

**SALIENT OBSERVATIONS FROM THE PUBLISHED LITERATURE  
ON EXOGENOUS OCHRONOSIS REPORTEDLY ASSOCIATED  
WITH SKIN DISCOLORATION FADE PRODUCTS**

May 12, 1992

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**I. Executive Summary**

Exogenous ochronosis reportedly associated with use of skin discoloration fade products is apparently a rare event in the United States.

From the published literature, a total of 14 cases of medically-diagnosed HQ-associated ochronosis has been reported over the years 1976-1992 (to date). The vast majority of cases in the world literature are South African reports of HQ-associated ochronosis. Sixteen domestic reports of skin darkening associated with the reported use of HQ products have been reported to companies over this time period. The company reports appear to be qualitatively different from the medically-diagnosed cases of HQ-associated ochronosis and the result of either the transient darkening of minor skin discolorations during early treatment-induced stimulation of melanocytes or the relative faster lightening of skin surrounding the area of discoloration leaving an impression of darkening of hyperpigmented skin spots. Over this time, companies estimate that over 160 million units of HQ skin discoloration lighteners have been sold in the United States.

However, the South African experience appears to differ from the U.S. experience in a number of significant ways, including: a qualitatively and quantitatively more extensive use pattern in South Africa; the South African use of alcoholic vehicles which appear to enhance penetration of ochronotics in skin discoloration fade products; the presence of non-HQ ochronotics in South African HQ-containing products (e.g., resorcinol and phenol); much higher concentrations of HQ in OTC South African products (e.g., 6-8%). After a decrease in the HQ concentration of South African skin discoloration fade products, the apparent "epidemic" of exogenous ochronosis in South Africa was no longer reported.

A number of dermatologic clinics in the United States with African-American patient populations report either no cases of HQ-associated exogenous ochronosis or its rare occurrence, which itself is notable given the overt-cosmetic-related nature of this condition.

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## II. Exogenous Ochronosis

Exogenous ochronosis appears to be a progressive disorder involving a bluish hyperpigmentation followed by the formation of discrete "sooty" colored papules in the most extreme, and rarest of cases. The hyperpigmentation reportedly associated with HQ use in skin discoloration fade products can be reversible and can be treated successfully (e.g. topical hydrocortisone, dermabrasion, CO<sub>2</sub> laser; see for example: Cullison, 1983; Conner, 1987, Fisher, 1988; Diven, 1990). The degree of reversibility may be related to the timing of onset of treatment. As stated by Conner and Braunstein (1987):

"In most instances, the hyperpigmentation will fade dramatically over a period of years if the bleaching agent is discontinued. In severe cases, especially if papular lesions are present, the condition may be reversible."

Reports of HQ-associated ochronosis indicate that the condition occurs -- on "average" -- over a period of several years. This estimate comes from the case series, that of Findlay's South African experience (Findlay, 1985), and appears to be the best estimate from an overall clinical assessment of the situation, since a number of factors may affect the interpretation of case reports and epidemiologic data, such as ascertainment of: accurate product history and pattern use. For example, it is unclear from the report by Hoshaw (1985; 1982 case) whether or not the individual had been exposed to ochronotic agents at a younger age and only reported very recent use of skin discoloration lighteners. Additionally in this regard, it is unclear from many of the individual published cases the degree and extent of product use. Consequently, the "average" estimation of Findlay, who has been generally regarded as authoritative on the subject, is considered the best approximation. Use of the South African experience as a benchmark for time of onset also incorporates the fact that Findlay's cases derived from the so-called "epidemic" of exogenous ochronosis associated with heavy product usage by South African Blacks.

## III. Domestic Experience

### **A. Medically-Diagnosed Published Cases**

Table A provides a summary listing of the 14 published cases of HQ-associated ochronosis over the last sixteen and half years (1976-1992 to date). Over this time, company marketing data indicate that approximately 160 million units of HQ skin discoloration lighteners have been sold in the United States.

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Characteristics of the published medically-diagnosed cases of HQ-associated ochronosis include:

1. Domestic cases reported use of 1% - 4% concentrations of HQ.
2. Duration of use of the products was usually reported by the individual cases to be on the order of several years (confirmatory to Findlay's case series; Findlay, 1985), although one case reported development of ochronosis after 4 months (Howard, 1990; 1989 case). For this latter case reported by Howard (1990), it is unclear as to the prior product usage; in this regard note the case by Conner (1987) wherein one month of darkening was reported after use of skin lightening creams for a lifetime.
3. All cases were of African-American ancestry with the exception of the case of Mexican ancestry by Howard (1990).
4. All cases were female, with the exception of the case of Cajun ancestry of Davis (1990).
5. The age range of the cases was 36-75 years of age, which supports a longer rather than shorter timeframe of onset of exogenous ochronosis.
6. As stated above, successful treatment of HQ-associated ochronosis has been reported by Hoshaw (1985), Cullison (1983), Conner (1987), Fisher (1988), and Diven (1990).
7. The geographic distribution of cases are predominantly in the South (FL, GA, LA, TX, AZ) and Southwest, but also in the Northeast (NY, MD) and Mid-atlantic (NC) regions.
8. The distribution of cases by year is not remarkable, and as follows:

<u>Year</u>	<u>n</u>	<u>Year</u>	<u>n</u>	<u>Year</u>	<u>n</u>	<u>Year</u>	<u>n</u>
1976	1	1980	0	1984	0	1988	4
1977	0	1981	0	1985	3	1989	1
1978	0	1982	1	1986	0	1990	2
1979	1	1983	0	1987	1	1991	0
						1992	0

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## **B. Company Reports of Skin Darkening Effects**

Company reports of skin darkening effects following HQ use are listed in Table B for the years 1976-1992 (to date), over which time the companies estimate over 160 million units of HQ-containing products sold in the United States. None of the consumer reports solely to companies were medically-diagnosed cases of HQ-associated exogenous ochronosis. One medically-diagnosed case of HQ-associated ochronosis reported in the domestic literature (Howard, 1990; Mexican woman) was also reported to companies.

Where actual verbatim reports of these effects are available, they appear to be qualitatively different from the published reports of medically-diagnosed HQ-associated exogenous ochronosis. Some of the summarized verbatim comments relate to the following: "looks like it made my freckles darker;" "turned skin on freckles very dark;" "didn't lighten spots, made some darker;" "made spots darker/didn't work;" "discolored/darkened spots on face;" and "lightened skin on face, but darkened skin under the eyes."

While it cannot be absolutely ruled out that more than one case of exogenous ochronosis appears among these reports (i.e., one 1989 case to Company A, also reported by Howard, 1990), the mechanism of HQ in producing skin discoloration lightening effects is such as to legitimately question whether any of these reports represent ochronosis related to HQ use. Specifically, HQ is an irritant to some individuals and produces some degree of melanocyte stimulation prior to a lightening effect. Under these circumstances, an individual would notice a transient darkening of the skin. If the product is discontinued at this early point, then the individual would report a darkening effect. Similarly, it is also possible with HQ to observe in a dark-complected person lightening of the skin immediately adjacent to the skin discoloration spot to a degree greater, relatively, than that of the darker spot -- resulting in an impression that the darker spot had become even darker. In any case, there is reason to believe that these consumer reports for the most part are not specific instances of exogenous ochronosis.

## **C. FDA's Spontaneous Reporting System**

Three domestic cases related to HQ use have been reported to FDA's Spontaneous Reporting System. Although the task group has asked for copies of the 1639 forms, these are as yet not forthcoming, and the description of this material is not included in this report.

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**D. Domestic Clinical Experience**

Domestic clinical experience described to the task group by clinicians caring for patient populations in which HQ skin discoloration lightening products are used regularly indicate that HQ-associated exogenous ochronosis is a rare event, and often not seen in clinical practice.

**IV. Foreign Experience**

Table C (appended) lists published material from the foreign database. By far, the vast majority of cases come from the African experience in South Africa and Nigeria. There are a number of issues that distinguish the South African situation from the current situation in the United States, where the reports of HQ-associated ochronosis appear to be rare. These differences are outlined in the table below:

**Comparison of the South Africa Situation and the Current U.S. Marketplace**

<u>Parameter</u>	<u>South Africa</u>	<u>United States</u>
1. Units Sold/Year	25 million/year	10-15 million/year
2. Usage	Very Extensive Use	Limited Extensive Use
3. HQ Concentration	6-8% Concentrations OTC	1-2% Concentrations OTC
4. Vehicle	Alcoholic Vehicles, Which Enhance Penetration; Use of Creams and Lotions	Water-soluble creams; Relatively Poor Absorption
5. Use of Sunscreen	Typically No Sunscreen in Formula No Associated Labeling	Typically Use of Sunscreen in Formula Associated Labeling
6. Other Ochronotics in Formulae	Resorcinol and Phenol	None
7. Number of Cases	Hundreds	14 in medically-diagnosed cases, published literature

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In summarizing the South African experience, Findlay (1985) stated:

"A minor epidemic of ochronosis from bleaching creams is hard to trace to its sources, but in 1966 certain commercial preparations containing 3% hydroquinone were strengthened to 6 and 8% and put in a more adherent and penetrating base. It was from 1969 onward that we became increasingly familiar with this new disease."

Thus, as a result of a heavier use pattern, higher concentrations of HQ in skin discoloration lightening products, use of formulae with higher penetrating vehicles, with other ochronotics and with no sunscreens, and no associated labeling as to sun exposure, a number of factors converge to create the South African situation as described by Findlay (1985). After a decrease in the concentration of South African HQ skin discoloration lightening products to 2%, the apparent "epidemic" reported by Findlay was not longer in evidence. Cases were reported in the literature after the change in the marketing status (i.e., reduction in concentration of HQ-containing products), but this would be expected, since: (a.) it typically takes a year or two to push product through the distribution system; (b.) ochronosis associated with HQ use takes "on average" several years to develop.

## V. Summary

In summary, the number of cases reported in the literature of medically-diagnosed cases of HQ-associated ochronosis is small, and this fact, in addition to the reported clinical experience with HQ-containing skin discoloration lighteners and the known differences to the South African situation, lead to the conclusion that HQ-associated ochronosis in the United States is rare and that HQ-containing OTC products are safe and effective when used as directed.

## VI. References

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**TABLE A: Published Reports of Exogenous Ochronosis  
Reportedly Associated With Use of Hydroquinone-  
Containing Skin Lightening Preparations**

First Author Year	State	Age Race Sex	Domestic Experience		Outcome
			Reported Exposure	Treatment	
Hoshaw 1985 (1976 case)	AZ	75 B/F	2% HQ 2 years	No treatment for multiple pigmented papules on cheeks, and lateral to eyes	Four years after the first visit, improvement was seen in the size and number of forehead pigmented papules
Cullison 1983 (1979 case)	GA	58 B/F	2% HQ 2.5 years 5-6 x/d	2.5% hydrocortisone 18 months b.i.d. for sooty blue-black, relatively uniform hyperpigmentation of cheeks and forehead	Remarkable clearing of the hyperpigmentation except for some residual changes
Hoshaw 1985 (1982 case)	AZ	49 B/F	OTC skin lightening creams 2 months	Sunscreen & avoid sunlight for black- blue hyperpigmentation of cheeks, nose and chin	No change several months post visit
Pennys 1985	FL	NG	NG	NG	NG (Not Given)
Lawrence 1988 (1985 case)	LA	62 B/F	1% HQ 2-3 years	2.5% HC for bilateral speckled hyperpigmentation on molar regions of cheeks	Lost to follow-up
Lawrence 1988 (1985 case)	LA	46 B/F	1% HQ duration unknown	2.5% HC plus sunscreen for hyperpigmented macular eruption of nose, forehead and periorbital areas	"The treatment resulted in some decrease in the pig- mentation on the forehead but the periorbital and chin hyperpigmentation remain prominent." NOTE: the time at which this assess- ment was made was not given.

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First Author Year	State	Age Race Sex	Reported Exposure	Treatment	Outcome
Conner 1987	MD	72 B/F	1 month of darkening after using skin lightening creams since childhood	Treatment not discussed, confluent hyperpigmented blue-black macular and patches on forehead molar and temporal regions	"In most cases the hyper pigmentation will fade dramatically over a period of years, if the bleaching agent is discontinued."
Fisher 1988	NY	47 B/F	4% HQ 18 months	500 mg Tetracycline for discrete nonpruritic popular eruption of "dark spots" on cheeks	"After one month decided improvement was apparer and in 3 months the lesio had entirely cleared."
Carey 1988 (3 cases)	NC	NG	NG	NG	
	NC	NG	NG	NG	
	NC	NG	NG	NG	
Howard 1990 (1989 case)	TX	36 MEX/F	2% HQ 4 months	1% HC; 0.1% Retinoic Acid; 5% BP; sunscreen for symmetrical blue- black macular hyper- pigmentation of cheeks chin, and forehead	"Only minimal lightening the hyperpigmentation." NOTE: the time at which this assessment was made was not given.
Diven 1990	TX	53 B/F	2% HQ 2-3 months prior Hx unknown	Dermabrasion and CO <sub>2</sub> laser for "sooty blue-black macules and patches," especially in molar and periorbital areas.	"The patient was pleased with the final result."
Davis 1990	TX	40 Cajan male	NG	NG	

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TABLE B

**1985-1992 Domestic Company Reports by Consumers  
Of Skin Darkening Effects Following HQ Use**

Company	Date	State	Age/ Sex	%HQ, Snsrn & Exposure	Comment
A	1985	NG	NG	NG	
A	1985	NG	NG	NG	
A	1985	NG	NG	NG	
A	1985	NG	NG	NG	
A	1989	NG	NG	NG	
A	1989	NG	NG	NG	
A	1989	NG	NG	NG	
A	1989	TX	MEX/F	2% HQ	Only case reported in med. lit. (Howard, 1990)
A	1990	AZ	NG/F	NG	"looks like it made freckles darker"
A	1990	OH	NG/M	2% w/o snsrn.	"turned skin on freckles very dark"
A	1990	FL	NG/F	2% w/snsrn.	"didn't lighten spots, made some darker"
A	1990	CA	NG	2% w/snsrn.	"made spots darker/didn't work"
A	1991	NY	NG/F	NG	"seems to make skin darker"
B	1988	NJ	NG/F	2%	"black ring around the eye"
C	85-92	None			
D	85-92	None			
E	85-92	None			
F	1986	NG	NG	2%/2 weeks	"discolored/darkened spots on face"
F	1987	NG	NG	2%/6 months	"discolored cheeks, fingers broken out with sores and became discolored (darken); face started to form sores."
F	1989	NG	NG	2%/NG	"lightened skin on face, but darkened under eyes"

NG = not given

A,B,C,D,E,F = code letter given to different contributing companies

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**TABLE C: Published And Company Reports of Exogenous Ochronosis Page 11**  
**Reportedly Associated With Use of Hydroquinone-**  
**Containing Skin Lightening Preparations**

**Foreign Experience**

<b>Author Year</b>	<b>Country</b>	<b>(n) Age Race Sex</b>	<b>Reported Exposure</b>	<b>Comment</b>
Findlay 1985 (Cases From 1969-74)	South Africa	n=35 30-39 yr Black Female	6-8% HQ over 3-8 years	1. Ochronosis developed gradually over 1/2-3 years as a rule, or longer."  2. "A minor epidemic of ochronosis form bleaching creams is hard to trace to its sources, but in 1966 certain commercial preparations containing 3% hydroquinone were strengthened to 6 and 8% and pu in a more adherent and penetrating base. It was fro 1969 onward that we became increasingly familiar w this new disease."
Harwick 1989 Epi study from 1985 to 1986	South Africa	Sample n=195 14-73yr Black  53 males & 142 fem. in sample with 6/53 males as cases and 60/142 fem. as cases	3-8% HQ for < 6 months to > 16 yrs.	1. No ochronosis in the five subjects who had use HQ for less than 6 months.  2. 70% of subjects who reported HQ use for more than six months showed signs of ochronosis; 92% who used HQ > 16 years had signs of ochronosis  3. NOTE: case selection criteria poorly articulated in the published report. It is unclear how and if controls were selected. It is unclear the extent to which selection bias was operating. See page 230 o reference.

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## Foreign Experience: Continued

Author Year	Country	(n) Age Race Sex	Reported Exposure	Comment
Olumide 1990 (Epi study covered 1974-1984)	Lagos Nigeria	1,500 new cases per year in the LUTH skin clinic; n=54 exogenous induced photo- dermatoses -- or 0.4% of total; only 15 HQ-associ- ated cases of 1,500 cases	Not given	"In conclusion, light sensitive dermatoses do not constitute a major problem among the black people endowed with the melanin pigment against solar injury. Endogenous photodermatoses are rarely seen in clinical practice. The few patients that are seen result from exposure to exogenous photosensitizers."
Company report 1989	England	NG B/M	NG	"Darker around the eyes"
Hull 1990	South Africa	60 yr. old B/F	2% HQ/1 yr	Ochronotic fibers not present in patches of vitiligo skin, which contained no basal melanocytes.

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