. We hasten to add that we are not referring here to relative changes. Obviously, a 50% reduction in pigmentation will be more apparent in dark than in light skin.

Histologic Findings

Dopa-stained epidermal sheets were examined in six black subjects who had become completely depigmented after two to three months of twice daily application of the basic formulation. Nearby untreated skin served as controls.

Even at low magnification, one could observe that the quantity of dopa-positive melanocytes was increased. Melanocyte density in the control specimens ranged from 415 to 608/sq mm (mean, 527 sq mm), while in depigmented skin the range was 720 to 1,082/sq mm (mean, 903/sq mm). Moreover, the melanocytes were larger and more active enzymically.

In 12 specimens stained with hematoxylin-eosin that were taken from depigmented skin, there was slight acanthosis, an increased granular layer with larger granules, and somewhat increased basophilia and hypertrophy of the basal layer (Fig 1).

The only noteworthy dermal change was a slight increase in perivascular monocytic cells.

In two biopsy specimens taken two and three weeks respectively after starting treatment—when irritation was prominent—the principal findings were marked acanthosis, foci of parakeratosis, hypertrophy of epidermal cells, dilation of dermal venules, and a moderate perivascular infiltrate of mononuclear cells. These are rather typical findings of an ongoing irritancy reaction.

Silver stains of depigmented black skin (six specimens) showed finely dispersed melanin granules throughout the epidermis, including the stratum corneum (Fig 2). These granules were greatly reduced in quantity. Supranuclear caps were absent.

TREATMENT OF DISORDERS OF HYPERPIGMENTATION

We report here our preliminary observations. Far more extensive clinical studies will be necessary before the merits and limitations of this treatment can be appreciated.

We urged the patients to apply that amount of the formulation once or twice daily that would induce peeling. After that phase abated, application was once daily. The patients were counseled not to expect appreciable lightening until the agent had been tried for at least six weeks. The treatment was considered a failure if by 12 weeks the patient considered that depigmentation was not great enough to remedy social embarrassment.

The results are shown in the Table. It is clear that the agent was effective in cases of melasma, ephelides, and postinflammatory hyperpigmentation. It was ineffective in cases of "senile" lentigines of the dorsa of the hands.

Melasma patients registered great satisfaction with the results (Fig 3). These were young, adult, white women all of whom were taking contraceptive pills. The treatment had to be individualized. For most of the patients, once daily application was enough. With melasma, irritation apparently did not greatly enhance depigmentation as it did in black skin. Satisfactory results were obtained by some women who had little or no peeling. Depigmentation generally began earlier than in normal skin of black volunteers and was of satisfactory magnitude by five to seven weeks after the start of treatment. There was surprisingly little trouble with color balance in relation to surrounding normal skin. Normal skin in fact seemed to lighten only slightly, if at all. None of the cases was followed up beyond four months; no adverse effects were encountered.

The patients with ephelides were young, adult, white men; treatment was restricted to one area of the back. Longer treatment periods were required than with melasma; irritation promoted depigmentation in this

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 pharmacologic actions of the depigmenting formula.

Two black patients with extensive long standing vitiligo 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 histologic 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 lightening. To this might be added two additional effects. First, interference with pigment transfer. On the face of it, the presence of more numerous, more active melanocytes should cause hyperpigmentation not hypopigmentation. This suggests that the dendrites cannot donate pigment to surrounding keratinocytes. Such a situation prevails in psoriasis also. Stimulation of melanocytes is to be expected in all inflammatory reactions. Earlier we found at least a doubling of melanocytes after topical application of irritant chemicals.[25] Second, whatever pigment manages to get into keratinocytes is also lost more rapidly since retinoic acid accelerates epidermal turnover. Keratinocytes move from the basal layer to the horny layer in

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 corticosteroid, on the other hand, seems to antagonize the thinning effect of tretinoin on the stratum corneum. The horny layer seemed normal. It is not known whether the barrier function is intact in skin depigmented by our formula.

During the early inflammatory stage, the changes are dominated by the effect of tretinoin. The epidermis becomes acanthotic with variable parakeratosis. In depigmented skin, the presence of basophilia and hyperplasia of basalar keratinocytes suggests that there is a higher turnover rate. Therefore, depigmented skin cannot be said to be completely normal.

At first it seemed strange that it was easier to depigment blacks than whites. In fair-skinned whites, depigmentation takes a longer time and is frequently incomplete. Clinicians have long appreciated the greater lability of black skin with regard to pigmentary changes. Traumas and inflammatory episodes in black skin exhibit the paradox of being followed by either excessive hyperpigmentation or hypopigmentation. The controlling mechanisms, whatever they may be, are more readily unbalanced in the black.

The relative resistance of normal white skin has certain advantages in therapeutic applications. Hyperpigmented skin in the white tends to react like normal skin in the black. It is more susceptible to depigmentation and responds more swiftly and fully. The effect is, therefore, somewhat selective and blending of color tones with the surrounding skin is more easily attained. It is frequently difficult to restrict application solely to hyperpigmented areas. That is always the case in freckles, and because of odd patterns frequently applies to melasma as well. It would be a ghastly cosmetic debacle, worse perhaps than the original disorder, if in these instances the entire region became a gleaming ivory-white!

With his customary perspicacity Lerner has proferred some speculations that perhaps explain the greater tendency of black (or hyperpigmented) skin to become hypopigmented.[26] He theorizes that melanocytes have a built-in bias toward "self-destruction," noting that the more pigment produced by a given group of melanocytes, the greater the tendency for the cells themselves to disappear. Extreme examples are halo nevus and vitiligo, in which the melanocytes are completely eradicated. He postulates that melanocytes are exquisitely sensitive to phenolic materials, almost all of which—in proper concentration—inhibit the tyrosine-tyrosinase reaction. Significantly, tyrosine and dopa are also phenols. Some protective process normally prevents these substances from injuring the cell or inhibiting melanin protection. The loss of this regulatory control would expose the melanocyte to its own potentially deleterious phenols. Similar implications can be drawn from Riley's work.[27]

To date, we have encountered no adverse effects other than irritation. In his series, Spencer saw two cases of contact sensitization to hydroquinone.[18]

The well-known local side effects of corticosteroid therapy—atrophy, striae, acne, telangietasia—have not been noted and are very unlikely. Tretinoin is a recognized antagonist of steroid action; it counteracts, for example, steroid-suppressed wound healing.[28] At the clinical level, as well as the histologic one, tretinoin apparently overcomes the potentially deleterious effects of corticosteroids. Nonetheless, we shall have to be on the lookout for untoward effects from prolonged use. We have emphatically warned against the use of corticosteroids on the face, in particular where acneiform eruptions, rosacea-like erythemas, and even perioral dermatitis are possibilities.[29] The use of nonfluorinated corticosteroids would eliminate side reactions.

In view of the increased population of melanocytes, the extraordinarily rapid return of pigmentation after stopping treatment is readily explicable. Indeed, pigmentation may be even greater than originally. Once inhibition is lifted, the melanin factories go to work with full force. A melanogenic stimulus such as ultraviolet light will greatly accelerate repigmentation. These remarks apply mainly to normal skin of blacks but should be kept in mind when this formulation is used for treatment.

It is possible that the formulation we have evaluated is not optimal for routine clinical use. It might be advantageous, for example, to halve the concentration of each component. This would reduce irritation even though the response would be slower. Changes in the vehicle might bring other improvements. Disorders of hyperpigmentation are very diverse. Considerable clinical testing will be required to reduce to practice the findings reported herein.

It is already clear that not every pigmented lesion will respond to this treatment. Lesions in which most of the pigment is in the dermis cannot be benefitted. The formula is not a bleaching agent and will not decolorize melanin. We think that the combination will be found effective in the treatment of all hyperpigmented lesions in which epidermal melanocytes are the source of pigment, providing that penetration is adequate. We have some evidence that the poor results in the treatment of senile lentigines are attributable to this factor. Higher strengths of the formulation in special vehicles that promote diffusion across the horny layer might solve this problem.

It might be helpful to outline treatment guidelines from our present vantage point.

Enough of the formulation should be applied to effect peeling and modest reddening; this accelerates depigmentation but is not a prerequisite for it. Peeling helps the patient monitor the amount to be applied. Hardening occurs within four or five weeks; thereafter, skin reactions are scarcely perceptible.

The patient should avoid sunlight or use liberal amounts of sunscreens. Erythemic radiation strongly antagonizes the depigmenting effect. Patients should be cautioned about the

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 vitiligo.

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