# United States Patent [19]

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[11] 3,856,934

[45] Dec. 24, 1974


[54] **SKIN DEPIGMENTATION**


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[22] Filed: **Jan. 22, 1973**

[21] Appl. No.: **325,687**

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 49,523, June 24, 1970, abandoned.

[52] **U.S. Cl.** ..... **424/62,** 424/240

[51] **Int. Cl.** ..... **A61k 7/12**

[58] **Field of Search** ..... 424/62



[56] **References Cited**

UNITED STATES PATENTS

| | | | |
|---|---|---|---|
| 3,006,939 | 10/1961 | Pommer et al. | 260/413 |
| 3,060,097 | 10/1962 | Fellows | 424/62 |

OTHER PUBLICATIONS

Wells et al., – Cosmetics and the Skin, (1964), pages 109 and 609.

The Merck Index – 7th edition, (1960), page 1097.



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[57] **ABSTRACT**

The specification discloses that synergistic compositions for depigmentation by topical application have been found which comprise a mixture of hydroquinone, retinoic acid and a corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle. An illustrative composition comprising from about 2 percent to about 5 percent hydroquinone, from about 0.05 percent to about 0.1 percent retinoic acid and from about 0.05 percent to about 0.1 percent dexamethasone was particularly effective.


**8 Claims, No Drawings**

# SKIN DEPIGMENTATION

## CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending application Ser. No. 49,523, filed June 24, 1970, now abandoned.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a synergistic and nonsensitizing composition for depigmentation of mammalian skin for use by topical application.

2. Description of the Prior Art

So-called compositions for bleaching skin have been known for many years. The use of hydroquinone and its derivatives as agents in bleaching creams is shown in the following publications:

a. U.S. Pat. No. 3,060,097, issued Oct. 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant." Three British Pat. Nos. 763,029, 856,431 and 965,869 issued to the same inventor on similar compositions.

b. French Pat. No. 1,513,395, issued Jan. 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c. French Pat. No. 1,270,854, issued July 24, 1961 to a skin-bleaching composition comprising hydroquinone benzyl ether (l'ether de benzylhydroquinone) and an anti-oxidant. The product may be formulated to contain vitamins, amino acids, cholesterol, etc.

d. U.S. Pat. Nos. 2,274,725 (Mar. 3, 1942), 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sunscreen preparations comprising hydroquinone as the active sunfilter agent. These preparations are stabilized by the addition of certain antioxidants.

e. Zschr. Haut-Geschl.-Krkh. 42, 17: 711–716 reports studies of bleaching the skin using hydroquinone monobenzyl ether. When a subject was found to have sensitive skin, 5 percent hydroquinone monobenzyl ether and 4 percent prednisolone was used to prevent or control the contact dermatitis produced by the hydroquinone monobenzyl ether. No mention is made of an improved bleaching effect when the preparation contained prednisolone.

f. Some other articles reporting on skin-bleaching by the use of hydroquinone or its derivatives are:

1. Archives of Dermatology, 84, No. 1 131–184 (July, 1961).
2. Clinical Medicine, 70, No. 6, 1111–1114 (June, 1963).
3. Clinical Medicine, 73, No. 3, 87–80 (Mar., 1966).
4. Postgraduate Medicine, 37, No. 2, 198–201 (Feb., 1965).
5. J. Investigate Dermatology, 18, 119–135 (1952).
6. J. Am. Medical Assoc., 152, No. 7, 577–582 (June 13, 1953).
7. Dermatologica, 134, 125–128 (1967).
8. Archives of Dermatology, 93, No. 5 589–600 (May, 1966).

## SUMMARY OF THE INVENTION

Broadly stated the instant invention is concerned with a method for lightening or depigmenting mammalian skin and to compositions which are synergistic with respect to depigmentation and essentially nonsensitizing to the skin. These compositions comprise hydroquinone or a nonsensitizing derivative thereof, retinoic acid, and a corticosteroid.



The composition is used by applying, preferably on a regular treatment schedule to the area of skin to be treated until relatively complete and permanent depigmentation is achieved. The composition can be applied to the skin with or without any dressing but occlusive dressing has been found to facilitate depigmentation. In general, the depigmentation is reversible and cessation of treatment may lead to repigmentation unless a sustaining regimen to treatment is continued. Such a regimen may include less frequent application of the herein disclosed composition or daily treatment with hydroquinone alone.

It has long been desirable that certain skin disorders or diseases of the skin be treated to reduce hyperpigmentation generally caused by the deposition of excess quantities of melanin. This hyperpigmentation is generally viewed as cosmetically undesirable and psychologically disabling. Examples of such hyperpigmentation include freckles, senile lentigo, lentigines (liver spots), melasma, contact allergy pigmentation, vitiligo, sunburn pigmentation, post-inflammatory hyperpigmentation due to abrasion, burns, wounds, dermatitis, phototosic reaction and other similar small, fixed pigmented lesions. It is also often desirable to decolorize normally pigmented skin to generally increase "fairness" of appearance or to blend hypopigmented areas into surrounding normal skin, for example in the treatment of generally dark-skinned people suffering from vitiligo.

It is an object of this invention to provide an effective treatment for hyperpigmentation of skin.

Another object of the invention is to provide compositions which do not induce sensitization reactions in subjects treated for hyperpigmentation.

A further object of the invention is to provide an effective method for reduction of melanin levels in the tissue in both hyperpigmented and normally pigmented skin.

A still further object of the invention is to provide compositions which can effectively reduce pigmentation by a process which involves either or both the production of melanin or its transfer but without damage to the melanoblasts themselves.

These and other related objects are achieved by the compositions of this invention which comprise retinoic acid, a corticosteroid, and a depigmentation agent which operates by interfering with or inhibiting the normal pigmentation process. More specifically, a composition comprising retinoic acid, hydroquinone, and a corticosteroid has been found to be particularly effective in achieving a controllable degree of depigmentation of both hyperpigmentated and normally pigmented skin. Depigmentation is controllable to the extent that pigmentation in normally pigmented skin can be preserved at the normal level thus allowing blending of normal and hyperpigmented areas.

Compounds heretofore known as skin bleaching agents include hydroquinone, hydroquinone monoethyl ether, hydroquinone monobenzyl ether, ammoniated mercury, zinc peroxide, mercurous chloride and bichloride of mercury. These compounds are associated with disadvantages which include sensitization, ineffectiveness, irritation and lack of predictable results.

For the most part, useful levels of active ingredient provide only partial depigmentation. This is true even of hydroquinone, the material most widely recognized in the treatment of pigmentation conditions. However, when used in combination with retinoic acid and a corticosteroid, the melanin-inhibiting ability of the hydroquinone is synergistically and unexpectedly enhanced.

It has been found that a preparation containing about 2% hydroquinone without other ingredients is unpredictable and not always effective. Similar results have been reported in the literature, i.e., *Clinical Medicine*, 73, No. 3, 87–88 [Mar., 1966] wherein 35 percent of those subjects treated showed excellent results, 5 percent good, 35 percent fair and 25 percent poor.

Moreover, combinations of a corticosteroid such as dexamethasone and hydroquinone even under occlusion did not provide complete depigmentation after 6 to 8 weeks of twice-daily treatment. Similarly, the combination of hydroquinone and retinoic acid was ineffective to provide complete depigmentation, i.e., less pigmentation than is normally present in persons having white skin.

Other compounds capable of causing exfoliation of skin was substituted for retinoic acid but were not effective in achieving complete depigmentation.

Corticosteroids which can be used include those usually used in the topical treatment of skin conditions. Illustrative compounds include corticosteroids selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle. Esters of corticosteroids are disclosed in U.S. Pat. Nos. 3,694,471; 3,152,154; and 3,147,249.

Subsequent investigations to improve depigmentation has unexpectedly shown that a composition containing hydroquinone, dexamethasone, and retinoic acid produced good to excellent results in essentially all of the subjects treated. Results equivalent to those obtained with the combination can not be achieved by any of the individual components alone.

The compositions of the present invention are applied according to the following general regimen:
In the case of the formulation of example 1, the composition was applied two to three times daily to the areas to be bleached. The composition is preferably applied three times a day for 2 days, then two times a day till irritation (mild inflammation) can be seen. Depending upon the degree of irritation, the composition is applied once or twice a day till depigmentation occurs. Depigmentation usually begins to occur 5 to 21 days after the initial application. Depigmentation is usually complete within 6 to 10 weeks.

In patients with recurrent or permanent hyperpigmentation (Negroes, other dark-skinned races), depigmentation can be maintained by several applications per week.

The results produced by the application of the above composition are exceptionally good. In almost 100 percent of the subjects so treated, good to excellent depigmentation was obtained. The results were particularly dramatic in normal Negro skin, whereon the skin was bleached white in the majority of subjects so treated.

The active ingredients of this composition can be formulated into any cosmetically or pharmaceutically acceptable vehicle or base. Such vehicle formulations are well-known and are disclosed in the literature, e.g., in Cosmetics and The Skin by Wells and Lubowe, Reinhold Publishing Corporation, N.Y., 1964. A particularly suitable vehicle comprises a 1 to 1 mixture of ethanol and propylene glycol and may also include a stabilizer, perfumes and other usual adjuants.

The following examples illustrate formulations of hydroquinone, retinoic acid and suitable corticosteroid.

## EXAMPLE 1

| | |
|---|---|
| Hydroquinone | 2% |
| Retinoic Acid | 0.05% |
| Fluorometholone | 0.025% |
| Fragrance q.s. | |
| Propylene glycol | |
| Ethanol (95%) āā q.s. ad 100 ml. | |

Finely pulverize the hydroquinone, retinoic acid and fluorometholone and dissolve in about 80 ml. of the 50:50 mixture of propylene glycol and ethanol. Add the fragrance and q.s. ad to 100 ml. Mix well and apply to area to be bleached.

## EXAMPLE 2

Substitution in the formula of Example 1 for the fluorometholone used therein of 0.025 percent of desamethasone produces an equivalent formulation.

## EXAMPLE 3

| | |
|---|---|
| Hydroquinone | 2% |
| Retinoic acid | 0.05% |
| Fluorometholone | 0.025% |
| Vanishing Cream base q.s. as 100 gm. | |

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the vanishing cream base and mix well to obtain a gritless paste. Add additional vanishing cream base to make 100 gm. of product. Mix well and apply.

## EXAMPLE 4

| | |
|---|---|
| Hydroquinone | 2% |
| Retinoic acid | 0.05% |
| Fluorometholone | 0.025% |
| Emolient lotion q.s. ad 100 ml. | |

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the emolient lotion to the powder to make a gritless paste. Add sufficient lotion to make 100 ml. Mix well and apply.

## EXAMPLE 5

| | |
|---|---|
| Hydroquinone | 2% |
| Retinoic acid | 0.05% |
| Hydrocortisone | 2.5% |
| Vanishing cream base q.s. ad 100 gm. | |

This formulation was prepared according to Example 3.

## EXAMPLE 6

| | |
|---|---|
| Hydroquinone | 5% |

-Continued

| | |
|---|---|
| Retinoic acid | 0.05% |
| Fluoromethonone | 0.05% |
| Vanishing cream base q.s. ad 100 gm. | |

This formulation was prepared according to Example 3.

A particularly preferred formulation for depigmentation was found, by trial and error, to comprise dexamethasone about 0.1 percent, retinoic acid about 0.1 percent, and hydroquinone about 5.0 percent in a hydrophillic ointment (V.S.P.) base to make 100 percent by weight. This composition was found to regularly depigment black skin when used twice daily for a period of 4 to 5 weeks.

In general, it has been found that effective formulations having an unexpected degree of activity can contain from about 1 to about 5 weight percent hydroquinone and preferably from about 2 to about 5 weight percent hydroquinone.

The amount of retinoic acid can range from about 0.05 to about 2 percent by weight with the preferred range being from about 0.05 to about 0.1 weight percent.

Similarly the amount of corticosteroid can range from about 0.05 to about 2 weight percent depending on the particular steroid used. In a preferred formulation dexamethasone in amounts of from about 0.05 to about 0.1 weight percent has been found to give excellent results.

In a series of clinical studies, 69 patients with melasma were treated with topical preparations identified as A, B and C in a double blind manner. The composition of preparations A, B and C are set forth below.

| | |
|---|---|
| Preparation A — | 2% hydroquinone |
| Preparation B — | 2% hydroquinone, 0.05% retinoic acid, and 0.05% dexamethasone |
| Preparation C — | 5% hydroquinone, 0.1% retinoic acid, and 0.1% dexamethasone |

Results are expressed in terms of excellent, good, fair, and poor based on the observation of the melasma at the beginning and the end of the study and upon photographic comparisons.

Table I, below shows the number of subjects and the classification of results obtained for each of the test compositions.

Table I

| | A | B | C |
|---|---|---|---|
| Excellent | 3 | 10 | 9 |
| Good | 2 | 3 | 7 |
| Fair | 8 | 1 | 3 |
| Poor | 4 | 3 | 1 |
| Incomplete | 6 | 6 | 3 |

Table II shows the total number of subjects falling into the excellent and good classes and the corresponding percentage for these completing the study for each composition.

Table II

| | A | B | C |
|---|---|---|---|
| Number | 5 | 13 | 16 |
| Percentage | 29% | 76% | 80% |

These results indicate that the presence of retinoic acid and dexamethasone unexpectedly increase the degree of depigmentation which can be achieved by the hydroquinone and that increasing the amounts of the active ingredients above the level of composition B does not greatly alter the results.

Some of the topical medication used in the above study invoked moderate irritation. This irritation was present within the first 1 to 4 days of use of medication and became more severe with continued twice a day application. Those patients who discontinued the medication for 1 to 2 days and then gradually resumed use of the topical medication at once daily or occasionally twice daily, were able to tolerate the medication. Although in some patients the inflammation continued throughout the study it could be easily managed by occasionally skipping a day of use of the medication or reducing the frequency of use to once a day. Many of the patients who noted inflammation believed that the improvement or lightening of the skin followed soon after the period of inflammation. Those patients who made this observation were therefore motivated to continue the use of the medication and these patients seemed to improve more than the other subjects. Most patients who improved did so during the second and third week of use of the medication, although some did not improve unitl after the 6th week.

There were no incidences of contact dermatitis, allergic manifestations to medicine, or idiosyncratic reactions. The only side effect was the inflammation discussed above. In all cases the inflammation was quickly reversible with discontinuation of the medication. At its worst it consisted of erythema, itching, minimal desqualmation and some mild burning of the skin.

What is claimed is:

**1.** A skin depigmenting composition for topical application to the skin comprising a melanin inhibiting amount of hydroquinone, retinoic acid and a corticosteroid.

**2.** A composition according to claim **1** comprising a melanin inhibiting amount of hydroquinone, retinoic acid, and a corticosteroid selected from the group consisting of dexamethasone, hydrocortisone, hydrocortisone-17-valerate, and progesterone.

**3.** The composition of claim **2** consisting essentially of from about 2 to about 5 weight percent hydroquinone, from about 0.05 to about 0.1 weight percent retinoic acid, and from about 0.05 to about 0.1 weight percent dexamethasone in a pharmaceutically acceptable vehicle for topical application.

**4.** A composition according to claim **2** consisting essentially of from about 2 to about 5 weight percent hydroquinone, from about 0.05 to about 0.1 weight percent hydrocortisone-17-valerate, and from about 0.05 to about 0.1 weight percent retinoic acid in a pharmaceutically acceptable vehicle for topical application.

**5.** A method for inhibiting the production of melanin which comprises topical application of a composition comprising hydroquinone, retinoic acid, and a corticosteroid, in amounts sufficient to cause depigmentation.

6. The method of claim 5 wherein said composition consists essentially of hydroquinone, retinoic acid, and dexamethasone.

7. A method according to claim 5 which comprises topical application to pigmented skin of a composition comprising from about 2 to about 5 weight percent hydroquinone, from about 0.05 to about 0.1 weight percent retinoic acid, and from about 0.05 to about 0.1 weight percent hydrocortisone-17-valerate in a pharmaceutically acceptable vehicle for topical application and continuing such application until depigmentation is achieved.

8. A method according to claim 5 which comprises topical application to pigmented skin of a composition comprising from about 2 to about 5 weight percent hydroquinone, from about 0.05 to about 0.1 weight percent retinoic acid, and from about 0.05 to about 0.1 weight percent dexamethasone in a pharmaceutically acceptable vehicle for topical application.

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