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An Official Publication of

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DIFFERIN® (adapalene) LOTION, 0.1%—
THE ONLY RETINOID IN A LOTION FORMULATION

ON THE JOB
WITH GENTLE EFFICACY

58.2% MEDIAN TOTAL LESION COUNT
REDUCTION BY WEEK 12

TOLERABILITY PROFILE SIMILAR TO
DIFFERIN® (adapalene) CREAM, 0.1%

AVAILABLE IN AN EASY-TO-USE
PUMP DISPENSER

RESULTS PATIENTS WANT IN A FORMULATION THAT DOES THE WORK—
PREScribe DIFFERIN® LOTION, 0.1% TODAY!

*A 12-week, multicenter, randomized, double-blind, parallel-group study of patients 12 to 18 years of age with acne vulgaris (N=1075).
†The most frequent adverse event reported was dryness. Erythema, stinging/burning, and scaling may also occur.

Important Safety Information
Differin® Lotion, 0.1% is indicated for the topical treatment of acne vulgaris in patients 12 years and older. A thin film of Differin® Lotion, 0.1% should be applied once per day to the face and other areas of the skin affected by acne. In clinical trials, the most common adverse event (>1%) reported with use of Differin® Lotion, 0.1% was mild to moderate skin dryness. Erythema, scaling, stinging and burning may also occur. Excessive exposure to sunlight and sunlamps should be avoided during treatment, and use of sunscreen products and protective clothing is recommended. Concomitant use of drying or irritating topical products (like products containing resorcinol, salicylic acid or sulfur) should be used with caution. Instruct patients to avoid the eyes, lips and mucous membranes when applying Differin® Lotion, 0.1%, and not to apply to areas that have been depilated with wax products. Differin® Lotion, 0.1% has not been tested in pregnant or nursing women, or with the elderly. Pregnancy Category C.

www.differin.com/HCP

Please see Brief Summary of Prescribing Information on adjacent page.
DIFFERIN® Rx only
(adapalene) Lotion 0.1%
For Topical Use Only
Not For Oral, Ophthalmic, or Intravaginal Use.

BRIEF SUMMARY

INDICATIONS AND USAGE

DIFFERIN Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided.

ADVERSE REACTIONS

Dry skin of mild to moderate severity was the most frequently reported treatment related adverse event. Erythema, scaling, dryness, burning/stinging were also seen during treatment.

DRUG INTERACTIONS

Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Lotion. Wax depletion should not be performed on treated skin.

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women. However, animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of human response.

Human Data

In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris, women of childbearing potential initiated treatment only after a negative pregnancy test. Two women became pregnant while using DIFFERIN Lotion, 0.1%. One patient delivered a healthy full term baby and the other patient electively terminated her pregnancy.

Animal Data

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of DIFFERIN Lotion. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Systemic exposure (AUC 0-24h) to adapalene at topical doses (6.0 mg/kg/day) in rats represented 101 times the exposure to adapalene in patients with acne treated with DIFFERIN Lotion applied to the face, chest and back (2 grams applied to 1000 cm² of acne-involved skin).

Nursing Mothers

It is not known whether adapalene is excreted in human milk following use of DIFFERIN Lotion. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of DIFFERIN Lotion in pediatric patients under the age of 12 have not been established.

Geriatric Use

Clinical studies of DIFFERIN Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity and impairment of fertility studies were conducted with DIFFERIN Lotion.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test).

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/ day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F1 males and females, or growth, development and reproductive function of F1 offspring.

PATIENT COUNSELING INFORMATION

• Apply a thin film of DIFFERIN Lotion to the affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning.

• Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply DIFFERIN Lotion to the entire face or other acne affected areas as a thin layer, avoiding the eyes, lips and mucous membranes.

• Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis and eye irritation.

• Patients should be advised not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

• Advise patients to minimize exposure to sunlight including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.

• Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.

• This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.

• Wax depletion should not be performed on treated skin due to the potential for skin erosions.

• This product is for external use only.

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VELTIN Gel—A Topical Treatment for Patients 12 Years or Older With Acne Vulgaris

Once-daily application in the evening

Important Safety Information for VELTIN Gel

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
- Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
- Observed local treatment-related adverse reactions (≥1%) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of actively assessed local skin reactions peaked at week 2 and then gradually decreased
- VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component
- Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. VELTIN Gel should be used with caution in patients receiving such agents
- VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- It is not known whether either clindamycin or tretinoin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Due to possible serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug. Exercise caution if administering VELTIN Gel to a nursing woman
- The efficacy and safety have not been established in pediatric patients below the age of 12 years
- VELTIN Gel is not for oral, ophthalmic, or intravaginal use

Please see brief summary of Prescribing Information on the next page.
VELTIN™ (clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

The following is a brief summary only; see full prescribing information for complete product information.

INDICATIONS AND USAGE
VELTIN Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS
VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS
Colitis
Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhoea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhoea occurs, VELTIN Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death. Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.

Ultradiffuse Light and Environmental Exposure
Exposure to sunlight, including sunlamps, should be avoided during the use of VELTIN Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with VELTIN Gel.

ADVERSE REACTIONS

Adverse Reactions in Clinical Studies
The safety data reflect exposure to VELTIN Gel in 1,104 patients with acne vulgaris. Patients were 12 years or older and were treated once daily in the evening for 12 weeks. Observed local treatment-related adverse reactions (>1% in clinical studies with VELTIN Gel were application site reactions, including dryness (6%), irritation (5%), exfoliation (5%), erythema (4%), pruritus (2%), and dermatitis (1%). Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased. Local skin reactions were also assessed at baseline and at the end of 12 weeks of treatment in patients exposed to VELTIN Gel. At baseline (N=476), local skin reactions included erythema (24%), scaling (8%), dryness (11%), burning (8%), and itching (17%). At 12 weeks of treatment (N=409), local skin reactions included erythema (21%), scaling (19%), dryness (22%), burning (13%), and itching (15%). During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

DRUG INTERACTIONS

Erythromycin
VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component. In vitro studies have shown antagonism between these 2 antimicrobials. The clinical significance of this in vitro antagonism is not known.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, VELTIN Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C. There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A limited teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 0.5 μg/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50 kg person.

Tretinoin: Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates. It was teratogenic and fetotoxic in Wistar rats when given orally at doses greater than 1 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison). However, variations in teratogenic doses among different strains of rats have been observed. Data from the cyogenetic analysis of a species in which tretinoin metabolism is closer to humans than in other species examined, fetal malformations were reported at oral doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (324 times the recommended clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related teratogenic effects and increased abortion rates were reported in pigtail macaques.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to fetus is not known.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VELTIN Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of VELTIN Gel in pediatric patients below the age of 12 years have not been established. Clinical trials of VELTIN Gel included 2,086 patients 12-17 years of age with acne vulgaris. [See Clinical Studies (14) of full prescribing information.]

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of VELTIN Gel or the effect of VELTIN Gel on fertility. VELTIN Gel was negative for mutagenic potential evaluated in an in vitro Ames Salmonella reversion assay. VELTIN Gel was equivocal for clastogenic potential in the absence of metabolic activation when tested in an in vitro chromosomal aberration assay.

Clindamycin: Once daily dermal administration of 1% clindamycin phosphate in the VELTIN Gel vehicle (32 mg/kg/day, 13 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenicity.

Tretinoin: In two independent mouse studies where tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years no carcinogenicity was observed, with maximum effects of dermal amyloidosis.

However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 μg (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz[a]anthracene (DMBA). In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol 13-acetate or mezerein for up to 20 weeks. Topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas per mouse. However, papillomas resistant to topical tretinoin suppression were at higher risk for pre-malignant progression.

Tretinoin has been shown to enhance photo-co-carcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photo-co-carcinogenic potential of the clindamycin tretinoin combination is unknown. Although skin irritation may cause an increase in sun sensitivity with VELTIN Gel.

PATIENT COUNSELING INFORMATION
[See FDA-approved Patient Labeling in full prescribing information.]

Instructions for Use

• At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips).

• Patients should be advised not to use more than a pea sized amount to cover the face and not to apply more often than once daily (at bedtime) as this will not make for faster results and may increase irritation.

• A sunscreen should be applied every morning and reapplied over the course of the day as needed. Patients should be advised to avoid exposure to sunlight, sunlamp, ultraviolet light, and other medicines that may increase sensitivity to sunlight.

• Avoid using other topical products with a strong drying effect, such as abrasive soaps or cleansers, may cause an increase in skin irritation with VELTIN Gel.

Skin Irritation
VELTIN Gel may cause irritation such as erythema, scaling, itching, burning, or stinging.

Colitis
In the event a patient treated with VELTIN Gel experiences severe diarrhea or gastrointestinal distress, VELTIN Gel should be discontinued and a physician should be contacted.

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With the advent of PowerPoint presentations and digital photography, the slide, sometimes referred to as a Kodachrome or diapositive, has been relegated to the attic or, even worse, the recycling bin. Glass projection transparencies have long since disappeared from department collections, with a few water-colored illustrations clinging on in an occasional clinic as a reminder of the past; yet, one vehicle survives, even with its rocky history, the wax model. The wax model, sometimes referred to as a moulage, provides a wonderful three-dimensional view of skin disease. The coloring can be so realistic that the model is almost life-like. While significant collections remain extant at institutions such as l’Hôpital St Louis in Paris, “Andreas Sygros” Hospital in Athens, and the University of Zurich, other collections of yesteryear are nowhere to be found or have been markedly reduced in numbers and prominences.

**A REBIRTH**

Dermatologists and historians have begun to rediscover the almost-forgotten three-dimensional models of the skin. Many have been molded from patients with the use of a plaster cast to provide unique exhibits of skin diseases, often of yesteryear. In some cases, the patient histories have also survived to provide a window into earlier times.

In the early 1960s, Kodachromes had replaced the moulages at Zurich as teaching aids, but then an exhibition in the Museum of Medical History in Zurich changed the course of wax model history. The exhibit drew new attention to the nearly forgotten medical wax figures. By 1993, the growing public interest finally led to the opening of the modern Museum of Wax Moulages of the University Hospital and the University of Zurich.

**A CURRENT EDUCATIONAL TOOL**

After showing several special exhibitions on historical topics, the Museum of Wax Moulages in Zurich now provides a complete tour for the specialty of dermatology and venereology. This is based on the Swiss catalogue of learning objectives for undergraduate medical training. Despite the objections of some who view new as good and old as bad, this, being the oldest of dermatologic teaching aids, has proven to be of great

*When the Duhring models were exhibited at the American Academy of Dermatology Meeting in 1971, the porters were afraid to approach the booth for fear of contracting the diseases depicted (Figure 1).*

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**Figure 1.** An exhibit of the Collection of Wax Models of the University of Pennsylvania at the 30th Annual Meeting of the American Academy of Dermatology, Chicago, IL, December 4–9, 1971.
value for the medical students. The collection complements the teaching of skin diseases, providing a more realistic approach, along with e-learning and digital imagery.

For more than 5 years, the introduction to dermatologic training has taken place in the museum itself and has been met with great success. These wax moulages have regained their position as important teaching aids, thanks to their outstanding quality and quantity, with there being more than 1800 models in the collection (600 on display). Pictures of some of these models are currently published in many issues of SKINmed.

THE FUTURE

We recognize that not all dermatology programs have or will have wax models; however, we believe that they are highly useful for teaching students and dermatologic neophytes (Figure 4). Where else can the morphology of various skin diseases be introduced so well?
REFERENCES


In a clinical study, 77% of subjects noted moderate to significant improvement in scars treated with Mederma® in terms of redness, texture and overall appearance. 98% of patients completed the study without any adverse events.

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888.925.8989

1 Draelos, Z. The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. Cosmetic Dermatology, June 2008.
There is a prevalent belief in the lay public that there exists a connection between diet and acne. Although much has been elucidated about the pathogenesis of acne, the role of diet has long been debated. Several studies have implicated dairy products or high-glycemic–loaded foods with prevalence and/or severity of acne. Based on these data, some researchers have suggested that patients with acne eliminate all dairy products from their diet and eat only foods with a low glycemic index. Such a diet is suggested in the Clear Skin Diet Book, for instance. Although such ideas may be popular or prevalent, it is important to keep in mind that these studies are not evidence-based. Many patients may expect information from their doctors on what foods they should eat or avoid to improve their acne; however, evidence is lacking to make any recommendation in regard to diet and acne.

YouTube is a popular video-sharing Web site. A search of the term acne on YouTube yields more than 30,000 videos. Discussed are a broad range of topics in relation to acne, oftentimes with the maker of the video offering their personal advice regarding prevention and treatment options. This study uses YouTube to elicit public opinion on the role of diet and nutrition in acne pathogenesis.

METHODS

During July and August of 2009, YouTube was searched with the following keywords: “acne diet,” “acne nutrition,” and “acne food.” Videos were included only if they mentioned or discussed a component of diet as it related to acne. Videos that appeared under more than one keyword were included only once. Advertisements were omitted. Most videos were excluded as they did not discuss nutrition and its relation to acne.

RESULTS

Of the 87 videos included in the study, more than 85% suggested at least a moderate correlation between diet and acne. Specifically, 50% of videos suggested a strong correlation, while 37% suggested moderate, 3% suggested minimal, and 9% suggested no correlation. Fruits and vegetables, as well as nutritional supplements, were suggested as alleviating factors. Dairy products were generally regarded as aggravating factors. Sugary and oily/greasy foods were generally regarded as aggravating factors, although a significant percentage stated that these foods had no effect on acne (Table). Very popular videos had been viewed more than 10,000 times. The three most popular videos, which had been viewed more than 100,000 times, all suggested a strong correlation between acne and nutrition. All three recommended increased consumption of fruits and vegetables. Two videos suggested that dairy products...
should be avoided, while one video suggested that dairy products can help alleviate acne. Two videos suggested that sugar and sweets should be avoided, and one video suggested that oily foods should be avoided.

**DISCUSSION**

Despite the long-running controversy regarding acne and diet, dermatologists as a rule do not manage acne by modifying diet. Yet, more than 85% of videos viewed on YouTube suggest at least a moderate correlation between diet and acne, even though little scientific proof of this exists. This is noted to be a source of frustration in some videos. Indeed, many people who stated that there was a strong correlation between diet and acne also suggested that viewers “not waste time and money” visiting dermatologists, whom they felt were not treating the source of the problem. Awareness of this perception is important, as it may play a role in patient compliance.

**CONCLUSIONS**

The controversy about the role of nutrition in acne remains unresolved. Studies continue on the subject, and, until better data are available, an open mind on this topic can only help in treating our patients.

**REFERENCES**


<table>
<thead>
<tr>
<th>NUTRITIONAL COMPONENT</th>
<th>ALLEVIATING, %</th>
<th>NO EFFECT, %</th>
<th>AGGRAVATING, %</th>
<th>TOTAL, %</th>
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<tr>
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<td>2.3</td>
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<td>29.9</td>
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<td>21.8</td>
<td>31</td>
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<tr>
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<td>5.7</td>
<td>13.8</td>
<td>19.5</td>
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**URTICARIA A-G**

**Drugs that may cause urticaria A-G**

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<thead>
<tr>
<th>Abbokinase</th>
<th>Calan</th>
<th>Duragesic</th>
<th>Flaygl</th>
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<tr>
<td>Atarax</td>
<td>Celebrex</td>
<td>Eidel</td>
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<tr>
<td>Caffeine</td>
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</table>

Adapted from Litt, JZ. *Curious, Odd, Rare, and Abnormal Reactions to Medications.* Fort Lee, NJ: Barricade Books; 2009: 126–128.
Important Safety Information for DUAC Topical Gel

• DUAC Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin
• DUAC Topical Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis
• Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus
• For dermatologic use only; not for ophthalmic use
• Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents
• The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures
• Clindamycin- and erythromycin-containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known
• DUAC Topical Gel may bleach hair and colored fabrics
• Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn
• DUAC Topical Gel should be given to a pregnant woman only if clearly needed
• It is not known whether DUAC Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
• Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established
• Adverse reactions may include erythema, peeling, burning, and dryness
• Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Please see brief summary of Prescribing Information on following page.

DUAC® Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)

The following is a brief summary only; see full prescribing information for complete product information.

For Dermatological Use Only.
Not for Ophthalmic Use.
Rx Only

INDICATIONS AND USAGE
DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris. DUAC Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS
DUAC Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS
ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA AND SEVERE COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTI-BIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOscopic EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR CLOSTRIDIUM DIFFICILE may reveal CLOSTRIDIUM DIFFICILE. THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTI-INFECTIVE AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against CLOSTRIDIUM DIFFICILE colitis.

PRECAUTIONS
General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents. The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures. Avoid contact with eyes and mucous membranes. Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vivo antagonism is not known.

Information for Patients: Patients using DUAC Topical Gel should receive the following information and instructions:

1. DUAC Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician. Patients who develop allergic symptoms such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.

5. DUAC Topical Gel may bleach hair or colored fabric.

6. DUAC Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.

7. Before applying DUAC Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in solution at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment. The clinical significance of this is unknown.

In a 2-year dermal carcinogenicity study in mice, treatment with DUAC Topical Gel at doses up to 8000 mg/kg/day (16 times the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m²) did not cause an increase in skin tumors. However, topical treatment with another formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, or 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats.

In a 52-week photocarcinogenicity study in hairless mice (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumors was 38 weeks for male and 49 weeks for female treated animals. Therefore, clindamycin and 5% benzoyl peroxide at doses up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with DUAC Topical Gel or benzoyl peroxide. It is also not known whether DUAC Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DUAC Topical Gel should be given to a pregnant woman only if clearly needed. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity. Nursing Women: It is not known whether DUAC Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The percentage of patients that had symptoms during clinical trials were as follows:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>28%</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
<td>&lt;1%</td>
<td>0</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
<td>&lt;1%</td>
<td>0</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
<td>&lt;1%</td>
<td>0</td>
</tr>
</tbody>
</table>

(Percentages derived by # subjects with symptom score/# enrolled DUAC Topical Gel subjects, n = 397).

Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with DUAC Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Tinea versicolor (TV) is a superficial cutaneous fungal infection characterized by pigment changes, pruritus, scaling, and erythema. This open-label, single-center pilot study evaluated the efficacy and safety of naftifine 1% gel applied twice daily for 2 weeks in 10 men and women (median age 38 years) with TV. Baseline mycology status was determined by potassium hydroxide (KOH) and microscopy and clinical symptom severity (CSS) scored by the investigator using a 0 to 9 scale (0=absent, 9=worst). Patients applied naftifine HCl 1% gel to the affected area twice daily for 14 days. They returned for follow-up efficacy and safety assessments at the end of treatment (week 2), 2 weeks after treatment (week 4), and 6 weeks after treatment (week 8). All patients had a positive mycology at baseline; one was KOH negative at week 2, two were negative at week 4, and five (50%) were negative at week 8. Mean investigator total CSS score decreased from a baseline value of 4.7 to 3.2 at week 2 (32% improvement), 2.6 at week 4 (45% improvement), and 2.7 at week 8 (43% improvement). The patients rated their symptoms to be improved at all follow-up visits. There were no treatment-related adverse events during the study. These results suggest that naftifine 1% gel is a safe and efficacious topical treatment for TV.

**METHODS**

**Patient Selection**
This was a single-center, open-label study conducted in the United States from November 2007 to April 2008. To participate, patients had to be at least 18 years of age, have a clinical diagnosis of TV by microscopy/potassium hydroxide (KOH) and microscopic and clinical symptom severity (CSS) score for erythema, scaling, and pruritus ≥3 on a 0 to 9 scale, where 0 was absent and 9 was worst. Evaluation of hypopigmented and hyperpigmented patches, although commonly associated with TV, was not an objective of this clinical trial. Women were either postmenopausal for at least 1 year or had agreed to use an approved method of birth control throughout the study. Study exclusion criteria included known allergy or sensitivity to the ingredients in the study drug formula or similar chemical structures; psoriasis; atopic dermatitis; or any clinically significant systemic or dermatologic disorder.

**ABSTRACT**
Tinea versicolor (TV) is a superficial cutaneous fungal infection characterized by pigment changes resulting from colonization of various yeasts and lipophilic fungi of the genus Malassezia, of which there are three dominant species: *M. globosa*, *M. sympodialis*, and *M. furfur*. The frequency of TV is estimated to be as high as 30% in humid tropical zones. It may occur at any age but is more common during adolescence and young adulthood, suggesting a relationship with androgen-induced sebaceous activity. In the United States from 1990 to 1999, TV was diagnosed at 2.9 million office visits, corresponding to a frequency of 110 visits per 100,000 population per year. Topical antifungal therapy, including zinc pyrithione and selenium sulfide shampoos, is often recommended initially or for limited cases of TV. Non-creamy forms of antifungal agents such as gels or sprays are generally preferred for treatment due to their lack of messiness and ability to be used under clothing areas.

Naftifine HCl 1% gel is a topical broad-spectrum fungicidal agent of the allylamine class. In the United States, naftifine 1% gel is indicated for the treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, and *Epidermophyton floccosum*. The purpose of this open-label exploratory study was to obtain preliminary data on the safety and efficacy of 2 weeks of twice-daily application of naftifine 1% topical gel in the treatment of TV.
that could interfere with the study results; uncontrolled diabetes mellitus; Parkinson’s disease; drug or alcohol abuse; a mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study; and use of any of the following medications: other topical antifungal treatments for TV, topical retinoids or corticosteroids within 4 weeks of screening, topical medication containing tar, selenium sulfide, zinc pyrithione, salicylic acid or sulfur within 2 weeks of screening; systemic use of corticosteroids, retinoids, erythromycin, tetracycline or their derivatives, trimethoprim/sulfamethoxazole, cytostatic or immunomodulating drugs, or other antymycotic drugs within 4 weeks of screening; inhaled/intranasal corticosteroids >800 μg/d 4 weeks prior to screening; or participation in any investigational drug or device study within 30 days of screening.

Participants signed a voluntary informed consent and Health Insurance Portability and Accountability Act authorization prior to screening. The protocol and consent form were approved by Independent Investigational Review Board, Inc, and the study was conducted in accordance with International Conference on Harmonisation Guidelines for Good Clinical Practice.

**DESIGN AND PROCEDURES**

The study consisted of a screening/baseline visit at week 0, twice-daily application of naftifine 1% gel for 14 days, and follow-up visits at week 2 (last treatment day), week 4 (14 days post-treatment), and week 8 (42 days post-treatment) for efficacy and safety assessments. At visit 1, after screening and enrollment, baseline CSS score and mycology status were obtained. The patients were then given two 40-g tubes of naftifine gel 1% to apply to the affected area twice daily for 14 days.

Mycology analysis was performed by scraping the epidermis of the periphery of the affected area with a sterile scalpel blade, placing the scrapings onto a microscope slide, adding 1 or 2 drops of 10% KOH solution onto the slide to dissolve epithelial tissue and keep the fungal hyphae intact, and visual inspection by light microscopy. CSS scoring was performed by the investigator by visual examination using the following 4-point scale: for erythema and scaling, 0 = absent, 1 = minimal involvement, 2 = distinctive presence, and 3 = marked/intense; and for pruritus, 0 = absent, 1 = at least occasionally present but not bothersome to patient, 2 = present and bothersome some of the time, and 3 = present and so bothersome that the patient thinks about it much of the time. Individual CSS scores were summed to obtain a total CSS score graded from 0 (absent) to 9 (worst). Each patient also rated his/her improvement from baseline at each follow-up visit using a 4-point scale: 0 = worse, 1 = no change, 2 = improved, 3 = much improved. Safety was assessed at each follow-up visit by the frequency and severity of adverse events. Due to the exploratory nature of the study and small sample size, data were analyzed with descriptive statistics.

### Table. Combined Mean CCS and KOH Mycology Status for All Patients at Baseline and at Follow-Up Visits

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Year</th>
<th>Location</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CSS</td>
<td>KOH</td>
<td>CSS</td>
<td>KOH</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>1999</td>
<td>Back, arms, shoulders</td>
<td>5</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>M</td>
<td>1990</td>
<td>Chest, arms, shoulders</td>
<td>4</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>1990</td>
<td>Trunk</td>
<td>6</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>F</td>
<td>1999</td>
<td>Neck</td>
<td>5</td>
<td>+</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>2004</td>
<td>Chest</td>
<td>3</td>
<td>+</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>2003</td>
<td>Back, chest, shoulders</td>
<td>4</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>M</td>
<td>2005</td>
<td>Back, flanks, shoulders</td>
<td>5</td>
<td>+</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>F</td>
<td>1990</td>
<td>Neck, chest, back, abdomen</td>
<td>6</td>
<td>+</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>M</td>
<td>1998</td>
<td>Chest</td>
<td>4</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>M</td>
<td>2005</td>
<td>Back, chest</td>
<td>5</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: CSS, clinical symptom severity score for erythema, scaling, and pruritus combined (scale for total symptom score ranged from 0 to 9 where 0 was absent and 9 was worst); F, female; KOH, potassium hydroxide; M, male; week 2, end of treatment; week 4, 2 weeks after treatment; week 8, 6 weeks after treatment.
RESULTS

Ten patients (7 men and 3 women) with a median age of 38 years (range 29–53 years) were enrolled and all completed the study. The median time since diagnosis of TV was 9 years (range 2–18 years).

Two weeks of naftifine 1% gel treatment lowered CSS scores from baseline in 9 of 10 patients at week 2, week 4, and week 8 (Table). The lower CSS scores corresponded with individual improvements ranging from 25% to 75% over baseline. Mean total CSS score for the 10 patients (all symptoms combined) was 4.7 at baseline, 3.2 at week 2, 2.6 at week 4, and 2.7 at week 8. The follow up scores at week 2, week 4, and week 8 corresponded to an improvement over baseline of 32%, 45%, and 43%, respectively, for combined clinical symptoms.

The proportion of patients who achieved mycological cure (negative KOH) at each follow-up visit is illustrated in the Figure. All patients were KOH positive at baseline prior to treatment. At the end of the 2-week treatment regimen (week 2), 1 patient (10%) was KOH negative, 2 (20%) were KOH negative at week 4, and 5 (50%) achieved mycological cure at week 8. The patients rated their clinical symptoms to be “improved,” 1.7 grades over baseline at weeks 2 and 4, and 1.9 at week 8 (0- to 4-grade scale).

Two treatment-emergent adverse events, low-grade fever and inflammation in the right hip, were reported in 2 patients during the study, but neither was considered related to naftifine treatment.

DISCUSSION

The efficacy responses observed in the present open-label study suggest that naftifine 1% gel applied twice daily for 14 days is an effective topical agent for the treatment of TV. These findings are in agreement with those of a 1986 efficacy study with naftifine 1% solution. To our knowledge, no other published data are available on naftifine therapy in TV. By week 4, nine of ten (90%) patients had >2-grade improvement from baseline in CSS score. Mycological cure at week 8 (42 days post-treatment) was achieved by 50% of the patients. There were no treatment-related adverse events during the study, which is consistent with the well-established safety profile for naftifine 1% topical cream and gel.

The 2-week treatment regimen for naftifine 1% gel is half the recommended duration for treatment of TV and other cutaneous fungal infections such as tinea pedis and tinea cruris. Higher cure rates for TV are generally associated with longer durations (>4 weeks) of daily antmycotic treatment. CSS scores and mycological cure rate after 2 weeks of treatment with naftifine 1% gel, however, were comparable with those reported for other topical therapies for TV including selenium sulfide and zinc pyrithione shampoos, topical terbinafine, ketoconazole, and clotrimazole formulations.

The progressive increase in mycological cure rate from 10% at week 2 (end of treatment) to 50% at week 8 (6 weeks post-treatment) is characteristic of naftifine’s therapeutic actions. Extended fungicidal activity and a delay in maximal treatment response have been consistently observed in previous clinical studies of naftifine 1% gel and cream topical therapy for tinea pedis, tinea cruris, and tinea corporis. The basis for these effects appears to be pharmacokinetic. Human radiolabeled drug distribution studies have shown that with daily topical application, naftifine accumulates and forms a depot in the stratum corneum at the application site. This depot effect, in turn, functions to maintain a continuous exposure of dermatophyte-infected epithelial tissue to naftifine for several weeks after treatment, resulting in a residual increase in mycological and clinical cure rate over time.

CONCLUSIONS

The results of this open-label pilot study suggest that naftifine 1% gel may be efficacious as topical therapy for TV.

Disclosures: Naftifine HCl 1% gel is marketed as Naftin gel by Merz Pharmaceuticals, LLC. This study was sponsored by Merz Pharmaceuticals, LLC, Greensboro, NC. Joy Willard, RN, BSN of Merz Pharmaceuticals, LLC, participated in study design and regulatory issues. Michael H. Gold, MD: clinical investigator with no conflicts of interest disclosed; Tancy Bridges, N-PC: research coordinator with no conflicts of interest disclosed; Edward Avakian, MA, PhD, Alan B. Fleischer Jr, MD, Stefan Plaum, MD, Eric J. Pappert, MD, and Bhushan Hardas, MD, MBA: employees of Merz Pharmaceuticals, LLC.
REFERENCES

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A New Tretinoin Therapy
From Triax Pharmaceuticals
In the past 15 years, research in dermatology has significantly increased. Dermatology-related contributions in premier medical journals such as *The New England Journal of Medicine* (NEJM) and *The Journal of the American Medical Association* (JAMA) are the representation of our field in the medical world. To analyze this representation, incidence of dermatology-related contributions in NEJM and JAMA during 3 separate years (during a 15-year period) was calculated. (SKINmed. 2011;9:288–292)

**ABSTRACT**

In the past 15 years, research in dermatology has significantly increased. Dermatology-related contributions in premier medical journals such as *The New England Journal of Medicine* (NEJM) and *The Journal of the American Medical Association* (JAMA) are the representation of our field in the medical world. To analyze this representation, incidence of dermatology-related contributions in NEJM and JAMA during 3 separate years (during a 15-year period) was calculated. (SKINmed. 2011;9:288–292)

**MATERIALS AND METHODS**

To assess whether the overall growth in dermatology literature is represented in two premier general medicine journals, we studied the incidence of dermatology-related contributions in NEJM and JAMA using a retrospective, cross-sectional study. Using a retrospective, cross-sectional analysis, we searched 3 years (June 1, 1993–May 31, 1994; June 1, 1999–May 31, 2000; and June 1, 2007–May 31, 2008) of publications in NEJM and JAMA during a span of 15 years. We did not include Editorials and Commentaries, Book Reviews, Correspondence, or any nonacademic contributions.

For NEJM, full text was accessed online for academic publications. Original Articles, Review Articles (Reviews, Clinical Therapeutics, Clinical Practice), and Case Reports (Case Records of Massachusetts General Hospital and Clinical Problem Solving) were evaluated via a word stem search using NEJM's online search engine. The word stems used for all searches were skin, derm, rash, ulcer, purpura, petechiae, urticaria, pemph, psor, and erythema. All contributions that were identified by the word stem search were categorized into Original Articles, Review Articles, and Case Report categories and graded as levels 1 (highest relevance to dermatology) through 3 (lowest relevance) (Table I). Images in the Images in Medicine section (including the Electronic Images) were graded as either related (level 1) or not related (level 3) to dermatology.

*Analysis conducted via Ulrich's Periodicals Directory Online.*

*Search via PubMed using “Skin Diseases” as Major Subject Heading and limits of time periods.*
A similar evaluation was conducted for *JAMA*, using the same periods and *JAMA* online search engine for the years 2007–2008 and 1993–2000. Original Articles (Original Contributions, Preliminary Communications, Clinical Investigations), Review Articles (Reviews, Clinical Reviews, Consensus Statements), and Case Reports (Clinical Crossroads, Caring for the Critically Ill Patient, Grand Rounds, The Rational Clinical Exam) were searched using identical word stems as above. Due to lack of electronic full texts of the contributions, the search for the year 1993–1994 was conducted by examining printed copies of the journals.

All contributions were graded by one of the authors (MK); contributions that were difficult to grade for level of relevance were reviewed by both authors to reach consensus.

**RESULTS**

In *NEJM*, not including contributions appearing in Images in Medicine, the overall incidence of level 1 contributions in *NEJM* was 2.7% in 1993–1994, 3.1% in 1999–2000, and 2.9% in 2007–2008 (not significant, \( P > .7; \chi^2 \) for all comparisons). For the 3 years combined, 4% of the Original Articles, 8% of the Review Articles, and 8% of the Case Reports in *NEJM* were graded as level 1 or 2 in their relevance to dermatology. The percentage of level 1 Original Articles decreased from 3.3% in 1993–1994 to 1% in 2007–2008 \( (P = .09; \chi^2) \). Compared with results from 1993–1994, the percentages of level 1 Review Articles and level 1 Case Reports increased in 1999–2000 and 2007–2008. The representation of dermatology was highest in the Images in Medicine section during the 3 years (25% in 2007–2008, 19% in 1999–2000, and 33% in 1993–1994).

In *JAMA*, the percentages of contributions related to dermatology were much lower than those in *NEJM*, particularly in the Original Article and Review Article categories, in which the representation of dermatology was negligible. The percentages of Case Reports rated as level 1 or 2 were higher in all 3 years, although still lower than those in *NEJM* (Table II). No trends over time could be assessed because of the small number of dermatology-focused contributions.

**DISCUSSION**

We found that the overall percentage of level 1 dermatology contributions was stable during the selected time periods, with about a 3% incidence each year in *NEJM*, despite varying percentages in the individual categories of contributions. The stable representation of dermatology over time in *NEJM* despite growth of the dermatology literature worldwide may be due to various factors, the most likely being competition from other advancing medical fields for limited publication space.

Even so, is dermatology over- or under-represented in *NEJM*? According to the American Medical Association's Physician Characteristics and Distribution in the United States, 1.2% of physicians in 2005 as well as in 1993 were self-designated as dermatologists. Comparing the percentage of dermatology-focused contributions (about 3%) with the percentage of dermatologists in the United States (1.2%) suggests that dermatology is well represented in *NEJM*.

The continued over-representation of dermatology in *NEJM* is a reflection of interest of the medical community in the diagnostic and management issues posed by dermatologic conditions. While we should have pride in this, Case Reports had one of the highest representations (8%) in the various categories of contributions graded as level 1 and 2 in their relevance to dermatology for the 3 selected years. Case Reports usually are of limited, if any, value as models of research efforts in dermatology. Research papers in dermatology are declining as a percentage of published contributions. A reader of *NEJM* during 2007–2008 was exposed to only two Original Articles and three Review Articles graded as level 1.

The decreasing trend of published level 1 Original Articles over time (Table II) along with a low number of level 1 Review Articles is concerning. Does it represent a declining interest in dermatological clinical research? Or does it reflect decreasing quality of well-designed clinical trials with potential to make an impact on the world of medicine? The answer is unclear; however, increasing the number of well-designed clinical trials to study, understand, and manage dermatologic and systemic diseases is the most natural solution.
Table II. Relevance of Contributions to Dermatology by Journal and Type of Contribution

**THE NEW ENGLAND JOURNAL OF MEDICINE (NEJM)**

2007–2008 (N = 335)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Original Articles (n = 208)</th>
<th>Review Articles (n = 75)</th>
<th>Case Reports (n = 52)</th>
<th>Images in Medicine (n = 100)</th>
<th>Total (n = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>2 (1%)</td>
<td>3 (4%)</td>
<td>5 (9.6%)</td>
<td>25 (25%)</td>
<td>10 (2.9%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>7 (3.4%)</td>
<td>3 (4%)</td>
<td>2 (3.9%)</td>
<td>12 (3.6%)</td>
<td>12 (3.6%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>199 (95.7%)</td>
<td>69 (92%)</td>
<td>45 (86.5%)</td>
<td>75 (75%)</td>
<td>313 (93.1%)</td>
</tr>
</tbody>
</table>

1999–2000 (N = 321)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Original Articles (n = 206)</th>
<th>Review Articles (n = 70)</th>
<th>Case Reports (n = 45)</th>
<th>Images in Medicine (n = 52)</th>
<th>Total (n = 321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>2 (1.5%)</td>
<td>6 (10%)</td>
<td>0 (0%)</td>
<td>10 (19.2%)</td>
<td>8 (3.1%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>2 (0.5%)</td>
<td>2 (1.4%)</td>
<td>1 (2.2%)</td>
<td>5 (0.9%)</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>202 (98%)</td>
<td>62 (88.6%)</td>
<td>44 (97.8%)</td>
<td>42 (80.8%)</td>
<td>308 (96%)</td>
</tr>
</tbody>
</table>

1993–1994 (N = 377)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Original Articles (n = 243)</th>
<th>Review Articles (n = 70)</th>
<th>Case Reports (n = 64)</th>
<th>Images in Medicine (n = 52)</th>
<th>Total (n = 377)</th>
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</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>8 (3.3%)</td>
<td>0 (0%)</td>
<td>2 (3.1%)</td>
<td>17 (32.7%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>4 (1.6%)</td>
<td>3 (4.3%)</td>
<td>3 (4.7%)</td>
<td>10 (2.7%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>231 (95%)</td>
<td>67 (95.7%)</td>
<td>59 (92.2%)</td>
<td>35 (67.3%)</td>
<td>357 (94.6%)</td>
</tr>
</tbody>
</table>

**THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA)**

2007–2008 (N = 215)

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<thead>
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<th>Review Articles (n = 33)</th>
<th>Case Reports (n = 28)</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (3.5%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>154 (100%)</td>
<td>33 (100%)</td>
<td>27 (96.5%)</td>
<td>214 (99.6%)</td>
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</table>

1999–2000 (N = 297)

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<th>Case Reports (n = 34)</th>
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<tr>
<td>Level 1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>209 (99.5%)</td>
<td>53 (100%)</td>
<td>32 (95.2%)</td>
<td>294 (99%)</td>
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</table>

1993–1994 (N = 266)

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<th>Case Reports (n = 27)</th>
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<td>Level 1</td>
<td>2 (0.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Level 3</td>
<td>220 (99.1%)</td>
<td>17 (100%)</td>
<td>26 (96.3%)</td>
<td>263 (98.8%)</td>
</tr>
</tbody>
</table>

(Continued)
To ensure an uptrend in dermatology literature reaching the medical community, we need a continuous supply of physician-scientists. Yet, the number of physician-scientists has been decreasing in our country for the past 2 decades. From 1983 to 2003, the percentage of physicians engaged in research decreased from 4.6% to 1.8%.2 In dermatology, the growth rate of full-time academic dermatologists has been estimated to have decreased from 4.3% in 1994–1995 to 2.8% in 2001–2002.3

The decrease in original research is especially concerning because early exposure to well-designed research projects could be a means to stimulate interest in dermatology among research-oriented medical students.4–9 If exposure to dermatology research articles would bring our specialty to the attention of medical students, the declining representation of such contributions in NEJM and their virtual absence in JAMA could be leading research-oriented students to explore other fields.

For the month of July 2010, 0.9% of JAMA recipients were dermatologists and 27% were family practice physicians. This was significantly higher compared with NEJM (0.6% and 3%, respectively; P<.0001; χ² test).10,11 This is surprising in view of the significantly lower representation of dermatology-related articles in JAMA. The low representation of dermatology in JAMA is important because of its wide circulation within the medical community, including the Student American Medical Association.

LIMITATIONS

Our search of dermatology contributions in general medicine journals was not meant to be exhaustive. We limited ourselves to only two general medicine journals and we searched 3 selected years, which may not be representative of the 15-year span. Any suggestion of a trend was applicable only to NEJM, and we are unable to evaluate the effects, if any, of changes in editors or editorial policies. We did not search journals with predominantly international circulations that might demonstrate a different incidence of dermatology contributions. We focused on clinical medicine journals, because the information is more directly applicable to medical practice. Quantifying the incidence of dermatology-related articles in prominent basic science journals, such as Nature, is an unexamined aspect of the manifestation of dermatology in the medical literature.

CONCLUSIONS

Representation of our field in premier general medicine journals is a medium to enlighten practicing physicians, as well as residents and medical students, about the breadth and depth of dermatology research, clinical diagnosis, and management. The overall over-representation of dermatology in NEJM, which has been stable throughout the 3 years selected for analysis, reflects ongoing and undisputed interest of the medical community toward clinical issues and research advances in dermatology, and we hope this will continue in a similar direction in the future.
Disclosures: Supported by the clinical funds of and alumni donations to the University of Michigan Department of Dermatology.

REFERENCES

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PHOTOCHEMICAL REACTIONS ARE ADVERSE SKIN REACTIONS TO THE COMBINED ACTIONS OF CHEMICAL AGENTS SUCH AS DRUGS, PLANTS OR CHEMICALS (PHOTOSENSITIZERS), AND UV OR VISIBLE RADIATION. PHOTOCHEMICAL REACTIONS MAY BE PHOTOTOXIC OR PHOTOALLERGIC. PHOTOTOXICITY IS A DOUBLE-EDGED SWORD. ON ONE HAND, IT INDUCES SUNBURN, PIGMENTATION, AND MELASMA; IN THE LONG-TERM, IT MAY ALSO CAUSE PHOTOAGING AND SKIN CANCERS. ON THE OTHER HAND, IT CAN BE USED THERAPEUTICALLY. FOR EXAMPLE, PHOTOCHEMOTHERAPY USING PSORALEN AND UV-A (PUVA) AND PHOTODYNAMIC THERAPY (PDT) ARE USED WIDELY IN DERMATOLOGY.

DERMATOLOGISTS TEND TO BE FAMILIAR WITH PHOTOTOXIC MEDICATIONS (PSORALEN, PORPHYRIN, HYDROCHLOROTHIAZIDE, QUINOLONE ANTIBIOTICS, PHENOCHLORINES), COSMETIC INGREDIENTS (BALSAAM OF PERU, MUSK AMBRETTE, HEXACHLOROPHENE, TETRACHLOROSALICYLANILIDE, FENTICLOR, BENZOPHENONE), AND FOODS (LIME, CELERY, ST JOHN'S WORT). EVEN IN ASIA, HOWEVER, MOST DERMATOLOGISTS KNOW VERY LITTLE—IF ANYTHING—ABOUT PHOTOSENSITIZERS IN ORIENTAL MEDICINAL PLANTS. YET, ORIENTAL HERBAL MEDICINE IS USED WIDELY IN CHINA, KOREA, JAPAN, AND MANY OTHER COUNTRIES IN THE WORLD. IN KOREA, ORIENTAL MEDICINAL PLANTS HAVE BEEN USED FOR MORE THAN 2000 YEARS, AND THEIR NAMES AND CLINICAL APPLICATIONS ARE SIMILAR TO THOSE FOUND IN TRADITIONAL CHINESE OR JAPANESE MEDICINE. IN MOST CASES, ORIENTAL MEDICINES COME IN THE FORM OF DECCTIONS, A METHOD OF EXTRACTION BY BOILING OF DRIED MEDICINAL PLANTS, OR ARE EATEN AS VEGETABLES OR SALADS. DERMATOLOGISTS OCCASIONALLY OBSERVE PHOTOSENSITIVITY OR AGGRAVATION OF MELASMA THAT IS SUSPECTED TO HAVE BEEN INDUCED BY ORIENTAL MEDICINES. THEY FIND IT DIFFICULT TO INVESTIGATE SUCH CASES, HOWEVER, BECAUSE ORIENTAL MEDICINES COME IN DECOTTED MIXTURES OF SEVERAL MEDICINAL PLANTS, AND INFORMATION ABOUT THE PHOTOTOXICITY OF THOSE PLANTS IS SCARCE. CONSEQUENTLY, THE PHOTOTOXIC POTENTIAL OF ORIENTAL MEDICINES HAS REMAINED UNDERSTUDIED.

THE MAIN INGREDIENT OF PHYTOPHOTODERMATITIS—A PHOTOTOXIC DERMATITIS INDUCED BY PHOTOSENSITIZERS IN PLANTS, VEGETABLES, AND FRUITS THAT ARE ABSORBED OR HAVE COME INTO CONTACT WITH THE HUMAN BODY—IS FUROCOUMARIN. OTHER COMPONENTS, HOWEVER, ARE ALSO INVOLVED. THE MAIN FAMILIES OF PHOTOTOXIC PLANTS INCLUDE CHENOPODIAEAE, COMPOSITAE, CONVOLVULACEAE, CRUCIFERAE, HYPERICACEAE, LEGUMINOSAE, MORACEAE, RANUNCULACEAE, ROSEA CEAE, RUTACEAE, AND UMBELIFERAE. WE STUDIED THE PHOTOTOXICITY OF DRUGS OR ORIENTAL MEDICINAL PLANTS BY WOOD LIGHT SCREENING, FLUORESCENCE SPECTROSCOPY, CANDIDA ALBICANS TEST, PHOTOHEMOLYSIS TEST, AND IN VIVO MOUSE EXPERIMENTS. IN OUR STUDIES, WE FOUND THAT MORE THAN A QUARTER OF ORIENTAL MEDICINAL PLANTS CAN BE PHOTOTOXIC IN VITRO, AND WE WERE ABLE TO CONFIRM THE PHOTOTOXICITY IN MICE EXPERIMENT IN 5 MEDICINAL PLANTS TESTED.

PHOTOTOXIC SKIN LESIONS

In phototoxicity, once the photosensitizer is activated by light, it directly damages the subcellular target. The damage is manifested in sunburn-like skin lesions such as tender erythema or edema...
Phototoxicity can occur if there are sufficient amounts of physical and chemical factors. It is more common and different from photoallergy, which is mediated by a type IV delayed-type hypersensitivity reaction in which a photosensitizer becomes a complete antigen by binding to a carrier protein after activation by light. When photosensitivity due to an exogenous factor persists for a longer period, it can progress to a more chronic type of photosensitivity, such as chronic actinic dermatitis.1–3,5

In our clinics, we encountered many patients showing features of photosensitivity mediated by exogenous factors, and, in some of those cases, oriental medicinal plants were suspected as the cause. One of these patients took *Zanthoxylum schinifolium* seed oil, which was proved by oral provocation test revealing markedly decreased minimal erythemal dose to UV-A. It was that experience which led us to investigate the phototoxicity of oriental medicinal plants.11

Phototoxicity also affects some diseases that are sensitive to UV, such as melasma. If melasma patients take photosensitizers orally or apply them on the skin, they can easily aggravate their melasma, even if they apply quality sunscreen diligently. Melasma is an important issue for Asian women, as it is difficult to control completely even through combination treatment with the Kligman formula, intense pulsed light or laser treatments, chemical peels with glycolic or lactic acid, and other supportive treatments.12,13 In patients with severe melasma, oriental medicinal herbs or plant extracts that are phototoxic can easily aggravate melasma, and information and recommendations may prevent risks of aggravation. In view of studies of melasma that suggest the importance of the dermal milieu and stem cell factors,14 as well as the possible importance of visual light,15 it is possible that phototoxicity may play more important roles as it is induced by longer-wavelength UV-A or visual light that can penetrate deeper.6,10

Finally, long-term exposure to phototoxicity may increase chronic unwanted effects of UV such as photoaging and photocarcinogenesis. Photoaging is an important cosmetic problem in middle-aged to older populations. Phototoxicity may increase photocarcinogenesis by combined actions of mutation, sunburn apoptosis, and immune suppression.6,10
MEASUREMENT OF PHOTOTOXICITY

Most photosensitizers are photochemically unstable. When they receive physical energy sufficient to induce structural change, they usually show significant fluorescence. In the subcellular level, it can damage the cell wall, nuclei, or other subcellular targets. In vivo experiments, they induced sunburn erythema and edema, induction of sunburn cells, and immune suppression. Many experimental models have measured phototoxicity.

FLUORESCENCE SCREENED BY WOOD’S LIGHT EXAMINATION AND FLUORESCENCE SPECTROSCOPY

Because photosensitizers are photochemically unstable, they emit fluorescence. Dermatologists can perform a Wood’s light examination to screen oriental medicinal plants for fluorescence. In the case of extracted solution or crushed live oriental medicinal plants, those materials can be screened by definite change of color or evident fluorescence in Wood’s light.

Another approach to measuring fluorescence is to measure the absorption and fluorescence spectra. Chemicals have their own absorption spectra, and when those chemicals are hit by the same wavelengths in the absorption spectra, photosensitizers frequently emit strong fluorescence. This method proved efficient in screening dried oriental medicinal plants for phototoxicity.

CANDIDA ALBICANS TEST AND OTHER MICROORGANISMS

Phototoxicity affects many different microorganisms such as C. albicans, Salmonella typhimurium, or Pseudomonas or cells such as fibroblasts. Consequently, such microorganisms or cells can be used to measure phototoxicity in vitro. Two sets of culture plates containing those microorganisms or cells and photosensitizer are prepared, and light (usually UV-A) is irradiated to one of them. In light-irradiated plates, cellular destruction by phototoxicity occurs, which decreases the number of microorganisms or cells.

The Candida albicans test is an inexpensive, efficient, and easy method to measure photosensitizers that target cellular nuclei. A disadvantage is that it frequently shows false-negative results to photosensitizers that target subcellular structures other than cellular nuclei. For example, quinacrine, nalidixic acid, ofloxacin, mequitazine, and chlorpromazine are positive to the Candida albicans test, but sulfonamides or thiazide diuretics show negative results.

Among the screening methods using cells, photohemolysis is a useful and easy method to screen photosensitizers. Since a red blood cell (RBC) does not have a nucleus, it is sensitive to a photosensitizer that targets the cellular membrane. In photohemolysis, most photosensitizers do not induce spontaneous hemolysis of RBC. It facilitates the experiment, but this is difficult to follow.

The MTT assay is another useful method to measure phototoxicity. The MTT assay using cultured fibroblast is used widely in various experiments to measure apoptosis, and it can be useful to measure phototoxicity that targets cellular mitochondria. It is suitable for large samples because it can use 96 well enzyme-linked immunosorbent assay plates. The disadvantage of the MTT assay is that repeated and detailed pilot experiments are needed for every sample to prevent spontaneous apoptosis.

LIPID PEROXIDATION

When unsaturated fatty acid is exposed to phototoxic reaction, it undergoes oxidation by reactive oxygen species and can be
measured by spectrophotometer. Linoleic acid, cholesterol, or squalene can be used for that purpose.\textsuperscript{17,18}

**IN VIVO EXPERIMENT TO MEASURE PHOTOTOXICITY**

In vivo experiments for photoxicity include the measurement of skin swellings of the ears, tail, or back skin; colorimetric or visual scoring of erythema in hairless mice; evaluation of sunburn apoptosis cells by hematoxylin and eosin stain (H&E) stain or terminal deoxynucleotidyl transferase dUTP nick end labeling assay; depletion of Langerhans cell count in epidermal sheet; and suppression of local immune response measured by contact hypersensitivity (CHS).\textsuperscript{6,10,17}

Sunburn includes sunburn edema and formation of dyskeratotic sunburn cell in the epidermis. Dorsal skin swelling in mice is a good in vivo method to measure the inflammation induced by sunburn. Sunburn cells are keratinocytes, undergoing apoptosis when the skin is exposed to UV irradiation.\textsuperscript{10,17}

Langerhans cells are dendritic cells present in the epidermis. When UV-B is irradiated, the number of these cells decrease and a loss of dendrite is observed. Langerhans cells play important roles in antigen presentation and in the suppression of immune response by UV irradiation. When mice were irradiated with photosensitizer and UV-A, the number of Langerhans cells significantly decreased.\textsuperscript{6,10,17}

The observation of CHS, which is a model of allergic contact dermatitis using hapten, is a popular method for evaluating UV-induced suppression of cell-mediated immunity in vivo. The local suppression of CHS is mainly concerned with antigen-presenting cells,\textsuperscript{19} and phototoxic reaction suppressed local CHS.\textsuperscript{6,10}

**PHOTOTOXICITY OF ORIENTAL MEDICINAL PLANTS**

**FLUORESCENCE SPECTROSCOPIC STUDY OF ORIENTAL MEDICINAL PLANTS**

We screened 62 live oriental medicinal plants for their potential phototoxicity by Wood’s light examination. We crushed live plants and observed them with Wood’s light. If there was evident fluorescence or change of color, we selected them for fluorescence spectroscopy.

Seventeen oriental medicinal plants out of the 62 tested showed fluorescence or change of color in the Wood’s light examination. All of them showed significant absorption peaks in the UV range and showed strong fluorescence when they were excited by the corresponding wavelengths of the absorption spectra in that study (Table).\textsuperscript{9}

**PHOTOHEMOLYSIS AND *CANDIDA ALBICANS* TEST**

We examined the phototoxicity in vitro by using the photohemolysis and *Candida albicans* tests. In the photohemolysis test, 16 of 17 plants showed positive results. *Cocculus trilobus* was negative in the photohemolysis test (Table and Figure 1) but showed a definite fluorescence response. The results suggested that *C. trilobus* may not be phototoxic or that it may have a different mechanism of phototoxicity involving subcellular targets other than DNA or cell membrane.\textsuperscript{6,17}

As most medical plants that had strong fluorescence showed positive in vitro phototoxicity in the photohemolysis test except *C. trilobus*, phototoxicity screening by measuring absorption and fluorescent emission spectra may be better because it is more convenient, does not need blood experiment, and covers various subcellular targets.

In the *Candida albicans* test, 5 medicinal plants showed significant phototoxicity (Table). According to the results, the 16 species of medicinal plants showed significant photohemolysis indicating that the tested medicines show phototoxicity targeting the cellular membrane. Because a marked suppression of growth of fungi was observed for 5 medicinal plants in the *Candida albicans* test, it appears that these plants also target the cellular nuclei.\textsuperscript{6,18}

These data suggest that more than a quarter of oriental medicinal plants can be phototoxic. As a typical dose of medicine given to a patient includes a mixture of 5 to 10 medicinal herbs, many oriental medicines will probably raise the possibilities of phototoxicity.\textsuperscript{6}

**IN VIVO EXPERIMENT**

We performed an in vivo mouse experiment for 5 medicinal plants that showed phototoxicity in the photohemolysis and *Candida albicans* test. Models included in the in vivo experiment were swellings of back skin, evaluation of sunburn cells and measurement of CHS.
stain, depletion of Langerhans cell count in the epidermal sheet, and suppression of local immune response measured by CHS to dinitro-fluoro-benzene.\(^6\)

When the mice received 50 J/cm\(^2\) UV-A, all the treated groups showed significantly increased dorsal skin swellings compared with the UV-A–only irradiated group (Figure 2). Compared with the UV-A–only irradiated group, a significant increase in sunburn cells showing dark and crushing nucleus and eosinophilic cytoplasm were observed in the treated groups.\(^6\)

In the Langerhans cell study, the treated groups showed a decreased number of Langerhans cells, and the number of dendrites and the ATPase activity of Langerhans cells were also markedly decreased by UV-A irradiation compared with the UV-A–only irradiated group (50 J/cm\(^2\)). Local CHS decreased significantly in all the UV-A irradiated groups. The medicine-treated groups showed significant decrease of local CHS, however, compared with the UV-A–only group.\(^6\)

**SIGNIFICANCE OF PHOTOTOXICITY FROM A CLINICAL PERSPECTIVE**

For clinical dermatologists, researching the phototoxicity of oriental medicines can be fruitful on two accounts. Not only can it enlighten dermatologists regarding the adverse side effects of herbal medicines in terms of their phototoxicity, but it can also indicate positive ways in which phototoxic reactions can be used in some treatments.\(^3,6\)

On the negative side, the phototoxicity of oriental medicinal plants may induce sunburn, pigmentation, and melasma, and may also cause photoaging and skin cancers in the long-term.\(^4\) Because a doctor’s precise recommendation is important for patients to prevent not only the aggravation of disease but also legal conflict for doctors, information about oriental medicinal plants is important.

japonica (皂角刺，皂荚), Glycyrrhiza glabra (甘草, licorice), Lomatium parishicus (桑寄生), Morus alba L. (桑白皮), Myristica fragrans (肉豆蔻), Poncirus trifoliata (枳椇, 枸椇), Psoralea corylifolia L. (補骨脂, 破故紙), Rheum coreanum (朝鮮大黃), Scutellaria baicalensis Georgi (黃芩), Schisandra chinensis (五味子), Schizonepeta tenuifolia (菥蓂), Thuja orientalis (側柏), Uncaria sinensis (釵鉤藤) showed significantly strong fluorescence and could be regarded as possible photosensitizers (precise data are not shown here).

The phototoxic reaction induced by medicinal plants can also be harnessed as a positive side effect. For example, phototherapy using PUVA and PDT are widely used in dermatology. In Korea, oriental therapists use Xanthium strumarium and Agrimonia pilosa in the treatment of vitiligo that exhibit strong phototoxicity. This example shows that the phototoxic reaction induced by plants can constitute some of the therapeutic value of oriental medicine. Another example is PUVA therapy. Psoralen, which is used in PUVA therapy, is widely distributed in medicinal plants, and some of the oriental medicinal herbs contain a large amount of furocoumarin (psoralen).

Other photosensitizers can also exhibit the therapeutic effect of phototoxicity.

PDT is yet another model of treatment that uses phototoxic reaction. In PDT, porphyrin is the main photosensitizer and several additional photosensitizers are under investigation. Porphyrin has a major absorption peak at UV-A to blue light range and a minor peak at longer-wavelength visual light.

When we measured oriental medicinal plants with fluorescence spectroscopy, we obtained very interesting findings. Some of the plants showed emission spectra in the red light range, such as porphyrin, and others at the infrared range (TH Kim et al, in preparation). We personally suggest that screening of strong fluorescence and emission spectra enables us to find newer therapeutic phototoxic materials.

Four medicinal plants, Agrimonia pilosa, Cnidium officinale, Xanthium strumarium, and C trilobus showed absorption bands at the UV-A or blue region of visible light, and a strong fluorescence emission at red light in our previous study. Oral intake of these plants and exposure to sunlight filtered with window glass for 30 minutes was effective for the supportive treatments of atopic dermatitis and keloid (TH Kim’s personal experience).

At the present time in Korea, research is actively progressing to analyze the components of oriental medicinal herbs. For example, the investigated components of Zanthoxylum schinifolium are Asararin, 3,7,8-trimethoxy-2H-1-benzopyran-2-one, acetoxyauraptene, acetoxycollinin, α-sanshool, bergaptan, epoxycollinin, estragole, N-methylschinifoline, schinifoline, schinilenol, schininallyl, and schinindiol.

Taking the chemical components of oriental medicines into consideration, phototoxicity can be induced by similar chemicals or by different chemicals. Somewhat prospective results will be obtained if the extracted samples are separated into several ingredients and the phototoxicity of these fractions are examined (study in progress). When we measured the phototoxicity of purified ingredients from two oriental medicinal plants, they showed stronger phototoxicity compared with 8-methoxy psoralen (Figure 3). The difference between these materials is their fluorescence emission spectra, one in the red light and the other in the infrared range.

CONCLUSIONS

In previous studies, we showed that more than a quarter of oriental medicinal plants can be phototoxic in vitro or in vivo and that strong fluorescence measured by absorption and fluorescence spectra can be an easier way to screen for phototoxicity. Phototoxicity can not only have a negative side effect but can also constitute a therapeutic effect of oriental medicines. Photosensitizers present in oriental medicinal plants may be responsible for the therapeutic effect of some of these drugs. Further studies regarding the phototoxicity of active components extracted from oriental medicinal plants in progress may be useful to find newer therapeutic materials. Finally, since the experiments in previous studies were limited to the live herbs obtainable from the Medicinal Plant Institute, further experiments for evaluating phototoxic potentials of dried plants used in oriental medicinal shops, which are extracted by ethanol or hot water, will also give more informative data.

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REFERENCES

SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

Instructions: For each of the following numbered questions, choose the appropriate lettered response(s). Unless directed to choose only one lettered response, all, some, or none of the responses may be correct.

1) Decoctions are: (Choose the single best response.)
   a. distilled from residues of dried medicinal plants.
   b. extracted by boiling of dried medicinal plants.
   c. precipitated from acidic residues of dried medicinal plants.
   d. precipitated from basic residues of dried medicinal plants.
   e. separated from residues of dried medicinal plants using organic solvents.

2) The main ingredient(s) of photosensitizers that induce photophotodermatitis is (are): (Choose the single best response.)
   a. furocoumarin.
   b. glucoseaminoglycans.
   c. histones.
   d. membrane phospholipids.
   e. unsaturated fatty acids.

3) Dermatologists can best perform an examination using which of the following instruments/methods to screen oriental medicinal plants for fluorescence? (Choose the single best response.)
   a. Dermatoscope
   b. Dioscopy
   c. Light microscope

4) Which of the following may be useful to screen for photoreactive medicinal substances? (Answer as many as apply.)
   a. Candida albicans test
   b. MTT assay
   c. Hubble telescope
   d. Photohemolysis
   e. Spectrophotometer

5) In photodynamic therapy (PDT), the main photosensitizer(s) is (are): (Choose the single best response.)
   a. furocoumarin.
   b. glucoseaminoglycans.
   c. membrane phospholipids.
   d. porphyrin.
   e. unsaturated fatty acids.

ANSWERS TO SELF-TEST REVIEW QUESTIONS:
   1) b; 2) a, e; 3) c; 4) b, c, d; 5) a, c, d
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References:

*In vitro activity does not necessarily correlate to in vivo activity.*

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While the fascinating and precise account of necrobiotic lipoidica (NL) and granuloma annulare, non-insulin-dependent, diabetes mellitus (DM)-related dermatoses, formed the contents of Part I, the brief review of the other dermatoses is the subject of the current contribution.

DIABETIC DERMOPATHY

HISTORY

In 1964, Melin observed that his chief, Nils Tornblom, described characteristic, atrophic, circumscribed brown patches on the front and sides of the lower portion of the legs in diabetic patients. The term diabetic dermopathy (DD), however, was coined by Binkley in 1965. He believed that these lesions were etiologically related to diabetic microangiopathy and were as diagnostic as the associated nephropathy, neuropathy, and retinopathy. It was further labeled pigmented pretibial patches (PPP), shin spots, and spotted leg syndrome. Bauer and Levan believed that DD and NL were variants of the same cutaneous disorder, which they termed diabetic dermangiopathy.

EPIDEMIOLOGY

DD is the most common cutaneous manifestation in diabetics. The male to female ratio is 2:1. The frequency and specificity of these lesions in diabetics depend on the number of pretibial plaques, which is accepted as indicating dermopathy.

CLINICAL APPEARANCE

The primary lesion of DD, preceding the pigmented atrophic patches of PPP, has not been clearly defined. Lesions may be either discrete or grouped, and round to oval. Shin spots appear as multiple, bilateral, asymmetrical, annular, or irregular red papules/plaques on the extensor surface of the lower leg (Figure). The borders are well-defined and sloped and evolve into atrophic, thin, hyperpigmented macules. The lesions disappear in one or more years, while new lesions may develop. Lesions are asymptomatic and often overlooked by the patient and physician alike. Rarely, a bullous stage may exist.

PATHOPHYSIOLOGY

The genesis of shin spots is unclear. Similar lesions develop in patients who had preexisting DD after experimental thermal trauma. Patients who develop the lesions are typically elderly or young patients with diabetes of long duration. The frequency of changes over bony prominences, and reports linking dermatosis to peripheral neuropathy suggest that trauma may be a modifying/trIGGERING factor but blunt trauma does not elicit lesions.

HISTOPATHOLOGY

The epidermis in patients with DD is thin, with thickened vessels in the papillary dermis showing increased periodic acid–Schiff–positive diastase-resistant material. There are often mild...
perivascular lympho-histiocytic infiltrates and scattered hemosiderin deposits following extravasation of red blood cells from the vessel wall. Acute lesions, however, show edema of the epidermis and papillary dermis. The incidence of DD increases not only with each of the three complications (retinopathy, nephropathy, and neuropathy), but also in relation to the number of complications in each patient. As these lesions precede abnormal glucose metabolism, their presence in nondiabetics should alert a physician to possible early diabetes. DD does not, however, correlate with obesity or hypertension in patients with DM. The differential diagnosis includes NL, stasis dermatitis, pigmented purpuric dermatoses, and post-traumatic scarring.

TREATMENT
The lesions associated with DD are largely asymptomatic. They do not respond to any treatment nor to control of hyperglycemia.

DIABETIC BULLAE

HISTORY
In 1963, Rocca and Pereya described bullous lesions of the feet that developed without trauma in 14 diabetics. The name bullous diabeticorum was coined by Cantwell and Marts in 1967. Approximately 0.5% of diabetics develop diabetic bullae. Although not common, it is considered a clinically distinct diabetic marker.

CLINICAL APPEARANCE
Spontaneous and sudden appearance of bullae on the hand and forearm is characteristic. The bullae are several millimeters to several centimeters in size and may be recurrent. Typically, the blister starts as a tense lesion, but, as it enlarges, it becomes flaccid. The blister contains clear sterile fluid and is not surrounded by erythema. It is largely painless and nonpruritic and usually resolves after 3 to 6 weeks.

PATHOPHYSIOLOGY
Mechanical trauma or UV radiation in conjunction with nephropathy may be a cofactor in the evolution of diabetic lesions. There has been speculation about the role of altered carbohydrate, calcium, or magnesium metabolism, or vascular insufficiency, microangiopathy, or reaction imbalance secondary to renal failure in many patients with diabetic bullae.

Epidemiology
Diabetic bullae have only been reported in adults aged 40 to 77 years. They are commonly seen in men with longstanding, established peripheral neuropathy affecting the extremities. Spontaneous nonscarring bullae containing clear sterile fluid are the most common clinical features.

Histopathology
These lesions may show intraepidermal cleavage without acantholysis and may be hemorrhagic. Subepidermal cleavage without acantholysis may also be seen. The third type, as reported in this case, consisted of multiple, tender, nonscarring bullae on sun-exposed and deeply tanned skin of the feet, legs, and arms. Immunofluorescence and porphyrin studies are negative and the cleavage plane is seen at the level of the lamina lucida. This bullous disease runs a benign course without involvement of large body surface areas. Secondary infection may be the only complication, which may be managed with appropriate antibiotics. Separation between the cell membrane and basal lamina, preceded by almost complete disappearance of anchoring filaments and hemidesmosomes, has been demonstrated on electron microscopy. Differential diagnosis includes bullous pemphigoid, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous impetigo, bullous erythema multiforme and blisters from barbiturate, carbon monoxide poisoning, and insect bite reaction. Bullosis diabeticorum remains a diagnosis of exclusion with negative immunofluorescence studies, porphyrin levels, and cultures.

TREATMENT
Treatment is conservative and based on symptoms using aluminum subacetate or saline compresses.

ACQUIRED PERFORATING DERMATOsis

HISTORY
Cohen and Auerbach described the acquired reactive perforating collagenosis associated with severe DM and chronic renal
failure. The term acquired perforating dermatosis (APD) was proposed by Rapini and colleagues in 1989.

**CLINICAL APPEARANCE**

Cutaneous perforating disorders, characterized by the transepidermal elimination of altered components of the dermis, have been divided into 4 classic types: (1) elastosis perforans serpiginosa, (2) reactive perforating collagenosis, (3) Kyrle’s disease, and (4) perforating folliculitis. The degenerated altered dermal material consists mainly of collagen and elastic fibers. APDs are seen in patients with chronic renal failure and DM with or without hemodialysis. Other associations are abnormal glucose metabolism, hepatic insufficiency, albuminuria, and congestive heart failure. APD consists of 2- to 10-mm pruritic, hyperkeratotic dome-shaped, often umbilicated papules and nodules, some of which may coalesce as a result of severe pruritus and rubbing to form small verrucous plaques. They may be either clustered or arranged in a linear distribution. The smallest lesions are pinhead-sized follicular or perifollicular papules, while the largest lesions are dark brown nodules with a central crust, filling a central depression. Koebner’s phenomenon may occur. Lesions present chiefly on the legs; however, the trunk and face may also be involved. Spontaneous resolution is unlikely. Most patients with APD are middle-aged black men.

**PATHOPHYSIOLOGY**

The metabolic derangements caused by chronic renal failure and diabetes lead to superficial dermal connective tissue change and trigger transepidermal elimination. There may be deposition of uric acid or hydroxyapatite that induces a foreign body inflammatory reaction resulting in transepidermal elimination. Pruritus caused by uremia or diabetes may result in epidermal injury secondary to scratching, whereas the altered blood supply of diabetic vasculopathy results in localized dermal necrosis and extrusion of dead tissue through the epidermis. Microangiopathy and dysregulation of vitamin A or D have also been proposed.

**HISTOPATHOLOGY**

APD shows an area of basophilic staining of the papillary connective tissue and atrophy of the suprapapillary plate. The basophilic collagen bundles are gradually taken into the epidermis through the intercellular spaces and foci of epidermal disruption. This forms a crateriform invagination of the epidermis filled by a parakeratotic plug and basophilic cellular debris.

**TREATMENT**

Treatment of APD is largely unsuccessful. The patient is advised to avoid scratching and trauma. Retinoic acid, topical keratolytics, topical and systemic retinoids, psoralen–UV-A (PUVA), UV-B, topical and intralesional steroids, and oral antihistamines have been used with partial success.

**DIABETIC THICK SKIN**

**CLINICAL APPEARANCE**

Diabetics, in general, have an asymptomatic, often unnoticed but measurable increase in skin thickness. At least 20% of diabetic patients have such measurable skin thickness. Using the technique of palpation and tenting of the area, thickening has been demonstrated in both type 1 and type II diabetics. The pathogenesis of diabetic thick skin has not yet been fully elucidated; however, potential explanations include the monoenzymatic glycosylation of collagen, making it less soluble; collagen hydration secondary to polyol accumulation; and nonenzymatic glycosylation of albumin resulting in endothelial cell extravasation.

The diabetic hand syndrome is characterized by limited joint mobility, cheiroarthropathy, waxy skin and stiff joints, scleroderma-like syndrome, and diabetic sclerodactyly. It presents as stiffness, primarily of the small joints of the hands. It begins in the metacarpal-phalangeal and proximal interphalangeal joints. It is bilateral, symmetrical, and painless. The limitation of movement initially in active and later even in passive extension may less frequently involve larger joints of the wrist, elbow, and the spine. Despite the name, the joints themselves are not directly involved. Microvascular complications such as retinopathy, nephropathy, and peripheral neuropathy have been associated. Diabetic scleredema is the association between scleredema and diabetes and was emphasized for the first time by Fleischmajer and colleagues in 1970. Diabetic scleredema is present in 2.5% of patients with type II diabetes.

Insulin acting as a growth factor in combination with decreased local oxygen pressure secondary to microangiopathy may increase collagen and glycosaminoglycan synthesis by fibroblasts.

Diabetic hand syndrome or digital sclerosis of DM is a syndrome that generally affects the 5th digit and may then progress laterally to involve other fingers. Stiffening of the collagen in periarticular tissue is common. The degree of skin collagen fluorescence correlates with these complications.

According to one study, thick skin, like glycosylated hemoglobin, is a marker of glycemic control, which has been demonstrated by a decrease in skin thickness toward normal following pump administration of insulin and achievement of tighter control. The most accurate sign, however, is limitation of extension with the examiner passively testing the interphalangeal and metacarpophalangeal joints. Thickening can also be demonstrated by
ultrasound scanning, microscopic measurement, caliper measurement, and radiological investigations. Due to the miniature cobblestone-like appearance, this velvety skin is described as having finger pebbles or knuckle pebbles. It occurs in 10% to 39% of diabetics and is found in patients with both type I and type II DM. Decreased ability to produce tenting of the skin and wrinkling following immersion in water is characteristic of diabetic thick skin. Histopathology shows epidermal hyperkeratosis and hypertrophy of the papillary dermis. The collagen in the papillary dermis is vertically oriented and streaked.

SCLEREDEMA ADULTORUM

CLINICAL APPEARANCE
Scleredema adultorum (SA) is characterized by a marked increase in dermal thickness on the upper back and nape of the neck in overweight, middle-aged patients with longstanding severe DM. The onset of SA is insidious, with loss of skin markings, which may extend to the face, arm, chest, and abdomen. SA is usually asymptomatic; however, neck discomfort and back pain may occur in severe cases. Patients may experience decreased sensation to pain and light touch over the affected area. SA does not correlate with retinopathy, nephropathy, neuropathy, or peripheral vascular disease.

HISTOPATHOLOGY
Patients with SA may show a thickened dermis with swollen collagen bundles separated by wide-clear spaces previously occupied by mucin and by an increased number of mast cells.

TREATMENT
Treatment of SA is usually unsuccessful; however, radiotherapy, low-dose methotrexate, prostaglandin E1, topical/intralesional steroids, penicillamine, intralesional insulin, bath PUVA, and pentoxifylline have been advocated.

DUPUYTREN’S CONTRACTURE
Dupuytren’s contracture exhibits fibrosis and thickening of the palmar fascia, usually involving the aponeurosis over the 4th and 5th metacarpals. A gradual flexion deformity develops, which may extend to other digits. On microscopic examination, there are dense collections of fibroblasts, which mature into thick avascular collagen bundles. Pain may be relieved by heat, stretching exercises, or local steroid injection. Repeated surgical procedures may be necessary.

ERUPTIVE XANTHOMA

CLINICAL APPEARANCE
Eruptive xanthoma mainly appears in patients with severe, poorly controlled DM. Xanthomas occur in about 0.1% of diabetic patients. Serum triglyceride levels are increased in patients with eruptive xanthoma and serum is turbid. Increased serum triglycerides are also found in familial type I, II, IV, and V lipoproteinemias, nephrosis, pancreatitis, alcohol-induced lipemia, myxedema, hemochromatosis, and glycogen storage diseases. The common factor in hyperlipidemic states is decreased lipoprotein lipase activity or increased hepatic products of low-density lipoproteins, making chylomicrons less able to compete with low-density lipoproteins for lipoprotein lipase.

There is some evidence that eruptive xanthomas in diabetics result from macrophages incorporating plasma lipoproteins forming foamy or xanthoma cells. Polyphagia in uncontrolled diabetes accelerates the formation of very low-density lipoprotein and chylomicrons.

Xanthelasma may be associated with hypercholesterolemia and hypertriglyceridemia. Palmar/plantar xanthomas show a yellow discoloration of the palmar creases. Typical skin involvement is the sudden onset of crops of yellow papules, each with an erythematous rim, often presenting as Koebner’s phenomenon. The lesions are located mostly over the extensor surfaces, knees, elbows, back, and buttocks. Papules may coalesce to form tuberous xanthomas and lesions may be pruritic/tender.

Tendon xanthomas are more persistent, tender on pressure, and often seen over pressure areas. The lesions are yellow thick nodules attached to the underlying subcutaneous tissues.

HISTOPATHOLOGY
Foamy, lipid-laden histiocytes, with a mixed lymphocytic and neutrophilic infiltrate accumulation in the dermis are characteristic of eruptive xanthoma.

TREATMENT
It is imperative to control diabetes or underlying inherited hyperlipidemia, which includes weight reduction, if indicated, and carbohydrate restriction. It may be necessary to add clofibrate.

CAROTENODERMIA (CAROTENEMIA/CAROTENOSIS)

Up to 10% of diabetic patients have carotenodermia (yellowing of skin), where blood levels of carotene exceed 0.2 mg/100 mL to 0.8 mg/100 mL for carotenemia to become evident in the skin. In the past, carotenemia was considered to be a manifestation of the diabetic diet (carrot, spinach, apricots, yellow vegetables). Yellow discoloration of the skin, however, may be the result of nonenzymatic glycosylation and its products. They are apparently yellow, long-lived proteins. Dermal collagen could become glycosylated to eventually appear yellow.
conversion of carotene to vitamin A in the diabetic liver may have a similar outcome.

In carotenodermia, deposits of yellow pigment may be found in the nasolabial folds, on the forehead and axillae, and areas that are rich in sebaceous glands. The palms, soles, nostrils, and bony prominences have a thickened stratum corneum and also show this yellow discoloration; however, it does not cause scleral icterus as in jaundice.

**RUBEOSIS FACIEI**

Although difficult to quantify, flushed face or rubeosis faciei has been reported in 3% to 59% of diabetics. In a study comparing facial redness with diabetic parameters, 59% of patients had markedly red faces. Rosy color of the face and occasionally the hands and feet is seen even in mild diabetics as well as in latent diabetic patients. There seems to be a familial tendency. The red color may be caused by microangiopathy evident as decreased tone and dilatation of venules in the cheek mucosa, increased solar sensitivity, or dehydration. This facial blush lacks the warmth and elevated border of erysipelas and the telangiectasia of carcinoid flush. Tighter glucose control may improve the appearance of rubeosis faciei.

### ACANTHOSIS NIGRICANS

#### HISTORY AND CLINICAL APPEARANCE

The term acanthosis nigricans (AN) was coined by Unna in 1889. In one study of the condition, 50% of patients in their 5th decade of life had type II DM. AN is characterized by symmetric, velvety to verrucous, hyperkeratotic, and hyperpigmented plaques that have a predilection for the axillae, anterior and posterior neck, umbilicus, areola, hands, and especially flexural areas such as in the groin, submammary regions, and antecubital and popliteal fossae. The degree of cutaneous involvement varies from subtle hyperpigmentation and papillary thickening affecting a few areas to a deeply pigmented and verrucoid process that involves the entire integument including the mucous membrane (Table).

#### CONCLUSIONS

DM, an endocrine disorder, is characterized by dysfunctional metabolism of sugar. It is a scourge of all the communities at global level. Most diabetics manifest cutaneous lesions at some point in time. These cutaneous lesions are not only a marker of the disease, but they may also reflect the status of blood
sugar control. It is, therefore, imperative to understand these cutaneous manifestations of diabetes. Besides, necrobiosis lipoidica diabeticorum, diabetic bullae (bullosis diabeticorum), certain acquired perforating dermatoses, diabetic thick skin, SA, Dupuytren’s contractures, certain xanthomas, carotenoderma, ruberosis faciei, and AN are the other important diabetes related dermatoses.

REFERENCES


Courtesy of Michael Geiges, MD
Sulfur mustard is a vesicant with a mustard-like odor that can affect the skin, eyes, respiratory and gastrointestinal tracts, and bone marrow, and can be lethal at certain doses. Throughout its years of use, various names have been used for this infamous gas. “S-mustard” distinguishes it from nitrogen mustard, “Lost” or “S-Lost,” represent contractions of the names of two chemists who suggested it be used as a war gas (Lommel and Steinkopf), and “Yellow cross” as the identifying mark on World War I (WWI) shells containing the chemical. It has also been called “Yperite,” the name of the site of its first use in 1917 during WWI.

The German Imperial Army began using chlorine, phosgene, and sulfur mustard gas as weapons in WWI, vesicants producing chemical burns, to drive the Allied Forces from the relative safety of their trenches. The German Army launched their first sulfur mustard gas attack on July 12, 1917, against British troops in Ypres, Belgium (hence “Yperite” as a name used for the gas). The gas was loaded into large artillery shells marked with a yellow cross (hence referred to as the “Yellow cross” or “Gelbkreuz”).

The introduction of sulfur mustard to the German’s armamentarium provided several advantages over the previous agents. In addition to its colorless and mustard/garlic-like odor, making it less detectable, sulfur mustard is a vesicant capable of sticking to and penetrating most clothing, therefore rendering gas masks ineffective. The gas is highly lipophilic, with the skin playing a very important role as a portal of entry for sulfur mustard. The potential for blindness, disfiguring slow-healing lesions of the skin, and the rather painful death of those who had inhaled significant amounts (Figure), caused a significant blow to both sides. As a result of its effects, sulfur mustard became known as the “King of the Battle Gases,” as it was responsible for more chemical casualties than chlorine, phosgene, and cyanogen chloride combined.

FUTILE PREVENTION

Despite efforts to prevent further use of chemical weapons at the Chemical Convention Talks as part of the Geneva Protocol in 1925 and as recently as the Chemical Weapons Convention in 1993, history continues to repeat itself with its use. Mustard gas was used in the War of the Rif in Morocco (1925), the Second Italo-Abyssinian War in Ethiopia (1935), World War II,
The Yemini Civil War (1962–1970), and most recently in the Iran-Iraq War (1980–1988). Much of the information on the toxic effects of mustard gas that we have today come from studies of victims of the Iran-Iraq conflict.


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Claude Huriez (1907–1984) (Figure 1) was a world-renowned French professor of dermatology and venerology. Among his great contributions to dermatology, he is credited for describing a syndrome, later known as Huriez syndrome.

HURIEZ SYNDROME
Scleroatrophic syndrome of Huriez, also called sclerotylosis, is a rare autosomal-dominant condition, with which few families are affected worldwide. It is characterized by congenital scleratroph of the distal extremities, palmoplantar keratoderma, and hypoplastic nail changes. Huriez initially described this condition in 42 of 132 members of two families from northern France. Subsequently, sporadic and familial cases developed in Germany, England, Morocco, India, Tunisia, Japan, Italy, and Scandinavia.

The term sclerotylosis was proposed, based on the pseudosclerodermatous appearance of the hands and digits. Additional hallmarks of this syndrome include poikiloderma-like changes on the nose, flexion contractures of the little finger, a distinctive nodule on the little finger, and telangiectasia of the lips.

Aggressive squamous cell carcinoma (SCC) of the affected skin can develop in this syndrome, occurring in approximately 15% of affected individuals. SCC in Huriez syndrome is characterized by early onset and metastasis.

CLAUDE HURIEZ (1907–1984)
Claude Huriez, born in 1907 in France, was precocious. At the age of 15, he passed his baccalaureate—a mandatory examination at the end of high school before entrance to college and university. He received his doctoral degree in medicine in early adulthood, and in 1943, he was appointed professor of clinical dermatology.

His work in public health was considerable, particularly in decreasing mortality from venereal diseases. He was a pioneer, believing that a cortisone-like cream that consisted of vitamin D had beneficial effects on many dermatoses. Cortisone was discovered a quarter of a century after his use of vitamin D–containing topical preparations. As determined later, these two have the same mode of action on nuclear receptors.

Huriez was at the forefront of investigational new drugs, using penicillin that he obtained from the US Army before it was available for regular use in any French hospital.

He was interested in many dermatologic diseases, but syphilis was one of his favorite topics. He is credited with first describing lipodermatosclerosis as hypodermite sclerodermiforme in his report on 1000 patients with leg ulcers of venous etiology.

Huriez was a diligent man with many endeavors. He saw patients very early in the morning at his home before making his hospital rounds between 10 AM and 1 PM. He would see patients at the hospital every day of the week, and later in the afternoon he would confer with his associates. Huriez designed a sliding cabinet of kodachromes for filing slides for teaching and presenting at meetings, dubbing it the “Kodatheque.” He used films and humorous drawings to illustrate diseases and concepts.

Huriez published 795 scientific articles and 48 monographs, 5 of which won a prize by the Academy of Medicine. For years...
More notably, Dr. Huriez was known for his eloquence, creativity, and leadership in northern France, where he was chairman of the Department of Dermatology at the chief hospital in Lille, the largest city in the province. Huriez was later the vice president of the hospital committee, which led the development of the most important university hospital in Lille, where a building was named after him.1–4

**REFERENCES**


**Figure.** Claude Huriez (1907–1984). Reprinted with kind permission from the Museum Association, Regional Hospital of Lille, France.

during the 1950s, Huriez taught venereology every Friday (Veneris Dies—as he said) from 2 pm to 6 pm. Huriez used to organize weekly patient presentations in a lecture room with projections of patient lesions in an adjacent room. These highly instructive sessions were called “the circus” by his associates.

Huriez sat on many boards and committees in northern France and nationwide, but the project of which he was most proud was the building that he called the “Medicopolis,” encompassing the Cité Hospitalière. This structure, of which he was vice president for 20 years, was later renamed Hôpital Claude-Huriez, comprising a geriatric hospital, nursing homes, a rehabilitation center, and a labor and delivery hospital. Huriez visited 55 countries and more than 100 university hospitals to learn and gather information on how to build and organize the Medicopolis.

**CONCLUSIONS**

Dr. Claude Huriez was an eminent professor of dermatology and a pioneer in the management of leg ulcers and skin diseases.

Figure. Claude Huriez (1907–1984). Reprinted with kind permission from the Museum Association, Regional Hospital of Lille, France.
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The amyloidoses are a group of several diseases sharing the feature of abnormal deposition of insoluble amyloid protein fibrils in the body leading to changes in tissue architecture and function. The disorders can be classified both clinically and biochemically, although most modern classification is based on the nature of the precursor plasma proteins that form the amyloid fibril deposits, since approximately 18 distinct forms of precursor protein-derived amyloid fibers have been identified. Dermatologists consider amyloidosis to be a depositional dermatosis, and generally classify disease states as systemic (with primary myeloma-associated and secondary forms), cutaneous (primary and secondary forms), and heredofamilial amyloidosis.\(^1\)\(^-\)\(^3\)

A specific fibril protein, such as keratin or immunoglobin, is the major constituent of amyloid. Minor components of the amyloid protein fibril include amyloid P protein, glycosaminoglycans, and apoE lipoprotein.\(^1\)\(^-\)\(^3\) The precursor amyloid proteins are initially soluble. Unknown factors cause the amyloid proteins to undergo changes that lead to their aggregation and polymerization, and ultimately lead to insoluble fibril formation and tissue deposition. Deposition of the protein fibrils in the skin and other organs affects normal functioning, leading to pathology. The exact disease pathophysiology has not yet been fully elucidated. Proposed mechanisms for the development of primary cutaneous amyloidosis include prolonged friction, Epstein-Barr virus infection, genetic predisposition, and environmental factors.\(^3\)\(^-\)\(^5\)

Primary cutaneous amyloidosis is generally restricted to the skin. The most common forms include macular, lichen, and biphasic amyloidosis. A less common entity is NCA. All are characterized

**CASE STUDY**

Vesna Petronic-Rosic, MD, MSc, Section Editor

### Nodular Cutaneous Amyloidosis

Jessica Borowicz, DO; Leah Shama, DO; Richard Miller, DO

A 56-year-old white man presented with a lesion on the right shoulder. The lesion developed during a short period and recently became irritated with occasional bleeding and mild pruritus. The patient denied pain. Medical history included melanoma, nonmelanoma skin cancer, diabetes mellitus type II, hyperlipidemia, multinodular thyroid goiter, and obesity. Medications and family and social history were noncontributory. Review of systems was negative. Examination revealed a slightly raised, friable yellow-pink waxy plaque located on the right shoulder (Figure 1). There was no evidence of excoriation, secondary infection, drainage, scale, crust, atrophy, lichenification, or telangiectasia. The patient had no mucosal or nail changes and the remainder of his skin examination was normal. A shave biopsy on the right shoulder revealed a nodular deposit of homogenous eosinophilic material associated with extravasated erythrocytes within the dermis. An infiltrate of lymphocytes and plasma cells was associated with the deposits. Immunohistochemical stains revealed positive plasma cells with kappa light chain and negative with lambda light chain. Congo red stain was positive and supported the diagnosis. The findings were consistent with nodular cutaneous amyloidosis (NCA) of the amyloid light-type. Initial work-up included referrals to hematology/oncology and to general surgery. The patient had a complete blood cell count (CBC), complete metabolic profile (CMP), serum protein electrophoresis (S-PEP), urine protein electrophoresis (U-PEP), 24-hour urine creatinine clearance, and protein, serum immunoglobulins and $\beta_2$ microglobulin. These were all within normal limits. Abdominal/pelvic computed tomography and positron emission tomography scan also were within normal limits. Bone marrow biopsy showed no abnormalities. The patient underwent both an abdominal fat pad biopsy as well as a colonoscopy with rectal biopsy. Both were negative for amyloidosis. Initially, the patient's cutaneous amyloidosis remained localized and mild pruritus was controlled by low potency topical steroids. The patient was closely monitored by hematology/oncology and general surgery on a biannual basis to assess the possibility of progression to systemic amyloidosis. Over the course of the subsequent two years, the patient developed multiple similar lesions across the back, shoulders, and chest, which were biopsied and found to be consistent with NCA. Progression of the cutaneous nodules led to disfiguring, painful, and friable pink to yellow waxy papules coalescing into plaques with obvious hemorrhage diffusely over the trunk (Figure 2). In lieu of the painful and disfiguring progression of disease, the patient desired a more aggressive treatment plan. At present, the treatment option recommended to the patient is carbon dioxide laser ablation. Hematology/oncology recommendation consists of a general systemic amyloid reevaluation annually, including CBC, CMP, S-PEP, U-PEP, 24-hour urine collection with creatinine clearance, and history and physical examination.
Nodular Cutaneous Amyloidosis

CASE STUDY

September/October 2011

SKINmed. 2011;9:316–318

by epidermal and dermal deposition of amyloid proteins, either of keratinocyte or immunoglobulin light chain (amyloid light) derivation. NCA is the rarest form of cutaneous amyloidosis. The fibrils are composed of amyloid light proteins of immunoglobulin light chains or β₂-microglobulin subtype. NCA presents as single, or less commonly, multiple pink to yellowish brown waxy nodules preferentially located on acral surfaces, although they may also be found on the trunk, genitalia, and face.4,6 Lesions may resemble large bullae (bullous amyloidosis), or the epidermis may appear atrophic or anetodermic.7 The nodules may have superficial telangiectasias and, as presented in this case, may be quite friable and hemorrhagic, as a result of perivascular deposition of amyloid.

Epidemiologically, women in the sixth to seventh decade of life were thought to be predominately affected, but more recent studies suggest that both sexes of middle age are affected.4,8 It is important to recognize NCA, because the lesions are indistinguishable from those of primary systemic amyloidosis (PSA). Rarely, NCA has been shown to progress to PSA and subsequent myeloma. NCA alone follows a relatively benign course, but the prognosis is poor for PSA, with a median survival of 1 to 2 years if untreated.5,9,10 There has been controversy regarding the risk of progression to PSA in patients with NCA. Earlier studies suggested this rate to be as high as 50%,6 although a recent case report by demonstrated that the rate of progression might be as low as 7%.11 Systemic disease should be ruled out in patients newly diagnosed with NCA, and these patients should be assessed annually for progression to PSA. Studies include CBC, CMP, urinalysis (proteinuria is not a feature of NCA), S-PEP, U-PEP, chest radiography, and electrocardiography.6,9,10

PSA and NCA share a common precursor protein derived from kappa and/or lambda types of immunoglobulin light chain proteins, termed “AL.” AL is unrelated to the keratinocyte-derived amyloid, as in macular and lichen amyloidosis, or to AA amyloid (acute-phase reactant protein), as in secondary cutaneous amyloidosis. In PSA, paraproteins circulate, deposit, and accumulate within tissues systemically and interfere with normal functioning. In NCA, local skin plasma cells produce aberrant immunoglobulin light chain amyloid proteins producing skin disease.3,12 The commonality of the amyloid protein derivation explains the relationship of NCA to PSA and warrants close follow-up of patients diagnosed with NCA to exclude progression to systemic disease.3,4,7,9

The diagnosis and differentiation of NCA from other types of cutaneous amyloidosis is established via tissue biopsy. Biopsy specimens should include full thickness skin into subcutaneous fat. In NCA, the locally produced immunoglobulin light chain–derived amyloid fibrils deposit in the dermis and subcutis and within blood vessel walls. In contrast, keratinocyte-derived amyloid deposits are more superficial, rarely extending beyond the upper dermal layer.13 Additionally, several studies have demonstrated a perivascular infiltrate of plasma cells within the lesions of NCA, suggesting that the amyloid AL protein deposits result from local plasma cell production of immunoglobulin light chain precursors. Therefore, some may consider NCA a form of plasmacytoma or plasma cell dyscrasia.3,12

Staining amyloid with hematoxylin and eosin (H&E) demonstrates amorphous, eosinophilic, fissured masses of amyloid protein fibril deposition at variable levels in the epidermis and dermis. Since amyloid proteins are often difficult to visualize with standard H&E staining, the most frequently utilized stain to highlight amyloid is Congo red. A common feature of all the amyloidoses is visualization of apple-green birefringence in polarized light with Congo red staining. This is due to the cross β-pleated sheet conformation characteristic of amyloid.1,2,9 Immunohistochemical studies of the NCA lesions may demonstrate positivity for immunoglobulin light chains (kappa and/or lambda) as well as for β₂-microglobulin partially modified by advanced glycation end products.13 Cytokeratin stains will generally be negative, as these stains would highlight the altered keratin proteins in the keratinocyte-derived forms of primary cutaneous amyloidosis. Electron microscopy reveals 7- to 10-nm–thick straight fibrils aggregated in an irregular network while x-ray crystallography and infrared spectroscopy show the cross β-pleated sheet conformation characteristic of amyloid.3,9,14

Treatment of cutaneous amyloidosis lesions is individualized, based upon the clinical presentation. Variable success has

Figure 1. Slightly raised, friable yellow-pink waxy plaque on the right shoulder.
been accomplished through treatment of amyloid lesions with physical removal or destruction of the lesions by shaving and desiccation or use of the carbon dioxide laser. A challenge in the treatment of NCA lesions is control of hemostasis due to tissue friability, imparted by perivascular deposition of amyloid. Additionally, local recurrence following surgical excision is common. Other modalities for treatment include dermabrasion and pulsed dye laser. Intralesional corticosteroid injection has been shown to exacerbate the lesions and should be avoided.

CONCLUSIONS

NCA is rare and has the ability to progress to systemic amyloidosis. Annual follow-up studies to exclude progression to PSA should be performed for patients diagnosed with NCA. The clinician should pay close attention to the evolution of current skin lesions and the formation of new lesions, as amyloidosis can lead to significant morbidity for the patient.

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A 70-year-old Caucasian man with a medical history of Parkinson’s disease presented with a 3-month history of violaceous reticulated patches on his upper and lower extremities. The lesions were asymptomatic. The patient did not have a history of cardioembolic events or autoimmune disorders. No new medications were started before the onset of the lesions. Review of systems was unremarkable. On examination, large erythematous to violaceous patches were present in a reticulated net-like pattern on the patient’s upper and lower extremities (Figure 1 and Figure 2). No edema, erosions, or ulcerations were noted. An extensive workup for autoimmune, infectious, and hematologic causes of livedo reticularis was performed. Complete blood cell count, anti-nuclear antibodies (ANAs), anti-Ro and anti-La antibodies, antiphospholipid antibodies, protein C and S levels, cryoglobulin screen, rheumatoid factor, and hepatitis screen were all within normal limits. After these potential other causes were excluded, the patient was diagnosed with amantadine-induced livedo reticularis (LR), a medication he had been taking for 2 years for Parkinson’s disease. The patient’s dose of amantadine was decreased from 100 mg to 50 mg twice daily and over the next few months, his lesions gradually faded. Because his neurologic condition benefited from amantadine and his lesions were asymptomatic, his neurologist continued the medication.

Amantadine is a synthetic antiviral agent initially developed to prevent and treat infection by influenza A. It is currently used to treat Parkinson’s disease, drug-induced extrapyramidal symptoms, fatigue associated with multiple sclerosis, and chronic hepatitis C resistant to standard treatments. Known side effects of the medication include nausea, dizziness, insomnia, LR, and lower extremity edema, possibly secondary to increased vascular permeability. Leg edema can be seen as an isolated finding but has also been documented by some to occur only when LR is concurrently present.

LR is a cutaneous finding that presents as a mottled network of erythematous to violaceous discoloration. LR can be physiologic, primary, or secondary to intravascular obstruction or vessel wall disease. Physiologic LR, also known as cutis marmorata, is a transient response to cold exposure. Primary LR is idiopathic and a diagnosis of exclusion. Secondary LR may be a result of a wide range of conditions including hematologic, autoimmune, embolic, neoplastic, infectious, and iatrogenic factors. An extensive workup should be performed to rule out these possibilities, including a complete blood cell count, biochemical profile, ANAs, antineutrophil cytoplasmic antibodies, complement levels, coagulation profile, and antiphospholipid antibodies.

Amantadine-induced LR has been documented in the medical literature since the early 1970s. The reported incidence is highly variable, ranging from 2% to 90%. Most cases involve the use of amantadine in patients with Parkinson’s disease or fatigue caused by multiple sclerosis. One report of LR was noted after treatment of chronic hepatitis C with amantadine.

The exact mechanism of amantadine-induced LR is unclear. Amantadine is known to cause the release and depletion of vasoactive compounds (epinephrine, norepinephrine, and dopamine) from nerve terminals. Proposed mechanisms include amantadine-induced vasoconstriction causing decreased blood flow in arterioles, with secondary dilatation of dermal blood vessels. Since amantadine is also an N-Methyl-D-aspartate (NMDA) receptor antagonist, other authors believe that its vasoactive effects may involve cutaneous NMDA receptors. Interestingly, another proposed mechanism involves the development of antiphospholipid antibodies in response to amantadine treatment. The authors documented a high incidence of antiphospholipid antibodies in patients with Parkinson’s disease being treated with amantadine; however, a causal relationship was not identified and larger studies with inclusion of other thrombotic risk factors were recommended.

Amantadine-induced LR is generally asymptomatic and has been reported to occur from 1 month to 4 years after drug initiation. Dosages prescribed in these cases have ranged from 100 mg 3 times weekly to 400 mg daily. The lower extremities are most commonly affected, although lesions can be generalized and involve the trunk and upper extremities. Women
appear to be more predisposed to developing this condition than men. LR is a reversible side effect of amantadine and lesions typically resolve a few weeks after drug cessation. Development of LR does not necessarily warrant discontinuation of amantadine, especially if the medication is beneficial for the patient. In severe cases, however, peripheral edema and ulceration can occur.

Rimantadine, an α-methyl derivative of amantadine, has been proposed by investigators as an appropriate substitute for amantadine in patients with significant adverse effects. These authors documented 7 cases where amantadine was replaced by rimantadine, with 4 patients experiencing significant improvement in peripheral side effects of LR and ulcerating leg edema.

REFERENCES


FORMULARY OF DR GEORGE C. ANDREWS

**Perspiration Corrective II**

<table>
<thead>
<tr>
<th>Ingredient</th>
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</thead>
<tbody>
<tr>
<td>Boric acid</td>
<td>1 ounce</td>
</tr>
<tr>
<td>Bismuth subcarbonate</td>
<td>1 ounce</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>½ ounce</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>3 ounces</td>
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</table>

15 drops to one ounce formalin being 40% solution of formaldehyde

Submitted by Douglas D. Altchek, MD, New York, NY

Figure 1. Photograph showing reticular net-like cyanotic patches symmetrically distributed on bilateral upper extremities.

Figure 2. Photograph showing similar reticular net-like violaceous patches on lower extremities.
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Cutaneous leiomyomas are uncommon benign smooth muscle neoplasms of skin that are frequently unrecognized by clinicians. These tumors are classified into four categories depending upon their respective sites of origin: (1) multiple piloleiomyomas, (2) solitary piloleiomyoma, (3) angioleiomyoma, and (4) genital leiomyoma. The genital group includes masses arising from the dartos muscle of the scrotum or from the labia majora, as well as those derived from the mammary muscle of the nipple in either sex. The most common type of presentation of leiomyoma is that of multiple piloleiomyomas. The lesions occur as grouped, linear, or dermatomal arrangements of firm, red to brown intradermal nodules that are fixed to the skin but not to the deeper tissues. Solitary piloleiomyoma and genital leiomyomas are clinically similar.1

Leiomyomas of the genitourinary tract may originate from any structure containing smooth muscle.2–5 These benign tumors have been described in the kidneys, ureters, bladder, urethra, prostate, seminal vesicles, spermatic cord, testis, epididymis, penis, and scrotum.4

Due to their rarity, scrotal leiomyomas are often confused with fibroma or an epidermal inclusion cyst and are nearly always preoperatively misdiagnosed.6 Scrotal leiomyoma appear most often between the fourth and sixth decades of life.2,7 They are typically painless, noninflamed, small cutaneous lesions usually present for an average of 7.6 years between patient recognition and surgical removal.2,8 They tend to be solitary, asymptomatic lesions measuring 1 to 14 cm, with a mean length of 6.4 cm.7

Histologically, vulvar and scrotal leiomyomas are larger, asymptomatic, and histologically deeper and better delimited exhibiting characteristic elongated, blunt-ended smooth muscle nuclei (cigar-shaped) and eosinophilic cytoplasm. Smooth-muscle fiber bundles interface with variable amounts of collagen. Masson trichrome, aniline blue, van-Gieson, phosphotungstic acid-hematoxylin, and desmin and actin immunohistochemical stains facilitate the histologic recognition of smooth muscle.

Although multiple cutaneous leiomyomas can be associated with internal tumors,1 no known association exists for solitary genital leiomyoma, and thus no further workup for the patient was required.

As a result of its location and symptoms, it is essential that the differential diagnosis with other benign and malignant paratesticular tumors be carried out, as malignancies occur in up to 20% of the cases.3 Although some leiomyosarcomas have been reported in genital skin, there is no evidence of malignant change in preexisting benign lesions. Sonography is a widely used imaging technique for distinguishing leiomyomas from other lesions.
modality for patients with suspected scrotal abnormalities. Both solid and multicystic lesions have been described in scrotal leiomyomas. As a rule, solid intratesticular lesions have a high likelihood of malignancy (about 90%-95%), while extratesticular lesions are usually benign. A review of the latter in the urology literature shows a malignancy rate of 3%. Another important role of sonography is that it can easily distinguish intratesticular from extratesticular lesions with an accuracy of 95%-100%.

The differential diagnosis of scrotal lesions distinctly separate from the testis and adnexal structures includes squamous cell carcinoma, basal cell carcinoma, Paget’s disease, fibroma, lipoma, myxoma, hemangioma, lymphangioma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, epidermal inclusion cyst, and leiomyoma.

Surgical excision or ablation of a solitary mass is another treatment option for painful lesions and carbon dioxide–laser ablation has also been employed in cases of symptomatic cutaneous masses. The prognosis for isolated lesions is excellent, particularly following surgical excision. Recurrences have been reported, however, following incomplete excision. There is no documented tendency toward malignant degeneration in cutaneous leiomyomas.

Although rare, leiomyoma should be considered in the differential diagnosis of a scrotal mass. If there is any doubt regarding the extent for surgical excision of scrotal masses not associated with the testicle or epididymis, ultrasonography and pathologic frozen sections should be used to confirm the clinical suspicion of a benign vs malignant scrotal lesion.

REFERENCES

HISTORICAL DIAGNOSIS & TREATMENT

Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of stereoptic cards published in 1910 by The Stereoscopic Skin Clinic, by Dr. S. I. Rainforth.

SCLERODERMA

SYNONYMS: Dermatosclerosis; Sclerema; Sclerosis; Sclerosisis; Hide bound disease.

DIAGNOSIS: The most characteristic feature of scleroderma is, as the name indicates, a hardening of the skin, and this may be the only feature in common between the two most widely separated varieties. The lesions may develop rapidly, or as is more common, very gradually; they may be single or multiple, diffuse and ill defined or localized and sharply circumscribed, level with the normal skin or slightly elevated or depressed, of an ivory like whiteness or a translucent yellow, or pigmented diffusely or in blotches. The patches sometimes have a characteristic violaceous areola. Their surface is usually smooth but may be slightly scaly or somewhat nodular and is often traversed by a network of dilated capillaries.

TREATMENT: It is difficult to estimate the value of various remedies. General symptomatic and tonic treatment is indicated. Thyroid extract has seemed to benefit some cases. Local massage with oil or a mildly stimulating ointment is usually employed.
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To the Editor:

I read with interest the recent report in *SKINmed* of idiopathic longitudinal erythronychia in a 71-year-old man.\(^1\) Longitudinal erythronychia has recently been classified into subtypes depending on the number of nails affected and the number of linear red bands on these nails (Table I).\(^2,3\) Similar to the patient described by Rashid and colleagues,\(^1\) nail findings in other patients with idiopathic monodactylous longitudinal erythronychia have previously been published.\(^4\) In addition to an idiopathic etiology for a single linear red band of the nail of only one digit, monodactylous longitudinal erythronychia has been observed in patients with either a benign or malignant-associated nail bed tumor (Table II).\(^2,5\)

In contrast to monodactylous longitudinal erythronychia, polydactylous longitudinal erythronychia presents with one or more nails that have either a single longitudinal red band or multiple linear red streaks. A 59-year-old man developed chronic graft-versus-host disease of the gastrointestinal tract and the skin following a matched unrelated donor stem cell transplant to treat his acute myeloid leukemia. His gastrointestinal and lichenoid skin changes of graft-versus-host disease essentially resolved after prolonged treatment with triple therapy including low-dose methyl prednisone, tacrolimus, and mycophenolate mofetil. In addition to his skin changes, however, he also developed chronic graft-versus-host disease nail changes that persisted: lamellar splitting of both great toenails (Figure 1), thinning with a central linear split of both thumbnails (Figure 2), and longitudinal erythronychia of the remaining 8 fingernails (Figure 3). Additional nail changes, that have previously also been associated with longitudinal erythronychia, are most prominent at the distal border of the red band on the free edge of the right middle fingernail (V-shaped distal nick) and the left middle fingernail (onycholysis and nail breaking) (Figure 4).

In addition to graft-versus-host disease,\(^3\) polydactylous longitudinal erythronychia can be a nail manifestation found in patients with systemic conditions such as amyloidosis and pseudobulbar syndrome.\(^3,6\) In addition, linear red bands on multiple nails have been observed in some individuals who have certain dermatologic conditions: acantholytic dyskeratotic epidermal nevus, acantholytic epidermolysis bullosa, acrokeratosis verruciformis of Hopf, keratosis follicularis (Darier’s disease), and lichen planus.\(^2\) Also, albeit less commonly, polydactylous longitudinal erythronychia has been reported as an idiopathic finding with no associated etiology.\(^7,8\)

### Table I. Classification of Longitudinal Erythronychia

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Type Ia</td>
<td>Monodactylous-single red band per nail</td>
</tr>
<tr>
<td>Type Ib</td>
<td>Monodactylous-bifid red bands per nail</td>
</tr>
<tr>
<td>Type IIa</td>
<td>Polydactylous-single red band per nail</td>
</tr>
<tr>
<td>Type IIb</td>
<td>Polydactylous-multiple red bands per nail</td>
</tr>
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### Table II. Conditions Associated With Monodactylous Longitudinal Erythronychia

- Glomus tumor
- Hemiplegia
- Idiopathic
- Malignant melanoma
- Onychopapilloma
- Scar (postsurgical)
- Squamous cell carcinoma
- Systemic conditions associated with polydactylous longitudinal erythronychia (initial stage)
- Warty dyskeratoma

---

Figure 1. Lamellar splitting of the great toenails in a man with graft-versus-host disease.
Longitudinal erythronychia can involve either a single nail or multiple nails, where one or more linear red bands are present on the affected nails. Indeed, this nail finding may be an associated manifestation of a local condition or a clinical feature related to an underlying systemic disease. Similar to the patient reported by Rashid and colleagues, monodactylous longitudinal erythronychia may be idiopathic. Involvement of only one red band on the nail of a single digit, however, raises the possibility of either a benign tumor or a malignant neoplasm of the respective nail bed. Multiple nails with longitudinal red bands may result from either a primary dermatologic disorder (most commonly either Darier’s disease or lichen planus) or a systemic condition (such as graft-versus-host disease in the described patient). Alternatively, polydactylous longitudinal erythronychia may be an idiopathic finding.
To the Editor:

I read with interest the contribution entitled “Vitiligo and Alopecia Aretae Associated With Subclinical/Clinical Hypothyroidism” by Dr VN Sehgal.1 The contribution describes 5 cases of concurrent vitiligo and alopecia areata with marked thyroid function abnormalities in patients ranging in age from 11 to 64 years. The author, however, does not address all the subtleties of overlapping autoimmune diatheses.

Overlapping alopecia areata and vitiligo can coexist in either a generalized or segmental distribution and is especially noticeable in the scalp area (men and women) and the beard area (men). The primary determinant of whether the generalized autoimmune risk exists is whether the overlap is segmental (autoimmune twin spotting/agminated type), which is caused by postzygotic mutations vs concurrent, generalized disease states, which would imply a generalized autoimmune risk.

The overlap of vitiligo and alopecia in a segmental area is a common phenomenon and is unlikely to be associated with autoimmune thyroid disease. Figure 1 demonstrates an example of such a patient. A 13-year-old African American boy presented with a few months’ history of a linear strip of vitiligo in which localized hair loss occurred overlying the vitiligo shortly after onset of the hypopigmentation. Figure 2 demonstrates partial repigmentation and hair regrowth following 3 months’ application of tacrolimus 0.03% ointment twice daily. This individual had normal thyroid function for the past 7 years.

In a cohort of 28 children with vitiligo, 7 (25%) had active thyroid disease; of the 7 children with segmental vitiligo, none had signs of thyroid autoimmunity. Other studies during the past 10 years have confirmed that the association of vitiligo with hypothyroidism appears to be unique to the generalized3,4 not the segmental forms. The presence of localized alopecia areata within a segmental case of vitiligo is likely caused by the common presence of antibodies to the melanocytes that are within the hair follicle and the epidermis, and is not part of generalized alopecia areata; furthermore, localization of the immune process to a single segment of skin suggests that a somatic mutation in this genetic segment resulted in localized autoimmune susceptibility. While generalized cases of vitiligo can occur concurrent with segmental disease caused by localized loss of heterozygosity, the majority of segmental vitiligo cases lack the generalized

Segmental Vitiligo May Not Be Associated With Risk of Autoimmune Thyroiditis

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propensity. Coexistence of autoimmune thyroid disease is only a risk when either the vitiligo and/or alopecia areata are generalized but not when both are in the agminated segmental form. Thyroid function screening, hence, is not needed in overlapping segmental alopecia areata/vitiligo but rather should be reserved for cases where one or both diseases are generalized and especially in the presence of two or more generalized cutaneous autoimmune illnesses.

REFERENCES

—Nanette Silverberg, MD, New York, NY. nsilverb@chpnet.org

Figure 2. The same patient after therapy with tacrolimus 0.03% ointment for 3 months.

Author’s Response

To the Editor:

The comments on the paper are welcomed and are in order. Indeed, they are well-conceived, outstanding, illustrated, and are laudable, once again reiterating the prevalent overtones on coexistence or overlap of vitiligo alopecia areata and subclinical/clinical hypothyroidism of autoimmune origin. Nonsegmental vitiligo alone has also been reported to occur in multinodular goiter with euthyroid status. The contents of the communication form a viable focus for the future execution. It is, therefore, mandatory to determine the status of thyroid in such cases through thyroid panel/capsule comprising triiodothyronine, total thyroxine, and thyroid-stimulating hormone irrespective of segmental and/ or nonsegmental vitiligo in the current context. In resource-crunched countries, however, the discretion is exercised by the treating clinician; nonetheless, it is claimed to be more useful in generalized and progressive vitiligo. This modality is indispensable, and may prove invaluable in evolving the future treatment strategies for vitiligo and alopecia areata in children in particular.

REFERENCES

—Virendra N. Sehgal, MD, Panchwati, Delhi, India • E-mail: drsehgal@ndf.vsnl.net.in
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BRIEF SUMMARY

INDICATIONS AND USAGE
Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS
Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticoid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid.

Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

ADVERSE REACTIONS
The most common adverse reactions (>1%) are HPA axis suppression and application site reactions.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lipocream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lipocream is administered to a nursing woman.

Pediatric Use
Safety and efficacy in pediatric patients below 3 months of age have not been established. Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (three times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 16 micrograms per deciliter after cosyntropin stimulation. Suppressed subjects ranged in age from 5 months to 16 years and, at the time of enrollment, had 25% to 95% BSA involvement. These subjects did not develop any other signs or symptoms of HPA axis suppression. At the first follow up visit, approximately one month after the conclusion of treatment, cosyntropin stimulation results of all subjects had returned to normal, with the exception of one subject. This last subject recovered adrenal function by the second post treatment visit, 65 days post-treatment.

Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have also been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use
Clinical studies of Locoid Lipocream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of Locoid Lipocream.

Hydrocortisone butyrate revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y/TK- mouse lymphoma assay) and one in vivo genotoxicity test (mouse micronucleus assay).

No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to and including 1.8 mg/kg/day (0.7X maximum topical human dose [MTHD]). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses ≥0.6 mg/kg/day (0.2X MTHD).

PATIENT COUNSELING INFORMATION
Patients using Locoid Lipocream should receive the following information and instructions:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from freezing. Keep out of the reach of children.
Now younger eczema patients have something to smile about

Now approved for use in children down to 3 months of age

Locoid Lipocream (hydrocortisone butyrate 0.1%) Cream

The power of an ointment with the elegance of a cream

Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. Safety and effectiveness in pediatric patients below 3 months of age have not been established. Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

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