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# Further experience with a topical cream for depigmenting human skin

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Synopsis

Satisfactory LIGHTENING of HYPERPIGMENTARY SKIN disorders was obtained by twice-daily APPLICATION for two to three months of a PREPARATION containing 5.0% hydroquinone, 0.1% Vitamin A acid (tretinoin) and 0.1% dexamethasone, a flourinated corticosteroid.

Excellent results were secured in melasma (chloasma) of white females. Two common pigmentary disturbances in blacks also responded well, namely, the residual hyperpigmentation left by inflammatory acne lesions and in bearded areas affected by ingrown hairs (pseudofolliculitis). Although senile lentigines were not moderated in patients over 65 years of age, good results were observed in patients 40 to 60 years old.

The depigmentation is completely reversible and is not attended by significant local or systemic side effects.

## INTRODUCTION

In a previous work, we showed that a formulation containing Vitamin A acid (tretinoin), hydroquinone and a corticosteroid could bring about complete loss of melanin from the skin of normal blacks and was highly beneficial in disorders of hyperpigmentation, notably melasma (chloasma), freckles and excess pigmentation following inflammation (1).

Bleaching occurred despite an increase in the density of pigment-forming cells (melanocytes). Each of the three components was essential for effectiveness. Hydroquinone is known to interfere with the tyrosine–tyrosinase pathway of melanin synthesis. This drug also causes subcellular membrane damage and inhibits the formation of melanosomes, the organelles in which melanin is packaged (2). By itself, its effectiveness is too limited. How tretinoin and corticosteroids contribute to the depigmenting action is conjectural. The latter may inhibit melanin production by melanocytes in the same way that it suppresses collagen synthesis by fibroblasts, presumably through a repression of the general metabolic activity of the cell; steriods are known to be cytostatic to the epidermis (3). Tretinoin, on the other hand, stimulates cell turnover (4)

and it seems a likelihood that the rapid outward migration of cells might interfere with the transfer of pigment granules from melanocytes to keratinocytes. Thus the triad of active components collaborate to curtail the synthesis of melanin, reduce the production of membrane-bound melanosomes in which the pigment is aggregated, impair the donation of melanosomes to keratinizing cells and promote the more rapid loss of pigment *via* increased epidermopoesis.

Before a combination of such pharmacologically potent drugs can come into general use, there must be extensive clinical evaluation to learn the advantages and limitations in the therapy of hyperpigmentary disorders. The latter are misery-inducing conditions which cause great emotional suffering; they should not be viewed as mere cosmetic nuisances. In this paper we shall report further experiences and a new indication for this depigmenting formulation.

## MATERIALS AND METHODS

### COMPOSITION AND SUBJECTS

The subjects were out-patients of the Hospital of the University of Pennsylvania and the test formulation was:

| | |
|---|---|
| Tretinoin | 0.1 per cent |
| Hydroquinone | 5.0 per cent |
| Dexamethasone | 0.1 per cent |
| Hydrophilic Ointment U.S.P. q.s. | |

and material was never more than two months old.

## CLINICAL STUDIES

### MELASMA

The subjects were 19 young adult females whose facial pigmentation was linked to the taking of contraceptive pills. The cream was applied before retiring once daily for the first week. In all but a few who experienced too much discomfort from peeling and dryness, the exposure was increased to twice daily to speed up the response.

Lightening was generally clear-cut by the third to sixth week. By 12 weeks, the hyperpigmented areas had virtually blended with the surrounding normal skin in 16 of the 19 patients. In these, the results were excellent. The normal skin of white persons is comparatively resistant to the lightening effect. The results were only moderately good, however, in two patients, though both expressed satisfaction with the result. One patient was inexplicably resistant and did not achieve a satisfactory result even after four months. Once-daily application was sufficient for maintaining the lightening at the desired level.

### POSTINFLAMMATORY HYPERPIGMENTATION

Hyperpigmentation is a very common residium of inflammatory disorders on the skin of blacks. Intense pigmentation may follow a variety of pathologic changes: *via* insect bites, contact allergy, abrasions, burns, etc. (Figures 1, 2). Damage to the skin, no mat-

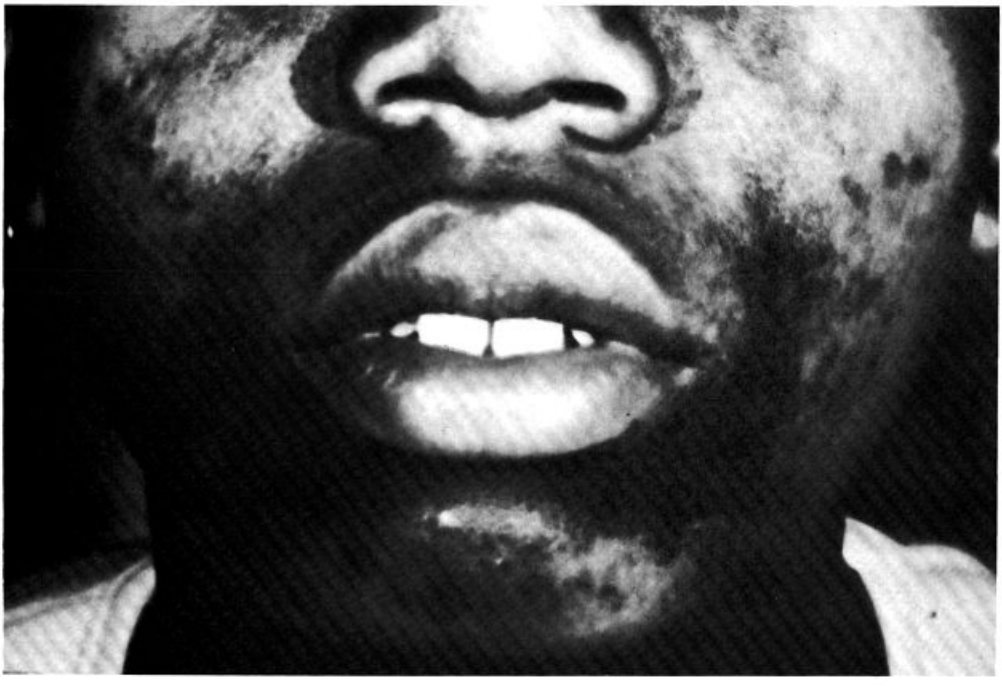

**Figure 1.** Postinflammatory hyperpigmentation following patient's use of abradant and anti-acne lotion to treat acne vulgaris

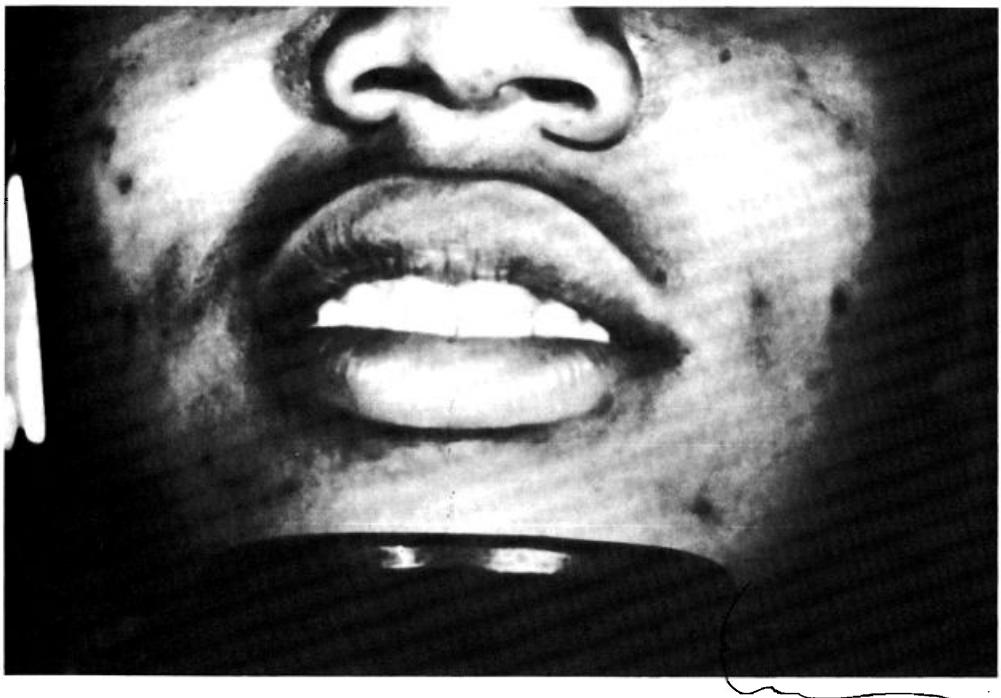

**Figure 2.** After 8 weeks of twice-daily application of depigmenting formula, hyperpigmentation was eliminated and acne vulgaris was under good control

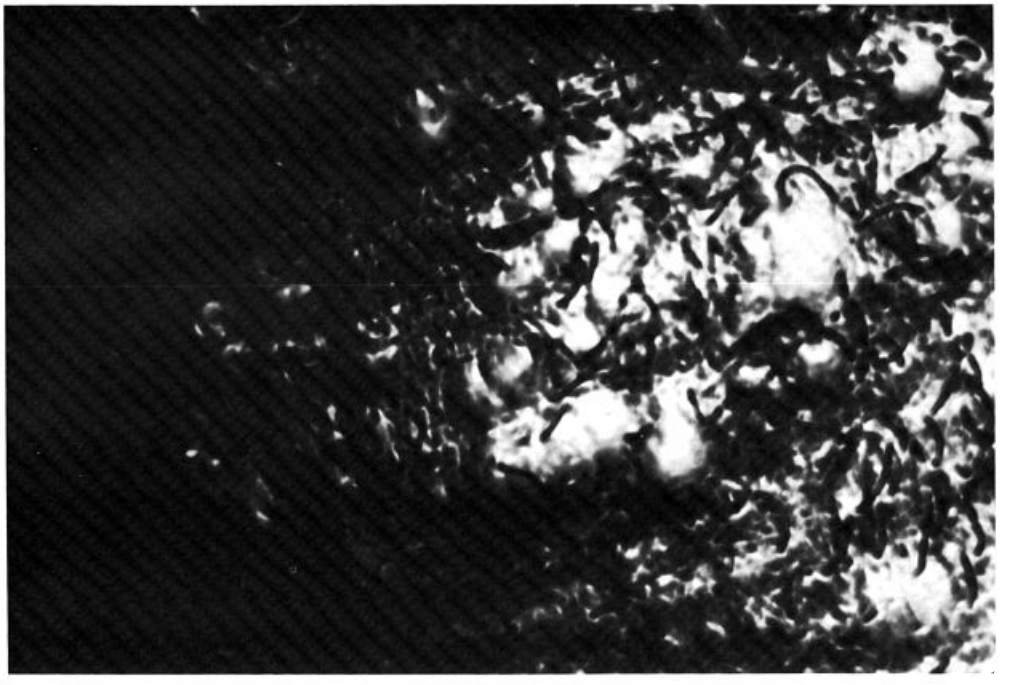

**Figure 3.** Papular lesions of pseudofolliculitis located on the neck of a 23 year old black male. Condition had persisted for approximately seven years

ter how induced, characteristically leads to an increase in the quantity of hyperfunctioning melanocytes.

Because of our interest in acne, we have come to appreciate how commonly inflammatory lesions leave conspicuous spots of hyperpigmentation on the face of blacks. Picking and squeezing of papulo-pustules, a pernicious habit of many acne patients, black and white, is particularly likely to induce excessive pigmentation. Another hyperpigmenting disorder, especially common in black males, is pseudofolliculitis of the beard in which ingrowing hairs produce inflammatory papules and pustules. The beard area shows a splotchy, mottled pattern of intense melanization. Speckling is prominent around the follicles. These are distressing, embarrassing afflictions with which we have long been concerned, ineffectively for the most part. The depigmenting formulation was adequately evaluated in 25 black acne patients, mainly females, and in 11 black males with pseudofolliculitis. These subjects completed three months of therapy. The patients were urged to use "spot" therapy, applying the medication with cotton-tipped applicators to each hyperpigmented site. The medication was applied twice daily using more of the material on the darkest spots. Peeling often occurred at the start, but generally abated after a few weeks.

Lightening was generally apparent by five to six weeks. Although the response was slower than with melasma, a satisfactory degree of lightening occurred in practically all acne patients by 12 weeks and in eight of the males with pseudofolliculitis (Figures 3 and 4). Color balance was more difficult to achieve in blacks. The best blending was achieved by patients who were concerned and adroit enough to confine the medicament precisely to the hyperpigmented spots. A small wisp of cotton wound around the tip of a toothpick was an effective applicator for spot therapy.

**Figure 4.** After 5 weeks of twice-daily application of formulation

A secondary benefit in some acne patients was a more rapid resolution of hyperpigmented papules. Probably both the tretinoin and the corticosteroid contributed to the healing effect of these long-lasting, hyperpigmented, inflammatory lesions.

### SENILE LENTIGINES

Earlier trials in treating these lesions produced disappointing results. This was the outcome in patients who were applying the formulations as many as three or four times daily. Despite these results, we continued to use the formulation, noting an occasional success. In one review of the data, we realized that depigmentation was occurring in patients aged 50 to 60 years. The original study had included patients 65 years and older with the majority being over 70 years. We have since concentrated the use of the formulation in patients under 65 years of age. Thus far, we have tested 11 patients (40 to 60 years), recording good results in nine. The favorable response is apparent at one to four months of treatment. Applications are once to twice daily, dependent on the rate of resolution. This group is being expanded and a more detailed report of the findings will be published.

## DISCUSSION

Adverse reactions to this combination have been very limited, the most common being mild to moderate irritation. We encourage patients to use enough medication to produce some scaling and dryness for the first few weeks of treatment. By deliberately provoking a mild irritant reaction, the patient is assured that sufficient drug has

penetrated. Actually, the skin becomes accommodated within a month or so of daily use and greater amounts can be applied without signs of irritation.

There have been no instances of contact sensitization or photosensitization. The skin may be more vulnerable to sunburning radiation during the irritative phase. Apart from this enhanced reactivity (*not* phototoxicity), there is a very important reason for avoiding midday erythemogenic sunlight or, alternatively, to use sunscreens, namely, that this radiation strongly antagonizes the lightening effect. Furthermore, after depigmentation has been secured, sun exposure may lead to rapid repigmentation within seven to ten days. In fact, there may be a genuine rebound in which the pigmentation becomes even greater than originally.

The depigmenting effect is always transient. Applications must be continued on a maintenance basis so long as the melanizing stimulus persists. Unlike substituted phenolic compounds such as monobenzyl ether of hydroquinone, hydroquinone itself does not destroy pigment-forming cells and the danger of permanent depigmentation does not exist. Indeed, we have demonstrated that the density of melanocytes is about doubled after depigmentation is achieved. (The added quantity of enzymically active melanocytes underlies the rebound phenomenon.) Again, in contrast to substituted phenols, we have never observed depigmentation in any region outside the area of application.

We have strenuously warned against the persistent use of flourinated steroids on the

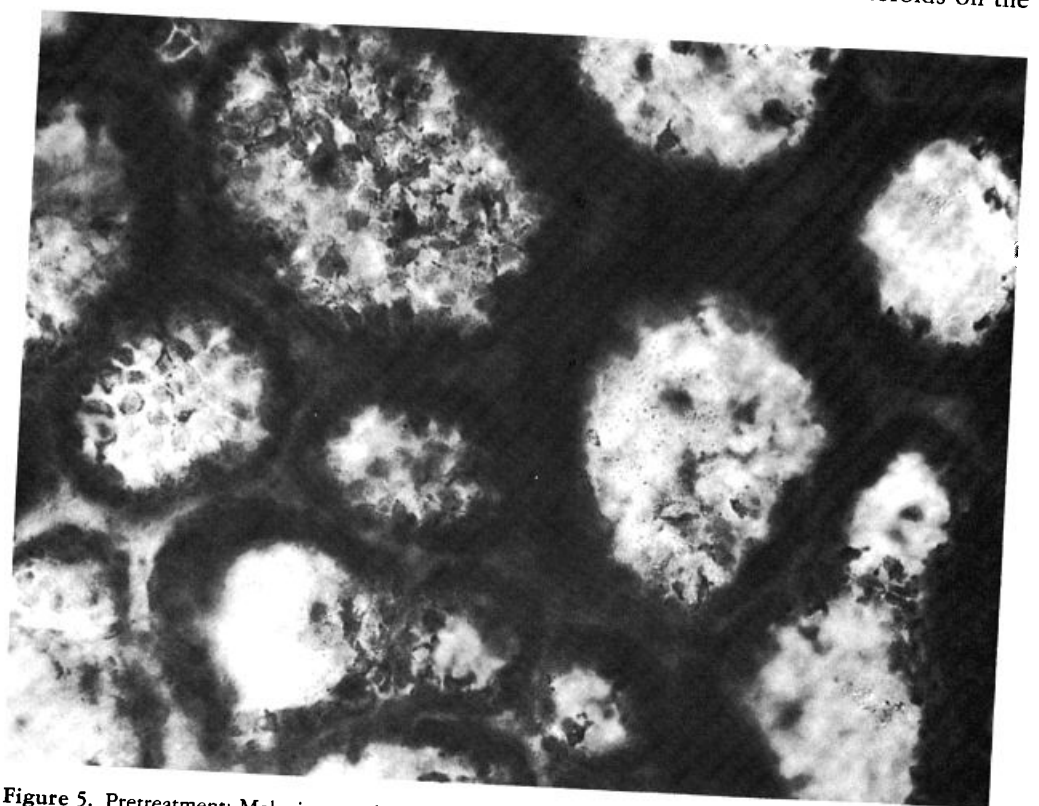

**Figure 5.** Pretreatment: Melanin granules are prominent in the basal layer, often in the form of caps over the nuclei. Pigment granules are visible in the horny layer of black skin (× 400)

face. All too often, middle-aged women will apply potent steroids for months or years to control some minor skin abnormality with the frequent result, usually without awareness of cause, of a steroid-induced eruption. The latter takes three forms: steroid acne, steroid rosacea and peri-oral dermatitis (5). Varying amounts of atrophy and dilated blood vessels are also well known steroid effects.

It is necessary to explain why we have never encountered adverse steroid effects in chronic users of the depigmenting cream. We think it exceedingly unlikely that steroid eruptions will ever turn up owing to the presence of tretinoin in the formulation. The biologic effects of tretinoin are virtually opposite to those of steroids. Tretinoin, for example, stimulates mitoses while steroids are inhibitory (3). Tretinoin promotes wound healing while steroids delay wound healing (6). The former is comedolytic (7), the latter enhances the formation of closed and open comedones (8). And so the potential damages that steroids could exert on skin structure, especially atrophy, are completely nullified by tretinoin.

A common condition which responds well to this formulation is freckles. Here there is no hope of restricting applications to the hyperpigmented spots. The whole area must be treated. This brings up the question of color blending—won't the normal skin between the freckles also become depigmented? One might end up with an ivory white landscape which would be a lot more noticeable than the original mottling. The fact is that normal skin is relatively consistant; the rule is that the greater the pigmenting, the

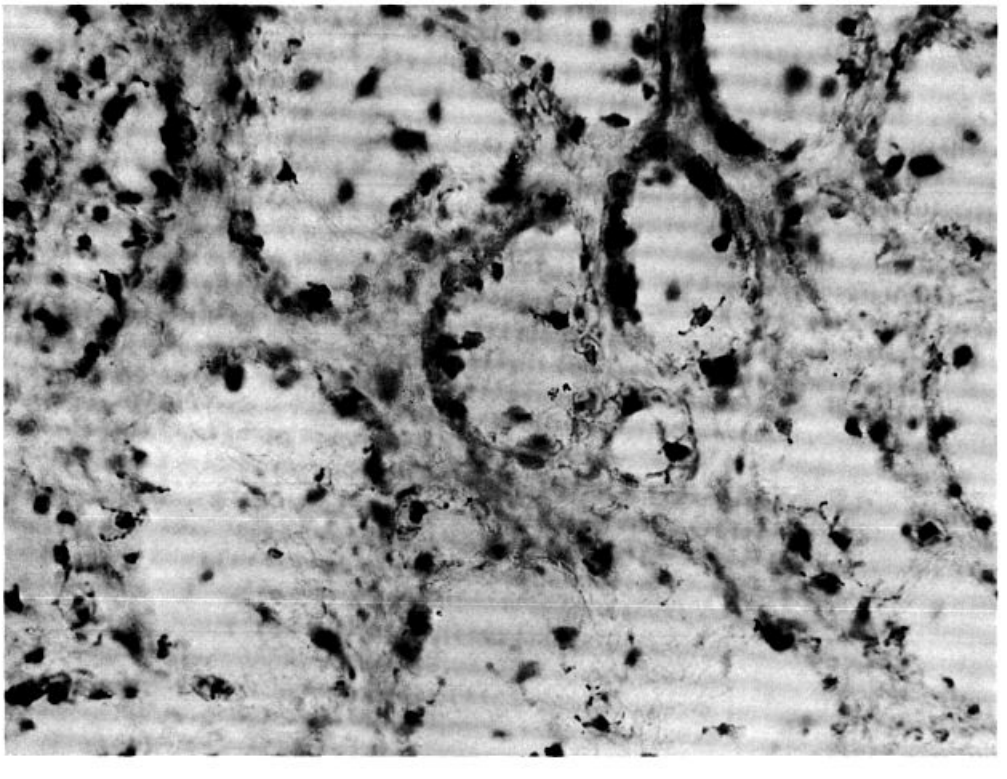

**Figure 6.** After 8 weeks of treatment, pigment granules, mainly in basal cells, can barely be made out (× 400)

easier it is to achieve depigmentation. The skin of blacks, paradoxical as it seems, is more readily lightened than the skin of whites (Figures 5 and 6). Complete depigmentation in comparison to hypopigmentation, can be attained in deeply pigmented blacks but not in whites. Hyperpigmented areas are more responsive than the surrounding terrain. Fortunately, the blending problem thus rather takes care of itself with some individual exceptions.

The reason for poor results in older patients with senile lentigines is presently under investigation. The clinical appearance of the lesions in the fourth and fifth decade may be a time when they are more susceptible to treatment. The dynamics of older skin functions may not be receptive to pharmacological intervention designed to alter melanin synthesis and transfer.

Modifications of the basic formulation are now being evaluated. It is already clear that good results can be secured, albeit more slowly, with half the concentration of steroid and tretinoin. A less greasy vehicle will certainly be developed; a gel form has much to recommend it.

Finally, there is one type of hyperpigmentation in which lightening is an impossibility, namely, when some sharp inflammatory process has caused melanin granules to be dumped into the dermis, literally a melanin tatoo. The formulation is not a bleaching agent in the sense that hydrogen peroxide is. Already formed pigment is not affected. It is the inhibitors' effect on the synthesis and transfer of melanin that underlies the depigmenting action.

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