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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® 
(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.

Erythema, scaling, dryness, and stinging/burning may occur 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
depilation should not be performed on treated skin.

Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women
treated with DIFFERIN Lotion. Therefore, DIFFERIN Lotion should be
used during pregnancy only if the potential benefit justifies the potential risk
to the fetus. 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,
care 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 F₀ males and females, or growth, development
and reproductive function of F₀ 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
erthema, scaling, dryness, stinging or burning.

• Advise patients to cleanse the area before application of a mild 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 depilation 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 (e.g., 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

Please see brief summary of Prescribing Information on the next page.

VELTIN Gel

Combinesthe acne-fighting properties of tretinoin and clindamycin
Contains tretinoin, solubilized in an aqueous-based gel
Combatssinflammatory and noninflammatory acne

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

VELTIN Gel

(clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

VELTIN Gel

Stiefel

a GSK company
VELTIN Gel should not be used in combination with erythromycin-containing products.

Erythromycin

DRUG INTERACTIONS

Combination of VELTIN Gel and erythromycin has been reported. If significant diarrhea 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.

Ultrasound Light and Environmental Exposure

Exposure to sunlight, including sunlamp, 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 sunscreens and protective apparel (e.g., a hat) are recommended. Weather conditions 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 (8%), 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.

Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased.

Studies with VELTIN Gel were application site reactions, including dryness (6%), burning (6%), and itching (17%). At 12 weeks of treatment (N=409), 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 two 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 limit teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2 mL/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 assuming 100% absorption and 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 dosing protocols among various species have been reported. In the cynomolgus monkey, 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 has been established from these cases, 5 of the reports described the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports is unknown.

Managing Mothers

It is unknown 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 when 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) in 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 tumour 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-ace-tate 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-ocarcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photo-ocarcinogenic potential of the clindamycin/tretinoin combination is unknown. Although the significance of these studies to humans is not clear, patients should avoid exposure to sun.

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. 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.

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 discomfort, VELTIN Gel should be discontinued and a physician should be contacted.

VELTIN is a trademark of Astellas Pharma Europe B.V.

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The following is a brief summary only; see full prescribing information for complete product information.
We are fast becoming a society of “germophobics,” if we are not already there. Hand washing and wearing protective gloves are a crucial part of this obsession that is playing a significant role in the 21st century. There is hardly a person, let alone a household pet, who is not affected by the situation. Let us pause to consider the ramifications.

HAND WASHING

Not since the days of Ignaz Semmelweis (1818–1865) and the subsequent adherents of hand washing has so much emphasis been placed on appropriate cleansing of the hands. There is hardly an office building that does not have the alcohol hand-washing dispenser in a prominent place, and hospitals have placed these devices at elevators, nurses' stations, and patient rooms. The obsession with cleanliness can reach the point of absurdity: ie, dispensers for paper for covering restroom doorknobs.

Elsewhere in this issue, we discuss the question of irritation from alcohol-based disinfectant usage. Curiously, such alcohol-cleansing had been suggested as early as 1888. Much to our surprise, use of the alcohol-based washes is not irritating. In fact, this procedure may reduce the irritation from scrubbing with soap by eliminating more of the irritant than simple rinsing with water might accomplish. This is not to say that there is not the uncommon person who may be allergic to the alcohol in the dispenser, but these devices are not the terror once presumed.

Consuming the alcohol-based washes is not recommended, needless to say. Until we searched the literature, we had not even imagined that the alcohol-based washings might also affect an alcohol intoxication test. Fortunately, two studies have shown that the absorption of ethanol from these washes is negligible and does not affect any breathalyzer testing used to determine whether someone is driving under the influence of alcohol. In fact, even countries whose religious laws forbid alcohol consumption have not found alcohol-based hand washing contradictory to their regulations and mores.

VINYL GLOVES

The use of vinyl gloves has mushroomed, as well, during recent years. While the adoption of protective gloves has been a part of medical practice for some time, we have witnessed with relief their implementation by food handlers and bathroom attendants. Curiously, airport screeners seem wedded to vinyl gloves, even when the apparent exposure to pathogens is limited, if nonexistent.

More questionable is the fact that bank tellers do not use such protection. There has always been the thought that money is dirty, and famous dermatologists such as Louis A. Duhring (1845–1913) and Henry W. Stelwagon (1853–1919) had a fear of handling money. While money may seem to be inundated with germs, there have been no studies to prove that disease has been transmitted by coins or even paper currency (Figure). Similarly, the mail, even when hysteria prompted disinfection, particularly from leprosy, was never found to transmit germs, unless laced maliciously with anthrax spores.

In the rush to adopt protective measures, the medical community embraced latex gloves 2 decades ago. With dramatic increase in the use of latex gloves, nosocomial infections may have been reduced but the incidence of latex allergy and the subsequent development of latex cripples increased dramatically. With the restrictions on the use of latex-based products and powdered gloves, the problem has fortuitously diminished.

CONCLUSIONS

The traditional proverb “cleanliness is next to godliness” is a worthwhile motto. Being appropriately clean can be recommended, but being crazy clean may be another story.
REFERENCES


PARESTHESIA (burning, tingling, prickling of the skin)

Medication known to cause such symptoms

- Adalimumab
- Arsenic
- Cyproheptadine
- Diphenhydramine
- Disopyramide
- Furosemide
- Hydroxyzine
- Isotretinoin
- Losartan
- Minocycline
- Quinapril
- Valsartan

Adapted from Litt, JZ. Curious, Odd, Rare, and Abnormal Reactions to Medications. Fort Lee, NJ: Barricade Books; 2009:108–113.

Figure. Germophobia can assume various poses.


Germophobia: The Dilemma of Hand Washing
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. The #1 doctor- and pharmacist-recommended brand for scars helps empower your patients to take charge of their appearance so they can get back their confidence. And you get a very satisfied patient. Available for office dispensing.

1 Draelos, Z. The ability of onion extract gel to improve the cosmetic appearance of post-surgical scars. Cosmetic Dermatology, June 2008.
**Mesotherapy**

Hassan Galadari, MD; Fatima Al Faresi, MD

While Michel Pistor (1924–2003) coined the term mesotherapy to describe a technique that used a cocktail of ingredients injected in the dermis and/or subcutaneous layer of the skin, historically, the procedure was first performed in 1931, when Drs Jose Salvador Gallardo and Jose Coenjo Mir described the treatment of alopecia areata by intradermally injecting milk. Although initially used for pain relief, modern use of mesotherapy has included many cosmetic conditions.

The ingredients used depend on the condition being treated and may vary between natural plant extracts, homeopathic agents, pharmaceuticals, vitamins, botanicals, and other bioactive substances. With the exception of local anesthetics, calcitonin, hyaluronidase, and collagenase (all of which were used off-label), the US Food and Drug Administration (FDA) has not approved or granted orphan drug designation to any other mesotherapy ingredients by subcutaneous delivery; furthermore, manufacturers fail to disclose the ingredients and their concentration. Although one might argue against its use, mesotherapy’s popularity has seen a rise. This has been attributed to the ease of injection and the popularity of affordable minimally invasive procedures.

In 1987, the French National Academy of Medicine acknowledged mesotherapy as an official specialty of medicine, and fellowship training has also become available. It has received wide acceptance in Europe and South America, and has recently begun to gain popularity in the United States. To lobby for its legitimacy and use, practitioners of mesotherapy, who range from having medical and nonmedical backgrounds, have started forming societies, organizing meetings, and setting up fellowship training programs on the field.

**INDICATIONS**

**INJECTION LIPOLYSIS OR LIPODISSOLVE**

This is perhaps the most popular indication of mesotherapy and it is mainly used for the treatment of fat aggregates, cellulite, and body sculpting. This occurs by the theoretical promotion of dissolution of fat deposits. The basic ingredients that are frequently used in the solution mixture for this purpose are phosphatidylcholine and/or deoxycholate. The FDA has yet to approve the use of these two substances for treatment and for safety. The cosmetic use of phosphatidylcholine, extracted from soybean lecithin, for body contouring began in the mid-1990s as off-label use in Brazil. Additionally, phosphatidylcholine was mixed with many other “fat-dissolving” substances. The mechanism of localized fat reduction is unknown. Some authors have theorized that the lipolytic effect of these subcutaneous injections relies on its lipid-modulating effects in the blood and liver and activation of cyclic monophosphate. There are no standardized trials or research studies reporting clinical, histopathological, and laboratory data that prove the effectiveness of phosphatidylcholine in the treatment of localized fat areas.

Although reports indicate its use in specific indications such as buffalo humps, lipomas, submental fat, and infraorbital fat herniation, no study has been able to standardize for dose. After many reported cases of scarring, dyspigmentation, and body contour irregularities, the Brazilian National Agency of Health Inspection (ANVISA), which regulates the use of medications in Brazil, published a resolution in January 2003 prohibiting the use of the agent in this form. This was later reaffirmed by the American Society of Plastic Surgeons in a statement warning against the use of these chemical compounds as an alternative to liposuction.

Recently, investigators have identified sodium deoxycholate, an emulsifier of phosphatidylcholine and a detergent that produces nonspecific destruction of cell membranes, as a major active ingredient in injection lipolysis. Injection of deoxycholate into lipomas causes focal necrosis, acute inflammation, and hemorrhage histologically. This has led some to believe that deoxycholate is the main cause of fat dissolution and not phosphatidylcholine, as previously noted.

**FACIAL REJUVENATION**

For mesotherapy to achieve rejuvenation, it should be able to increase dermal hydration and create a favorable environment to...
facilitate fibroblast activation. Most cocktail solutions used for facial rejuvenation contain hyaluronic acid (HA). Rejuvenation is achieved by the hydrating effects of HA in tissue or the trauma caused by repeated injections into the dermis triggering the healing process, activating fibroblasts and thus neocollagen. Investigators evaluated two patients at different time intervals before and after injection.12 The authors reported no significant clinical and histologic changes after multivitamin and hyaluronic acid solution mesotherapy for skin rejuvenation.

**Alopecia and Hair Loss**

Despite the fact that there are no controlled published studies about mesotherapy’s efficacy in hair disease, it has been used as a treatment for androgenetic alopecia and hair loss.13 Finasteride and minoxidil are possible components of the injected solution. These agents are the only FDA-approved agents for the treatment of androgenetic alopecia, when they are administered orally and topically, respectively. Data reporting efficacy of these agents in the form of mesotherapy have not been published and are not yet approved. In addition, manufacturers fail to disclose other ingredients used for the treatment of androgenetic alopecia and their concentrations. Publications of the use of mesotherapy in alopecia revealed many possible complications caused by treatment ranging from cicatricial alopecia to multifocal scalp abscesses.13

**CONCLUSIONS**

Given the ease of treatment and little-to-no downtime, mesotherapy has garnered great attention and has become extremely popular.14,15 Despite its growing popularity, which has relied primarily on marketing the treatment to lower-tier cosmetic outlets such as spas and beauty salons, it is postulated that 18,000 licensed mesotherapists exist in France alone, some of whom have no medical background. The lack of a precise treatment protocol, the unpredictable outcome, and the risk of localized adverse events has made many health regulatory bodies, including the FDA, slow to embrace the treatment modality. In April 2010, the FDA went further, to shut down outlets marketing mesotherapy under false pretenses and claims. These concerns have also been voiced by international societies, such as the American Society of Plastic Surgeons, which has expressed concern about the procedure and the chemicals used in it as an alternative to liposuction.14,15 The American Society for Dermatologic Surgery has stated that until further studies are published, the use of mesotherapy is not recommended. Due to a lack of data claiming efficacy and the rising barrage of possible complications, it is advised that the use of mesotherapy for whatever indication using untested ingredients be limited and practiced with extreme caution.

**REFERENCES**

Cutaneous conditions often present with characteristic primary lesions whose morphology can be described using a number of generally accepted terms. “Plaque” represents one such term and is used to denote an elevated, plateau-like area of integument that is greater in its diameter than in its depth, most often ≥0.5 or 1 cm in diameter. Regardless of the specific definition one uses, “plaque” always denotes an elevated lesion. Occasionally, the term “depressed plaque” is used to describe the morphology of a primary lesion, an inherently confusing term suggesting a depressed elevation of integument. Herein is an analysis of the prevalence and usage of the term “depressed plaque” within the medical literature.

METHODS
On May 30, 2010, an electronic literature search was performed on PubMed using the search term “depressed plaque.” Quotation marks were used around the term to force a phrase search. Titles and abstracts from all articles retrieved were included in the analysis. Each article was classified as dermatology- or nondermatology-related in nature. From the dermatology-related article abstracts the sentence using the term “depressed plaque” was recorded.

RESULTS
The search results consisted of 3 dermatology- and 4 nondermatology-related articles. The 3 dermatology-related articles were all case reports, each discussing a different cutaneous condition. The following are sentences from those articles using the aforementioned term: “The patient had a markedly deformed and depressed plaque surrounded by erythema on the right cheek.” “A 29-year-old man presented with a large, asymptomatic, brown, hyperpigmented, depressed plaque over his left upper back….” “[Premalignant circumscribed palmar hypokeratosis] presents clinically with a sharply circumscribed annular erythematous depressed plaque rimmed by a slightly hyperkeratotic border….”

COMMENT
The term “depressed plaque” is infrequently used within the medical literature to describe the morphology of a primary cutaneous lesion; therefore, given this infrequent use and that it represents an oxymoron, this author recommends avoiding the term. As an alternative, when a cutaneous lesion meets one’s criteria for a plaque, while also having a central depression or dell, describe the lesion as such (ie, a plaque with central depression or dell). If the cutaneous lesion is characterized only by depression without any areas of accompanying elevation, then the term “atrophy” would be most appropriate.

Disclosure: Dr Brendan Thomas had full access to all of the data in the commentary and takes responsibility for the integrity of the data and the accuracy of the data analysis. The commentary concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content were created and/or performed solely by Dr Thomas. Dr Thomas has no financial disclosures to report, having no relationships to industry, sponsors, or other sources of funding/support.

REFERENCES

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Address for Correspondence: Brendan Thomas, MD, University of Illinois College of Medicine at Chicago, Department of Dermatology, 808 South Wood Street, Chicago, IL 60612 • E-mail: bmthomas@uic.edu
DUAC Topical Gel is the once-daily clindamycin/benzoyl peroxide combination with a patented formula containing both glycerin and dimethicone

The contribution to efficacy by individual components of the vehicle has not been established.

- No therapeutically equivalent generic substitute
- More than 6 million prescriptions of DUAC Topical Gel dispensed since launch

PLEASE NOTE:
The soap-free cleanser is no longer included in the package. Please prescribe DUAC Topical Gel 45 g.

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.

**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 PSEUDOMEMBRANOUS 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 ANTIBIOTIC-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 AND STOOL ASSAY FOR CLOSTRIDIUM difficile TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIMICROBIAL 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 DISCONTINUATION OF THE DRUG. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. THE USE OF ANTIBIOTIC AGENTS MAY BE ASSOCIATED WITH THE OVERGROWTH OF NON-SUSCEPTIBLE 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 VITRO ANTAGONISM IS UNKNOWN.

**ADVERSE REACTIONS**

**Local reactions with use of DUAC Topical Gel**

<table>
<thead>
<tr>
<th>% of patients using DUAC Topical Gel with symptom present</th>
<th>Combined results from 5 studies (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment (Baseline)</td>
<td>During Treatment</td>
</tr>
<tr>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Erythema</td>
<td>28%</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</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.

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Skin Needling in the Treatment of the Aging Neck

Gabriella Fabbrocini, MD;1  Valerio De Vita, MD;1  Luisa Di Costanzo, MD;1  Francesco Pastore, MD;1  Maria Chiara Mauriello, MD;1  Ambra Monfrecola;1  Maria Carmela Annunziata, MD;1  Maria Gabriella Scotto di Santolo, MD;2  Norma Cameli, MD;3  Giuseppe Monfrecola, MD1

ABSTRACT

The aim of this study was to estimate the efficacy of skin needling in the treatment of the aging neck. Eight patients with aging necks were included in the study. Each patient was treated with 2 sessions of needling. The evaluation of treatment effectiveness was based on changes from baseline on the Global Aesthetic Improvement Scale, the Wrinkle Severity Rating Scale, photographic and ultrasonographic images, and silicone rubber microrelief impressions of a selected neck region before and after therapy. Analysis of the photographs, the degree of irregularity of the surface microrelief, and the ultrasound images showed that, after 2 sessions, the lesions’ severity grade was reduced in almost 90% of the patients. The present study presents evidence for the efficacy of skin needling for the aging neck. (SKINmed. 2011;9:347–351)

Skin needling or microneedling or collagen induction therapy is a dermatologic treatment performed to achieve percutaneous collagen induction (PCI) to smooth wrinkles, improve depressed acne scarring, and reduce the appearance of stretch marks. It is carried out using a skin roller that causes multiple tiny pin-point puncture wounds into the dermis. This dermal damage induces the release of growth factors that stimulate the production of new collagen and elastin in the upper dermis. Skin needling creates dermal damage without the removal of the healthy epidermis. There is proof that the needling procedure also stimulates filling of cutaneous wrinkles, revascularization, and repigmentation of stretch marks.1,2

Because the epidermis is left intact, the healing period during skin needling is swift, and the skin does not risk permanent structural damage, sun sensitivity, hypopigmentation, or hyperpigmentation.3

Ultrasound has been widely used since the 1980s to determine whole skin thickness and to evaluate age-related dermal changes.4

The aim of the present study was to evaluate the efficacy of skin needling in the treatment of the aging neck.

MATERIAL AND METHODS

This study was carried out in accordance with the Helsinki Declaration of 1975. An ethical committee approved the study (R.S. 36/09). Written and signed informed consent was obtained from all participants. In total, 8 patients were enrolled in the study (5 women and 3 men aged 45–65 years).

Before the treatment (baseline, T0), the severity of wrinkles in each patient was scored by a dermatologist with 15 years’ clinical experience involved in the study, using the Wrinkle Severity Rating Scale (WSRS)5 (Table I). All patients were rated on the Global Aesthetic Improvement Scale (GAIS)6 (Table II). Neck fine lines and wrinkle depths were captured by photographic digital technology. Photographs of the neck area of each patient were taken by a dermatologist not involved in the study and filed in a database. At baseline and at study end for each patient, silicone rubber microrelief impressions of a selected neck region were obtained and used to make computerized digital images and for optical profilometry. Furthermore, at the beginning and end of the treatment, skin ultrasonography was performed on the patient in the same spot from which the replica was taken. The second treatment (T1) was conducted 8 weeks after the first treatment and given in the same manner as the first treatment. A final follow-up visit was conducted 32 weeks after the second treatment (T2). Photographs were taken and compared with those taken before the first treatment. Each patient was given a new WSRS score and GAIS rating. In addition, we assessed the improvements induced by skin needling on neck wrinkles after two sessions of treatment. At this follow-up visit, a second skin replica was made on the same spot as the previous one and...
areas affected by wrinkles. Rolling entails moving 4 times in 4 directions (horizontally, vertically, and diagonally right and left) and, where not possible, just in 2 directions (horizontally and vertically). This ensures an even “pricking” pattern, which results in about 250 to 300 pricks/cm². Bleeding for a short time is expected after the treatment. When the bleeding has stopped, the serous ooze formed is removed from the skin surface with a sterile saline solution. Further wound treatment is not necessary and no dressing or topicals were used post-needling.

A week later, each patient was examined to gauge their response to skin needling and to determine any side effects that may have occurred.

### Statistical Analysis

Digital photographic data were analyzed using a test for non-parametric data (sign test for paired data). The null (H₀) is that the median of the difference is zero (P⁺ = P⁻) and the alternative hypotheses (H₁) is that the median of the differences is negative (P⁺ < P⁻), α = 0.05. The result is given by computing the binomial probability.

### Skin Replica and Image Analysis

The acquisition of skin casts was carried out using a stereomicroscope connected to an analog video camera.

The morphometric study of skin surface makes it possible to evaluate the surface’s irregularity (skin surface texture) and to determine any variation caused by the treatment. The microrelief’s irregularity degree was determined by studying the Fourier spectrum (Fast Fourier Transform) on skin cast images. In detail, using special software to process the skin texture’s images, makes it possible to evaluate the average values of “grey” obtained along the X axis and Y axis; the estimated indexes, IS1ox and IS1oy (Irregular Skin Index of ox-axis and oy-axis), are the integrals of areas bounded by the curves resulting from the pixels’ distribution along the X and Y axes.

Image processing was carried out by computerized image analysis. The skin casts are subjected to light at a 45-degree angle to create shadows along the ridges (= negative image of wrinkles). The shadows are converted into a gray scale, whose intensity is directly proportional to the shadows’ intensity and to the wrinkle depth. Once the images are displayed on the screen and the area to be studied is identified for each patient, the pixel-by-pixel definition of a series of lines (scanning) that perpendicularly pass through this area is initiated. The average intensity of gray for each pixel in the intercepted area is obtained. To achieve reproducible scanning (uncertainty level <13), care must be taken in obtaining the skin casts. The uncertainty is calculated in accordance with EN45001 rules. The following profilometric

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**Table I. Wrinkle Severity Rating Scale**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>5</td>
<td>Deep: Extremely deep wrinkles and folds, and visible V-shaped folds when stretched</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Very long and deep folds prominent facial features; &lt;2-mm visible folds when stretched</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Moderately deep folds; clear facial features visible at normal appearance but not when stretched</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Shallow to deep folds with a slight indentation; minor facial features</td>
</tr>
<tr>
<td>1</td>
<td>Absent: No visible folds; continuous skin line</td>
</tr>
</tbody>
</table>

**Table II. Global Aesthetic Improvement Scale**

<table>
<thead>
<tr>
<th>RATING</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much improved</td>
<td>Optimal cosmetic result for needling in this patient</td>
</tr>
<tr>
<td>Much improved</td>
<td>Marked improvement in appearance from initial condition, but not optimally so for this patient</td>
</tr>
<tr>
<td>Improved</td>
<td>Obvious improvement in appearance from the initial condition, but retreatment indicated</td>
</tr>
<tr>
<td>No change</td>
<td>Appearance essentially the same as the original condition</td>
</tr>
<tr>
<td>Worse</td>
<td>Appearance worse than the original condition</td>
</tr>
</tbody>
</table>

analyzed using optical profilometry and compared with those of the first treatment, and we assessed the degree of irregularity in the casts by means of computerized image analysis. To evaluate changes in the dermis induced by the treatment, skin ultrasonography was performed in the same spot from which the replica was taken for each patient.

Each patient was treated with a topical product containing α-omega hydroxyl acids, omega hydroxyl acids, enoxolone, and zinc for 3 weeks (preparation phase) before skin needling was started.

Each patient was prepared in a manner similar to a surgical procedure: the neck skin was disinfected and a topical anesthetic (eutectic mixture of local anesthetics) was applied for 60 minutes. Each area was treated with a highly specific tool (Dermaroller MF8; Dermaroller LLC, Thousand Oaks, CA): a 20-mm wide rolling barrel equipped with 192 needles in 8 rows. The needles used have a length of 1.5 mm and a diameter of 0.25 mm. According to the pressure applied, the needles penetrate the skin to between 0.1 mm and 1.5 mm. The diameter at maximum penetration level is 0.07 mm. The special tool is rolled over the skin in a grid pattern to a depth of 0.07–0.1 mm.
parameters are calculated: $R_a$ (average roughness), which is the arithmetic mean in absolute value of all variations of the mean; $R_t$, which is the maximum depth of the wrinkles in the considered area; $R_z$, which is the average depth of the wrinkles; $R_{max}$, which is the maximum height of the filtered profile; and $R_{min}$, which is the minimum height of the filtered profile.

**SKIN ULTRASONOGRAPHY**

Skin ultrasonography was carried out using Voluson-E SRT6, a 12- to 16-MHz ultrasound system (GE Healthcare, Waukesha, WI). The ultrasonic wave is partially reflected at the boundary between adjacent structures and generates echoes of different amplitudes: the intensity of reflected echoes (echogenicity) is evaluated by a microprocessor and visualized as a 2-dimensional image. The water-filled tank with the transducer is closed by a membrane and attached on the skin surface with a layer of gel. The axis of the probe is taken strictly perpendicular to the surface of the skin. We then measure the neck wrinkles. The thickness of the gel layer is adjusted to a horizontal position at 22 dB. The thickness of the dermis is determined in the B mode, excluding the hyperechogenic entrance echo and the hypoechogenic subcutis. Echogenicity (the average amplitude of the echoes in a defined area of the image) is determined in a region of interest. In a chosen area, including the whole dermis, the amplitudes of the echoes of the single image elements (pixels) is ascribed to a numerical scale. Values are given without dimension.

Ultrasonic measurements were performed by the same investigator under constant environmental conditions in each treatment.

**RESULTS**

The results achieved after two sessions of treatment were assessed. After each session, the neck skin appeared reddened and swollen, but the redness and swelling disappeared in 2 or 3 days as noted by the patients. No side effects were reported.

At the end of the study, the photographic comparison and the analysis of the WSRS scores, shown in Table III, highlighted that in almost all patients, the relative wrinkle depth was significantly reduced ($P<.05$). According to GAIS, 1 patient was very much improved, 3 patients were much improved, 3 patients were improved, and 1 patient showed no improvement.

Analysis of the surface microrelief from skin replicas showed a reduction in the degree of irregularity of skin texture in almost all the patients, with an average reduction of 29% in both axes. Wrinkle image processing showed a significant reduction in the average roughness and the maximum depth of the wrinkles in the considered area with respect to the basal corresponding to 24% for the average roughness and to 31% for the maximum depth of the wrinkles. Additionally, a clinically relevant increase in the minimum height of the filtered profile was estimated at $R_a$ equal to 23%. With regard to the average depth of wrinkles and the maximum height of the filtered profile, the profilometric evaluation did not show significant variations compared with baseline (Figure 1 and Figure 2).

The neck ultrasonic images showed first epidermis as a hyper-echogenic band (white area); under this zone, two poor echo bands (black areas), representing superficial dermis and deep

![Figure 1. Cutaneous replica at T₀ (before skin needling).](image)
dermis, respectively, were picked out. Adipose layer was displayed under deep dermis as a thick hypoechogenic band within hyperechogenic streaks. Epidermal thickness was measured from the first white band to the first black band; dermal thickness was measured from the first black band to the second white band. After these measurements, we determined the thickness of the whole epidermis and dermis layers, from the first white band to the second white band. We compared T0 echo images with T3 echo images and emphasized that the whole epidermal and dermal thickness was increased as shown in Figure 3 and Figure 4. This increase represents a skin texture improvement. In particular, we observed a statistically significant (P<.005) increase in dermal thickness in all patients with an average value of 0.45 mm, comparing the ultrasonic images before and 32 weeks after the treatment, as reported in Table IV.

### DISCUSSION

Our results demonstrate the effectiveness of skin needling in the treatment of the aging neck. We conclude our findings are not related to the topical chemical treatments used, even if each patient was treated with a topical product containing α-omega hydroxyl acids, omega hydroxyl acids, enoxolone, and zinc for 3 weeks before skin needling was started. The reason to believe that our findings can be considered as true in the absence of controls and not related to the topical chemical treatments is based on previous studies. These studies demonstrated that α-omega hydroxyl acids, omega hydroxyl acids, enoxolone, and zinc are not able to produce results such as we have observed during our study.~8,9~

Needling efficacy depends on its capacity to induce and, then, strongly stimulate the neo-collagenogenesis process and the normal wound healing process developing in 3 phases (inflammation, proliferation, and remodeling).~10,11~ The inflammation...
Table IV. Skin Ultrasonography Data

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>DERMAL THICKNESS AT T₀ (BEFORE NEEDLING), MM</th>
<th>DERMAL THICKNESS AT T₃ (32 WEEKS AFTER NEEDLING), MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>0.18</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>0.16</td>
<td>0.21</td>
</tr>
<tr>
<td>6</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>7</td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>8</td>
<td>0.13</td>
<td>0.20</td>
</tr>
<tr>
<td>Average</td>
<td>0.135</td>
<td>0.197</td>
</tr>
</tbody>
</table>

P<.05

phase starts soon after the injury: platelets, once activated, release chemotactic factors, which cause an invasion of other platelets, neutrophils, and fibroblasts. During the proliferative phase, neutrophils are replaced by monocytes that change into macrophages and release several growth factors including platelet-derived growth factor, fibroblast growth factors, transforming growth factor (TGF) α. and TGF-β, which stimulate the migration and proliferation of fibroblasts. They start producing all the components to reestablish the basement membrane with laminin and collagen, especially collagen type III. Finally, the remodeling phase starts and continues for several months: collagen type III is laid down in the upper dermis, just below the basal layer of the epidermis, and is gradually replaced by collagen type I.¹²

CONCLUSIONS

Our preliminary study suggests that skin needling may be an effective and safe treatment for the aging neck. In particular, skin needling in the aging neck has undisputable advantages compared with conventional methods of therapy. The most important is that the epidermis remains intact, eliminating most of the risks and negative side effects of chemical peeling or laser resurfacing.

REFERENCES


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In 1934, Astwazaturow took “notalgia” from the Greek “notos” and “algos” meaning “back” and “pain,” respectively, to describe a skin disorder combining pain and hypoesthesia.1–3 Notalgia paresthetica (NP) is currently considered a sensitive neuropathy restricted to the upper portion of the back, affecting the posterior rami of the spinal nerves of the dorsal segments T2 through T6.3 Brachioradial pruritus (affecting the dorsal cutaneous antebrachii nerve), meralgia paresthetica (lateral femoral cutaneous nerve), gonyalgia paresthetica (infrapatellar branch of saphenous nerve of foot), cheiralgia paresthetica (superficial branch of radial nerve), digitalgia paresthetica (digital nerve), thoracolumbar radiculopathy (radicular nerves), intercostal neuropathy (radicular nerves), and incisura scapulae syndrome (suprascapular nerve) are other well-known sensory mononeuropathies.3,4

GENERAL FEATURES

Since the first descriptions of NP, different authors have coined other terms (Table I) to describe similar clinicohistopathologic pictures.1,5,7,8 The possible relation among NP, macular amyloidosis (MA), and macular posterior pigmented incontinence (MPPI) is not currently clear. Some authors state that NP and MA are two different and independent conditions,6,8,9 while others suggest a probable overlap.2

The term macular posterior pigmentary incontinence was proposed to describe a group of patients showing pruritic pigmented macules in their back with no dermal amyloid deposits. The relation among NP, MA, and MPPI was discussed, but no clear differential definitions of these three entities or information on radiologic or neurologic studies performed were provided.6 In view of the data available to date, it seems probable that NP and MPPI are the same entity.

Histopathology is necessary to distinguish between NP and MA. The former shows unspecific findings including mild hyperkeratosis, pigmentary incontinence, a mild inflammatory infiltrate in the papillary dermis, and necrotic keratinocytes to a variable amount.4,10 These features may also be seen in MPPI. MA shows deposits of amyloid in the dermal papillae, which are not present in NP; however, there is no consensus on the presence of amyloid in NP, since it has been found in some patients with NP.11 Detection of dermal amyloid deposits can be difficult, as they are sometimes scarce and may go unnoticed.11 It is, therefore, probable that many of the patients diagnosed with NP would show amyloid deposits, if studied with more sensible histopathology methods.

A skin biopsy is also helpful in differentiating NP from other cutaneous disorders, including tinea versicolor, tinea corporis, neurodermatitis, parapsoriasis, contact dermatitis, cutaneous amyloidosis, fixed-drug eruption, leprosy, and postinflammatory hyperpigmentation.
PHYSIOPATHOLOGY OF NP

The exact cause of NP is still unknown, but localized trauma and spinal nerve impingement have been suggested to be the principal predisposing and etiologic factors9,12,13 (Table II).

The spinal nerves that branch out from the spinal cord in the dorsal segments (T2–T6) follow a right-angle course through the spinal muscles, making them more sensitive to mechanical trauma or entrapment by muscles.3,14

Spinal pathologies were present in the majority of patients studied, principally degenerative changes, disk herniation, and scoliosis. Cervical fibrous bands, muscle spasm, injury to the long thoracic nerve, or the cervical roots C5–C7 with serratus anterior dysfunction, dysfunction of other scapular stabilizers (rhomboid, trapezius), and injury to other nerves that stabilize the scapula such as the spinal accessory nerve may also contribute to the development of NP.9,14

Underlying individual predisposing factors might also play a role in the pathogenesis of NP.3

An association with multiple endocrine neoplasia type 2A in hereditary NP has been suggested in the literature.2,3 This association has also been described in patients with cutaneous amyloidoses.15

Some precipitating factors have been anecdotally reported to promote the development of NP, including saccharin intake, psychological trauma, vaccination, prolonged bed rest, gastroesophageal reflux,3 and sunburn reaction.6

The pruritus in patients with NP may be caused directly by compression of the unmyelinated C fibers (responsible for the transmission of itch and pain)16 or indirectly by mast cell degranulation secondary to substance P release.17 Relevant qualitative or quantitative changes in the cutaneous innervation of the affected area in NP are not constant.12,18–20

The skin hyperpigmentation might be the result of chronic rubbing and scratching.17 The latter has been suggested as a mechanical stimulus that might induce the apoptosis of the basal keratinocytes and subsequent amyloid K deposition21; however, a consensus as to whether amyloid deposition might be a primary feature or the consequence of the chronic rubbing has still not been reached.

CLINICAL PICTURE

NP may manifest with neuropathic itch, pain, paresthesias, tingling, burning, and hypoesthesia/hyperesthesia.22 One or more (Figures 1–3) ill-defined hyperpigmented macules can be seen in the affected area (unilaterally or bilaterally), but they are not always present.4,9 A reticulated pattern similar to that seen in MA, scaling, lichenification,9 and excoriations can sometimes be observed.

The symptoms typically appear affecting the T2–T6 dorsal segments in the patient’s back (interscapular, subcapsular, and dorsal paravertebral regions). Affectation of lower regions has been described in some patients,1 but these cases are probably thoracolumbar radiculopathies or intercostal neuropathies rather than true NP.

Table I. Notalgia Paresthetica and Clinically Similar Disorders1,5,6

<table>
<thead>
<tr>
<th>NOMENCLATURE OF DISORDERS MANIFESTING WITH PRURITUS AND A BROWNISH MACULA IN THE PATIENT’S BACK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notalgia paresthetica</td>
</tr>
<tr>
<td>Friction melanosis</td>
</tr>
<tr>
<td>Towel melanosis</td>
</tr>
<tr>
<td>Nylon clothes friction melanosis</td>
</tr>
<tr>
<td>Macular posterior pigmented incontinence</td>
</tr>
<tr>
<td>Puzzling posterior pigmented pruritic patches</td>
</tr>
<tr>
<td>Peculiar spotty pigmentation</td>
</tr>
<tr>
<td>Localized shoulder pruritus</td>
</tr>
<tr>
<td>Localized pigmentation</td>
</tr>
<tr>
<td>Macular amyloidosis</td>
</tr>
<tr>
<td>Friction amyloidosis</td>
</tr>
<tr>
<td>Cutaneous dorsal amyloidosis</td>
</tr>
</tbody>
</table>

Table II. Factors That Play a Role in the Pathogenesis of Notalgia Paresthetica2,3,6,9,12–14

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>OBSERVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized trauma, spinal nerve impingement</td>
<td>Disk herniation</td>
</tr>
<tr>
<td></td>
<td>Muscle contractures</td>
</tr>
<tr>
<td></td>
<td>Fibrous bands</td>
</tr>
<tr>
<td></td>
<td>Vertebral arthrosis</td>
</tr>
<tr>
<td></td>
<td>Spinal stenosis</td>
</tr>
<tr>
<td></td>
<td>Scoliosis</td>
</tr>
<tr>
<td></td>
<td>Spinal tumours</td>
</tr>
<tr>
<td></td>
<td>Dysfunction of scapular stabilizer muscles</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>Familial cases</td>
</tr>
<tr>
<td></td>
<td>Young patients</td>
</tr>
<tr>
<td></td>
<td>Association with multiple endocrine neoplasia 2A</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td>Individual factors (not yet identified)</td>
</tr>
<tr>
<td></td>
<td>Saccharin intake</td>
</tr>
<tr>
<td></td>
<td>Psychological trauma</td>
</tr>
<tr>
<td></td>
<td>Vaccination</td>
</tr>
<tr>
<td></td>
<td>Prolonged bed rest</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td></td>
<td>Sunburn reaction</td>
</tr>
</tbody>
</table>
Women are more frequently affected than men. The sex ratio can be as high as 9:1 (personal observation) but it is usually around 2 to 3:1. The median age of onset is around 54 to 62 years, but it may be much earlier in hereditary cases. No racial differences have been detected.

**MANAGEMENT AND TREATMENT**

The evaluation of a patient with suspicion of NP is usually an interdisciplinary process that may require assessment by different specialists (dermatologists, neurologists, orthopedic surgeons, neurosurgeons). The recommended work-up in patients with suspicion of NP is summarized in Table III.

The treatment of NP is still a challenge for clinicians. Different therapeutic alternatives have been used (Table IV), most of which only provide transient benefits.

Topical corticosteroids have shown little benefit in patients with NP. Topical capsaicin (0.025% and 0.075% cream) is known to decrease pain levels.

### Table III. Recommended Work-Up in Patients With Notalgia Paresthetica

<table>
<thead>
<tr>
<th>PROCEDURES</th>
<th>OBSERVATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed anamnesis</td>
<td>Inquire about history of osteoarthritis, vertebral trauma, vehicle accident, vertebral malignancy, sports, surgical procedures in the affected area, familial cases</td>
</tr>
<tr>
<td>Dermatologic examination</td>
<td>Location and affected dermatomes Size and number of the macules Associated findings: lichenification, excoriations, scaling Severity of the symptoms (VAS score)</td>
</tr>
<tr>
<td>Neurologic examination</td>
<td>Sensitivity, sweat test, motor function</td>
</tr>
<tr>
<td>Complementary tests</td>
<td></td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>Hematoxylin-eosin Search for dermal amyloid deposits (Congo Red, crystal violet, thioflavine T, CK monoclonal antibodies, electronic microscopy)</td>
</tr>
<tr>
<td>EMG</td>
<td>It may be normal or reveal neuropathy</td>
</tr>
<tr>
<td>Blood analysis</td>
<td>Complete blood count Blood biochemistry</td>
</tr>
<tr>
<td></td>
<td>In hereditary cases/young patients: serial blood to determine calcitonine levels and screening for medullary thyroid carcinoma</td>
</tr>
<tr>
<td>Image tests</td>
<td>Anteroposterior and lateral entire column x-ray MRI (if possible or if doubtful or inconclusive findings in x-ray)</td>
</tr>
</tbody>
</table>

Abbreviations: CK, cytokeratin; EMG, electromyography; MRI, magnetic resonance imaging; VAS, visual analog scale.
to deplete C fibers of their neuropeptides. It has been successfully used to control pruritus, but the symptoms relapse shortly after the treatment has been stopped.23,24 The most common side effect is a burning sensation on the treated areas, which disappears with repeat applications.

Topical anesthetics (pramocaine, 2.5% lignocaine and 2.5% prilocaine cream)25 have also induced partial relief and control of the symptoms, but relapse after withdrawal is common.

A topical formulation of 1% naltrexone has shown a significant reduction of the pruritus in more than 70% of patients with different itchy skin disorders treated in one study,26 and thus could be an interesting topical option to test in patients with NP.

Oxcarbazepine is an analog of carbamazepine that possibly acts by decreasing repetitive charges, blocking membrane sodium currents, and increasing the firing threshold in Aδ fibers. Partial relief of the pain and pruritus was observed in a group of patients with NP treated with oral oxcarbazepine for 6 months.27 Dizziness, headache, and gastric upset may be seen in some patients at the beginning of the treatment and resolve with withdrawal of the drug.

Table IV. Therapeutic Alternatives for the Treatment of Notalgia Paresthetica

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td>Corticoids1</td>
<td></td>
</tr>
<tr>
<td>Capsaicin23,24 0.025%, 0.075% cream</td>
<td></td>
</tr>
<tr>
<td>Anesthetics25 Lidocaine plus prilocaine cream</td>
<td></td>
</tr>
<tr>
<td>Intraleisional</td>
<td></td>
</tr>
<tr>
<td>Intradermal botulinum toxin A42 4 UI injected in the selected points, 2 cm apart</td>
<td></td>
</tr>
<tr>
<td>Corticoids9 Triamcinolone: 2.5 mg/mL</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine26 Initial dose: 300 mg bid Increase: 600 mg bid or 900 mg bid, according to the benefits achieved</td>
<td></td>
</tr>
<tr>
<td>Gabapentin24–30 Initial dose: 100–300 mg at bedtime Increase: 100–300 mg tid Maximum: 3600 mg/d Reduce if renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Pregabalin28 Initial dose: 50 mg tid or 75 mg bid Increase by 150 mg every 3–7 d Maximum dose: 600 mg/d Reduce if renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>TENS33 5 sessions a wk for 2 wk 50–100 Hz TENS applications of 20-min duration, pulse width 40–75 μs</td>
<td></td>
</tr>
<tr>
<td>EMS44 30 s on and 30 s off for 15 min bid 70 Hz with a pulse width of 300 μs</td>
<td></td>
</tr>
<tr>
<td>Paravertebral anesthetic block31 Bupivacaine 0.75% plus 40 mg of methylprednisolone</td>
<td></td>
</tr>
<tr>
<td>Surgical8 Surgical decompression, discectomy</td>
<td></td>
</tr>
<tr>
<td>Narrow band UV-B35 3 sessions per wk, following a phototype protocol Mean: 32.8 sessions</td>
<td></td>
</tr>
<tr>
<td>Osteopathic manipulative treatment34 Suboccipital decompression, inhibition and soft tissue techniques, rib raising and scapulothoracic fascial release 20-min session</td>
<td></td>
</tr>
<tr>
<td>Other alternatives1,13,16 Acupuncture, massage, multimodal physiotherapy, nonsteroidal anti-inflammatory drugs, antidepressants (selective serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants), oral muscle relaxants</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice a day; EMS, electrical muscle stimulation; TENS, transcutaneous electrical nerve stimulation; tid, three times a day.
Gabapentin and pregabalin bind to the α, δ subunits of the voltage-gated calcium channel and block neurotransmitter release. Resolution of the symptoms was observed with oral gabapentin (100–300 mg at bedtime; increase by 100–300 mg 3 times daily, to a maximum of 3600 mg/d). Pregabalin is used in the treatment of neuropathic pain and might also be useful in NP. Both gabapentin and pregabalin must be used carefully in patients with renal insufficiency.

Narrow-band UV-B also appears to be an effective, safe, and very long-term benefits are available. A local paravertebral block with bupivacaine (0.75%) and 40 mg of methylprednisolone acetate cleared the pruritus in one patient. One year after the procedure, the patient was symptom-free.

Resolution of pruritus and a decrease in hyperpigmentation was obtained in 2 women who received intradermal injections of botulinum toxin type A.

Transcutaneous electrical nerve stimulation (TENS) is a simple and safe therapy that consists of the application of electrical stimulation to the skin for pain control. It has been reported to partially relieve pruritus in a group of 15 patients with NP who received 10 high-frequency 20-minute applications. Five of the patients also received hot pack administration and an additional 20-minute cervical traction prior to TENS application.

Transcutaneous electrical muscle stimulation (EMS) of the serratus anterior muscle seems to be useful in patients with long thoracic nerve injury and has been proposed as a long-acting and effective treatment for NP.

Osteopathic manipulative treatment is another alternative that has shown benefit in patients with NP; however, no data about long-term benefits are available.

Narrow-band UV-B also appears to be an effective, safe, and very well-tolerated alternative treatment for NP, as shown in a recently published small series of 5 patients. The doses were administered following a phototype protocol in a UV 7002 cabinet (Waldmann, Herbert Waldmann GmbH & Co, Schwenningen, Germany). A significant improvement in the pruritus was achieved after a mean of 32.8 sessions and a mean cumulative dose of 33.76 J/cm².

Other therapies including surgical procedures, acupuncture, multimodal physiotherapy (radar, short waves, infrared and ultrasound physiotherapy), spinal manipulation, nonsteroidal anti-inflammatory drugs, antidepressants (selective serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants), and oral muscle relaxants may also be effective.

A therapeutic protocol for NP is not yet available and because results in only a small series of patients have been reported, it is quite difficult to offer a definitive approach. Patients must be informed of the possible options, and treatment can then be selected according to their individual picture and condition. The steps of a reasonable therapeutic approach might be as follows:

1. start with topical measures;
2. addition of oral antihistamines (sedative H1 or/plus non sedative H1 antihistamines);
3. change to oral oxcarbazepine/gabapentin/pregabalin or physiotherapy or osteopathic manipulative treatment or phototherapy;
4. TENS/EMS;
5. intradermal botulinum toxin;
6. paravertebral block; or
7. other measures including surgery or acupuncture. Combination of several different alternatives is also possible.

Although NP is not a rare disorder in medical practice, only a small series of patients and anecdotal cases have been reported in the literature to date.

The underreporting of this entity may have something to do with the fact that (1) a great number of patients do not consult their physician when they have symptoms, and (2) many cases are considered irrelevant or benign by primary care physicians and patients are not subsequently referred for assessment to a specialist. The diagnosis is easily established on clinical grounds and is reinforced with the histopathologic and radiologic findings; however, misdiagnosis may be a problem when physicians are not aware of the typical features.

CONCLUSIONS

NP may be a cutaneous sign of an underlying spine disease. Dermatologists and other physicians should recognize the disease in order to conduct a proper work-up and assign treatment, which may restore their patient’s quality of life to some degree.

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) Meralgia paresthetica affects the: (Choose the single best response.)
   a. digital nerve.
   b. dorsal cutaneous antebrachial nerve.
   c. infrapatellar branch of the saphenous nerve.
   d. lateral femoral cutaneous nerve.
   e. radicular nerves.

2) Notalgia paresthetica may manifest with: (Answer as many as apply.)
   a. burning.
   b. hypoesthesia/hyperesthesia.
   c. itch (pruritus).
   d. paresthesias.
   e. tingling.

3) Which of the following histological characteristics is least characteristic of notalgia paresthetica? (Choose the single best response.)
   a. Amyloid in the papillary dermis
   b. Hyperkeratosis
   c. Inflammatory infiltrate in the papillary dermis
   d. Necrotic keratinocytes
   e. Pigment incontinence

4) The clinical relevance of notalgia paresthetica is that it may be a cutaneous sign of an underlying: (Choose the single best response.)
   a. blood dyscrasia.
   b. congestive heart failure.
   c. diabetes mellitus.
   d. kidney failure.
   e. spine disease.

5) Appropriate treatment strategies for notalgia paresthetica may include: (Answer as many as apply.)
   a. intradermal botulinum toxin.
   b. oral antihistamines.
   c. oral oxcarbazepine/gabapentin/pregabalin.
   d. surgery.
   e. transcutaneous electrical nerve stimulation.

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

1) d; 2) a, b, c, d, e; 3) a; 4) e; 5) a, b, c, d, e

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Nicotinamide in Dermatology and Photoprotection

Devita Surjana, MBBS;1 Diona L. Damian, MBBS, PhD1,2

ABSTRACT

Nicotinamide (the amide form of vitamin B3) has been used in dermatology for more than 40 years for a diverse range of conditions including acne, rosacea, autoimmune bullous dermatoses, and now the treatment and prevention of photoaging and photoimmunosuppression. The broad clinical effects of nicotinamide may be explained by its role as a cellular energy precursor, a modulator of inflammatory cytokines, and an inhibitor of the nuclear enzyme poly(adenosine diphosphate-ribose) polymerase-1, which plays a significant role in DNA repair, maintenance of genomic stability, and cellular response to injury including inflammation and apoptosis. This review outlines the use of nicotinamide for inflammatory dermatoses and photoaging and focuses on its emerging role in photoprotection. (SKINmed. 2011;9:360–365)

Nicotinamide (niacinamide), an amide form of vitamin B3 (niacin or nicotinic acid) (Figure 1), is widely available in foods such as yeast, meats, liver, legumes, cereals, green leafy vegetables, milk, fish, coffee, and tea.1 Nicotinamide is also used in food fortification and is widely available as a nutritional supplement at doses of 20 mg/d to 500 mg/d. The adult recommended daily allowance for niacin (nicotinamide equivalent from food sources) is approximately 15 mg.2 The amino acid tryptophan, which constitutes approximately 1% of dietary protein, can also be converted into niacin in the liver, with 60 mg of tryptophan equivalent to approximately 1 mg of niacin.1 Excess nicotinamide is metabolized in the liver. Metabolites are renally excreted and can be measured in urine to diagnose nicotinamide deficiency.

NICOTINAMIDE DOSAGE AND SAFETY PROFILE

Nicotinamide has a high safety profile and is generally well tolerated at doses of 1 g/d to 3 g/d.1 Higher doses, up to 3.5 g/d, have been well tolerated in trials of type 1 diabetes prevention.3 Potential side effects, including nausea, vomiting, heartburn, headache, and fatigue, are rare even with these high doses.4 Unlike niacin, nicotinamide is not a vasodilator, and does not cause flushing or alteration in blood pressure, pulse rate, or body temperature.5 Nicotinamide does cross the placenta but is not teratogenic in mice6 and there is no reported teratogenicity in humans.5 Lifelong administration of 1% nicotinamide in drinking water (300-fold above requirements) is not carcinogenic in animals,7 with no evidence of carcinogenicity in humans.4 Because nicotinamide is an inhibitor of P450 enzymes, it may decrease carbamazepine clearance,8 although its interactions with other drugs and oral contraceptives have not been reported. Nicotinamide is used in a variety of cosmetic formulations at concentrations of 0.0001% to 3%, without evidence of skin irritation, sensitization, or photosensitization.6

CELLULAR FUNCTIONS OF NICOTINAMIDE

Nicotinamide is the main dietary precursor for nicotinamide adenine dinucleotide (NAD) synthesis, an essential coenzyme in oxidation/reduction reactions for the production of cellular energy, adenosine triphosphate (ATP). Cellular NAD content determines p53 expression and malignant phenotype in human skin cancers.9 The role of NAD in carcinogenesis is tightly linked to the nuclear enzyme, poly(adenosine diphosphate[ADP]-ribose) polymerase 1 (PARP-1), which catalyses cleavage of NAD into nicotinamide and ADP ribose.10 Poly(ADP)ribosylation of nuclear proteins has been implicated in chromatin remodelling, DNA repair, and transcriptional regulation to maintain genomic stability.10 PARP-1 has been shown to control cell replication and telomerase activity, which is increasingly recognized to be involved in regulation of cellular senescence, aging, and cancer.10 PARP-1 also plays a key role in nuclear factor-κB (NF-κB)–mediated expression of proinflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin (IL) 1β, IL-6, IL-8, and inflammatory
mediators including inducible nitric oxide synthase, intercellular adhesion molecule 1, major histocompatibility complex class II, and macrophage migration inhibition factor. Nicotinamide, which is an endogenous inhibitor of PARP-1, dose-dependently prevented the release of proinflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α in ex vivo human blood.

NICOTINAMIDE IN THE TREATMENT OF AUTOIMMUNE BLISTERING DISORDERS

Nicotinamide, as monotherapy or in combination with tetracycline, has been effective in the treatment of various inflammatory conditions, including granuloma annulare and erythema elevatum diutinum, but it is most frequently used as a steroid-sparing regimen in autoimmune blistering disorders. To date, there is only one open-labelled randomized trial comparing the efficacy of oral nicotinamide (1.5 g daily) plus tetracycline (2 g daily) with oral prednisone (40–80 mg/d) in 20 patients with bullous pemphigoid (BP), which showed that the combined therapy gave at least comparable efficacy. Although there are numerous case reports on the efficacy of combined oral nicotinamide and tetracycline in the treatment of BP, pemphigus, linear immunoglobulin A bullous dermatosis, lichen planus pemphigoides, dermatitis herpetiformis, and cicatricial pemphigoid (reviewed in Niren 2006), only one case report has claimed efficacy of oral nicotinamide as monotherapy (1.5 g/d) in a patient with localized BP. Topical nicotinamide may also be useful adjunctive therapy for pemphigus vulgaris. Eight pemphigus patients, all taking concomitant prednisone and azathioprine, were randomized to apply either 4% nicotinamide gel or vehicle gel once daily for 30 days. The percentage of the re-epithelialized area at day 30 was significantly greater with nicotinamide. Although the exact mechanisms of action of nicotinamide in these dermatoses are largely unknown, it does have inhibitory effects on the release of proinflammatory cytokines and neutrophil chemotaxis and may disrupt B-cell transformation from naïve to antibody-producing B cells.

NICOTINAMIDE FOR ACNE AND ROSACEA

A multicenter open-label cohort study of 198 patients with moderate to severe acne vulgaris and/or rosacea found that oral nicotinamide (1.5 g) given in combination with 50 mg of zinc and 1 mg of folic acid daily for 8 weeks significantly reduced inflammatory lesions compared with no treatment, and no added benefit of concomitant oral antibiotics was found. Randomized double-blinded studies in patients with inflammatory acne compared 4% nicotinamide gel with 1% clindamycin gel applied twice daily for 8 weeks. There was comparable efficacy in reducing inflammatory lesion counts, acne severity rating, and Physician’s Global Evaluation scale. A double-blinded randomized, controlled trial comparing 4% nicotinamide gel and 4% erythromycin gel (twice daily for 8 weeks) in 160 patients with inflammatory acne also found equivalent regression of inflammatory lesions and a greater decrease in cystic lesions and seborrheic scores in the nicotinamide arm.

Acne pathogenesis involves multiple factors including hyperkeratinization and reduced desquamation of follicular keratinocytes, leading to comedone formation, excess sebum production, inflammation, and Propionibacterium acnes. There is increasing evidence that keratinocytes and sebocytes within the pilosebaceous unit are able to recognize pathogens and be activated by P. acnes via toll-like receptors (TLRs) and CD14 and CD1 molecules, producing inflammatory cytokines in response to these stimuli. P. acnes activation of TLR-2 on the surface of keratinocytes, monocytes, and macrophages induces nuclear translocation of the transcription factor NF-κB, which then leads to the transcription of many immune response genes. In human keratinocytes, nicotinamide prevents P. acnes–induced activation of TLR-2 via inhibition of NF-κB and mitogen-activated protein kinase pathways, resulting in down-regulation of proinflammatory IL-8 production.

Nicotinamide may also inhibit sebaceous lipogenesis. In an ex vivo study of human skin, nicotinamide was shown to dose-dependently inhibit sebaceous triglyceride and fatty acid synthesis, which, in excess, are important contributors to acne pathogenesis. In a double-blind, placebo-controlled trial and a parallel, randomized split-face study, 2% nicotinamide gel reduced facial sebum production in 130 volunteers.

NICOTINAMIDE IMPROVES EPIDERMAL BARRIER FUNCTION

Topical nicotinamide, which has been investigated as a potential treatment for atopic dermatitis and dry skin associated with aging, has been shown to improve skin barrier function and

Figure 1. Both nicotinamide and niacin are water-soluble forms of vitamin B3. Nicotinamide is more stable in water and alcohol than niacin and is therefore more commonly used in topical preparations.
increase skin resistance to irritants such as sodium lauryl sulfate and dimethyl sulf oxide. In a right/left comparison study in 12 male volunteers with dry skin, 2% nicotinamide was evaluated against its vehicle. After twice-daily application of nicotinamide or vehicle for 4 weeks, transepidermal water loss (TEWL) was measured and the stratum corneum was stripped for lipid analysis. Nicotinamide reduced TEWL by 27% compared with its vehicle and increased stratum corneum free fatty acid and ceramide levels by 67% and 34%, respectively.

An in vitro study with human keratinocytes showed that nicotinamide dose-dependently increased ceramide and other sphingolipids by stimulating the activity and gene expression of serine palmitoyltransferase, the rate-limiting enzyme in de novo sphingolipid synthesis. Nicotinamide may also improve skin barrier function by increasing involucrin, filaggrin, and keratin. In 28 patients with atopic dermatitis, 2% nicotinamide cream was applied twice daily for 8 weeks, and TEWL and corneum barrier function and hydration as measured by TEWL and skin capacitance, respectively. An in vitro study with human keratinocytes provides further insight into the mechanism of nicotinamide prevention of TEWL. Aquaporin 3 (AQP3) mediates keratinocyte water transport, and in cultured human keratinocytes, nicotinamide treatment dose-dependently prevented retinoid-induced AQP3 overexpression.

TREATMENT OF PHOTOAGING

Topical nicotinamide at concentrations of 2% to 5% has been evaluated for the treatment of photoaging, characterized by fine lines and wrinkles, poor texture, and hyperpigmentation. In a split-face randomized, double-blinded, vehicle-controlled study of 50 women, 5% nicotinamide cream applied twice daily decreased facial erythema, dryness and peeling/scaling, and inflammatory lesion counts and significantly improved stratum corneum barrier function and hydration as measured by TEWL and skin capacitance, respectively.

An in vitro study with human HaCaT keratinocytes provides further insight into the mechanism of nicotinamide prevention of TEWL. Aquaporin 3 (AQP3) mediates keratinocyte water transport, and in cultured human keratinocytes, nicotinamide treatment dose-dependently prevented retinoid-induced AQP3 overexpression.

PROTECTION FROM PHOTOCARCINOGENESIS

Both UV-A (320–400 nm) and UV-B (290–320 nm) are complete carcinogens in that they are involved in the initiation, promotion, and progression of skin carcinogenesis. UV-B induces DNA adducts including cyclobutane pyrimidine dimers (CPDs) and (6–4) photoproducts in epidermal cells, whereas UV-A largely exerts its deleterious effects through reactive oxygen species–induced oxidative damage to DNA, proteins, and lipids.

In BALB/c mice treated with topical 2.5% nicotinamide or vehicle before chronic UV-B irradiation, tumor incidence (predominantly squamous cell carcinomas) was 75% with vehicle but only 43% with nicotinamide. Tumor numbers per mouse were also reduced by almost 50%. Supplementation with 0.1%, 0.5%, or 1% dietary niacin in mice irradiated with UV-B over 22 weeks dose-dependently decreased both tumor incidence (by 8%, 20%, and 40%, respectively) and tumor numbers (by 17%, 33%, and 44%).

NICOTINAMIDE PROTECTS FROM CELLULAR ENERGY LOSS DURING UV IRRADIATION

UV radiation depletes NAD levels and cellular energy in the skin. Cellular NAD content determines cell survival in UV-irradiated human fibroblasts, and addition of nicotinamide to the culture medium, which replenishes intracellular NAD, increases cell survival dose-dependently. We have also shown that in cultured human keratinocytes, nicotinamide prevented ATP depletion and reduction in glycolytic rate after UV irradiation.

NICOTINAMIDE, DNA REPAIR, AND MAINTENANCE OF GENOMIC STABILITY

In vitro studies with various human cell types have shown that nicotinamide enhances repair of irradiation or chemically induced DNA damage and that cultured human keratinocytes depleted of NAD showed increased DNA damage even without UV irradiation. Maintenance of adequate cellular energy is therefore critical in preserving genomic stability of skin cells. As well as its energy-replenishing effects, nicotinamide may enhance repair of UV-induced DNA damage by providing a substrate for PARP-1, which is activated by both CPDs and oxidative damage induced by UV-B irradiation, which triggers nuclear binding of PARP-1 and activates its catalytic activity and consumes NAD, forming nicotinamide and ADP-ribose polymers. Binding of the negatively charged ADP-ribose polymers...
to nuclear proteins has been suggested to loosen chromatin compact structure, which not only allows DNA regulatory and repair enzymes access to the damage sites, but also facilitates transcription of genes involved in cellular response to injury.10

In a negative feedback manner, nicotinamide also acts as a PARP-1 inhibitor.10 Excessive PARP-1 activation, for example, by high-dose UV irradiation, depletes cellular energy and leads to energy failure and necrotic cell death35 (Figure 2). Inhibition of PARP-1 overactivation by nicotinamide therefore serves as cellular damage control, preventing necrosis and preserving the remaining energy for DNA repair.

PROTECTION FROM PHOTOIMMUNE SUPPRESSION

Both UV-A and UV-B radiation are potent suppressors of skin immunity, which plays a critical role in preventing skin cancer progression, even at suberythemal doses corresponding to less than 6 minutes of noon summer sunlight.36 DNA damage, particularly CPDs, has been recognized as a key molecular trigger for UV-induced immunosuppression.30

In recent years, there has been growing interest in the use of naturally occurring, nontoxic compounds with immune-protective, anti-inflammatory, and antioxidant effects for protection against UV radiation. Nicotinamide was previously found to be immune protective in mice, when used topically or supplied in the diet.31,32 In humans, we have shown that both topical and oral nicotinamide prevent UV suppression of delayed-type hypersensitivity responses to intradermal tuberculin (Mantoux reactions). UV irradiation dose-dependently suppresses Mantoux-induced induration and erythema, and these measures can be used to assess UV immunosuppression.36–38 We irradiated the lower backs of 20 healthy Mantoux-positive volunteers with low-dose solar simulated (ss)UV, corresponding to approximately 0.35, 0.7, and 1 average minimal erythema doses (MEDs) for the group. Fifteen minutes before each of 3 daily ssUV exposures, 5% topical nicotinamide or its vehicle was applied to separate skin sites. Irradiation with the two highest UV doses significantly suppressed Mantoux-induced erythema and induration. At the sites of nicotinamide application, suppression of Mantoux responses no longer occurred. Nicotinamide was also immune protective when applied immediately after UV exposure, thus excluding the possibility of a sunsetting (UV filtering) effect of nicotinamide.37 Concentrations of nicotinamide as low as 0.2% were also protective against single or multiple UV irradiations.36 Using the same model, oral nicotinamide (500 mg or 1500 mg daily for 1 week) also protected against ssUV-induced suppression of Mantoux reactions.38 Despite preventing photoimmune suppression, nicotinamide does not prevent UV-induced erythema; it had no effect on MED when applied before or after irradiation.37 Nicotinamide protects against the immune suppressive effects of both UV-B and UV-A. We irradiated Mantoux-positive volunteers with narrowband UV-A (385 nm) or UV-B (300 nm), which both significantly reduced Mantoux reactions. Topical 5% nicotinamide appeared to provide equivalent immune protection from both wavebands36; hence, the broad-spectrum immune protection afforded by nicotinamide could complement the use of sunscreens, which tend to provide relatively less protection against longwave UV-A (and hence immune suppression)39 near the visible light interface.

FUTURE DIRECTIONS

We found photoprotective effects of nicotinamide in vitro and in vivo in healthy volunteers. Premalignant actinic keratoses (AKs) provide a useful surrogate measure of skin cancer to enable assessment of chemopreventive agents within relatively short timeframes. Recently, we conducted a double-blind placebo-controlled study in 26 heavily sun-damaged patients with multiple AKs randomized to apply either 1% topical nicotinamide or its vehicle to face, forearms, and scalp twice daily for 6 months. At 3 months, we found a significant reduction in AKs of 22% with nicotinamide, compared with a nonsignificant 10% reduction with vehicle. At 6 months, however, there was no longer a significant difference in AKs (22% reduction with vehicle vs 25% reduction with nicotinamide). Instead, seasonal regression of AKs was likely observed in both groups as participants moved from summer to winter.40

CONCLUSIONS

In this pilot study, nicotinamide appeared to enhance or accelerate the rate of AK regression, possibly by providing photoimmune protection during the summer and autumn months. Studies
using oral nicotinamide are now indicated. Nicotinamide is an inexpensive compound with a high safety profile. Given its significant photoprotective effects, nicotinamide is a promising agent for skin cancer chemoprevention.

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REFERENCES

7 Toth B. Lack of carcinogenicity of nicotinamide and isonicotinamide following lifelong administration to mice. Oncology. 1983;40:72–75.
22 Bissett D. Topical niacinamide and barrier enhancement. Cuts. 2002;70:8–12.
30 Halliday GM. Inflammation, gene mutation and photoinmunosuppression in response to UVR-induced oxidative damage contributes to photocarcinogenesis. Mutat Res. 2005;571:107–120.


**HISTORICAL DIAGNOSIS & TREATMENT**

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

(continued on page 376)
The power to calm inflammatory acne

- Inflammation is an important aspect in the pathophysiology of acne\(^1\)
- Both laboratory and clinical studies document the anti-inflammatory effects of minocycline\(^1\)

Complementary T\(^3\) Calming Wipes
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The power to eradicate \(P\) \(acnes\)

- Significant reduction in \(P\) \(acnes\) — even up to 3 weeks after discontinuation\(^2\)
- A decrease in \(P\) \(acnes\) can lead to a drop in pro-inflammatory cytokines and reduced inflammation\(^1\)
- Minimal resistance in an \textit{in vitro} study
  — The majority of tetracycline-resistant \(P\) \(acnes\) were cross-resistant to doxycycline — but sensitive to minocycline\(^*\)

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The most common adverse events associated with MINOCIN are nausea, vomiting, and diarrhea. CNS adverse effects may include dizziness, vertigo, and headache.

Important Information
The most common adverse events associated with MINOCIN are nausea, vomiting, and diarrhea. Central nervous system adverse events including light-headedness, dizziness, or vertigo have been reported with minocycline therapy, but are generally transient in nature. Other adverse events include tinnitus, headache, sedation, and skin pigmentation, particularly on the face and mucous membranes. MINOCIN is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or to any of the components of the product formulation. WARNING: MINOCIN Pellet-Filled Capsules, like other tetracycline-class antibiotics, can cause fetal harm when administered to a pregnant woman. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of teeth (yellow-gray-brown). Concurrent use of tetracyclines may render oral contraceptives less effective.


\(^*\)In vitro activity does not necessarily correlate to \textit{in vivo} activity.
Noninsulin-Dependent, Type II Diabetes Mellitus–Related Dermatoses: Part III
Virendra N. Sehgal, MD; Govind Srivastava, MD; Ashok K. Aggarwal, MD; Megha Gupta, MBBS; Sambit N. Bhattacharya, MD; Prashant Verma, MD

D iabetes mellitus (DM) related and/or associated dermatoses warrant periodic attention, and should be taken stock of both in insulin-dependent and noninsulin-dependent diabetes. Accordingly, the salient briefs of necrobiosis lipoidica (NL), and granuloma annulare (GA) formed the contents of Part I,1 while conditions like diabetic dermopathy, diabetic bullae, acquired perforating dermatosis (APD), diabetic thick skin, scleredema adultorum, eruptive xanthoma, carotenodermia (carotenemia/carotenosis), ruberosis faciei, and acanthosis nigricans (AN) are described in Part II.2 Whereas, insulin dependent diabetes mellitus (IDDM) type 1-related dermatoses form the subject matter of another exclusive dissertation. The current paper reviews the final part of this 3-part series.

Associated infectious bacterial diseases include impetigo, erysipelas, cellulitis, erythema, folliculitis, furuncles and carbuncles, necrotizing fasciitis, malignant otitis externa, erythrasma, and nonclostridial gas gangrene. Associated fungal infections include candidosis (including vulvovaginitis, paronychia, thrush, and balanitis), dermatophytoses, zygomycoses infections, and rhinocerebral mucormycosis. Associated inflammatory mucodermatoses include lichen planus (including oral lichen planus), other oral lesions, vitiligo, psoriasis, pigmented purpuric dermatosis, bullous pemphigoid, dermatitis herpetiformis, and other pruritic dermatoses. Associated metabolic/genetic associations include cutaneous porphyrias and lipoid proteinosis. Nail changes include onychomycosis, bacterial infections, Beau’s lines, onychauxis, pterygium, onychogryphosis, yellow nails, vascular changes, Rosenthal’s depression, onychomadesis, and leukonychia. Cutaneous and diabetic therapy, including insulin, are also reviewed.

CUTANEOUS INFECTIONS
Skin infections occur in 20% to 75% of diabetic patients. They are more frequently seen in noninsulin dependent, type II diabetes mellitus (NIDDM) and are classically associated with poor blood glucose control. The infectious lesions may be either fungal or bacterial; however, the former are more common.3 The lesions may be a precursor of diabetes and should prompt investigation for possible occult, early, or insulin-resistant DM.3

BACTERIAL INFECTIONS
The most common bacterial infections of the skin in diabetic patients are often caused by Staphylococcus aureus and beta-hemolytic Streptococcus. They include impetigo, erysipelas, cellulitis, erythema, folliculitis, furuncles, and carbuncles.6 Increased rates of nasal colonization by staphylococci have been reported in diabetics, especially in patients with poor metabolic control.7 Secondary infection of a leg ulcer can culminate in gangrene and amputation.8

NECROTIZING FASCIITIS
Approximately 10% to 60% of all cases of necrotizing fasciitis occur in patients with DM. It is a bacterial infection of soft tissue that spreads along fascial planes. The causative organisms are facultative gram-negative bacilli such as Escherichia coli and anaerobes such as bacteroides, peptostreptococcus, and clostridium species. The perineum, trunk, abdomen, and upper extremities are commonly involved. The clinical presentation is characterized by erythema, swelling, induration, and necrosis of the affected area. There is a high degree of pain and toxicity associated with necrotizing fasciitis.8 Treatment includes urgent abscess drainage, surgical debridement, and appropriate antibiotics.9

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MALIGNANT OTITIS EXTERNA
Malignant otitis externa is an uncommon but serious infection of the external ear canal that is caused most commonly by *Pseudomonas aeruginosa*. It apparently begins after minor trauma in the external auditory canal, mostly in elderly diabetics. Through the natural cleavage of the external auditory canal, pseudomonas gains access to deeper tissues, invades the cartilage, and ultimately reaches the bone. Diabetic patients are more susceptible, either because of the presence of small vessel occlusive disease or the defective chemotaxis of diabetic leukocytes.10

ERYTHRASMA
*Corynebacterium minutissimum* is the causative organism in erythrasma. It starts as an erythematous plaque, which turns into brown, hyperpigmented, fine scaly patches over body folds such as the groin, axillae, and submammary creases. The infection is confirmed by observing coral red fluorescence by Wood’s lamp examination. The organism can ferment glucose, which may be the cause of the higher than normal incidence of this condition reported in diabetics. Topical or systemic erythromycin or tetracycline is usually adequate treatment.11

NONCLOSTRIDIAL GAS GANGRENE
The causative organisms of nonclostridial gas gangrene are *Escherichia coli*, Klebsiella, pseudomonas, enterococcus, anaerobic streptococci, and bacteroides, often in combination. Gas, detectable as crepitus on palpation or as radiolucent bubbles on x-ray examination, is formed within necrotic tissue.12

FUNGAL INFECTIONS

CANDIDOSIS
Candidosis infection may be an early indicator of undiagnosed DM. It frequently causes symptoms such as vulvovaginitis, which is a common cause of localized itching in this region. There is vulval erythema with fissuring and satellite pustules. In a study, yeasts were isolated from the vagina of 35.5% of diabetic women, with *Candida glabrata* as the commonest yeast species isolated. Paronychia begins at the lateral nail fold and is characterized by erythema, swelling, and separation of the fold from the lateral margin of the nail. Thrush affects the buccal mucosa and tongue, and increased salivary glucose reportedly accounts for the *Candida* overgrowth. The white curd-like material adheres to erythematous and fissured areas. Balanitis is frequently seen in the elderly and uncircumcized men. It presents clinically as an erythematous, slightly indurated, and/or eroded red patch on the glans penis. Phimosis may occur in patients with chronic or recurrent balanoposthitis.7,12

HISTOPATHOLOGY
There are small collections of neutrophils in the stratum corneum with associated yeast and pseudomycelial phases of the organisms. A mixed dermal inflammatory infiltrate may exist that can become granulomatous.13

*Candida albicans* is the most commonly detected species.14 Treatment for candida infection includes normalization of blood sugar and use of topical and oral antifungal medications.15

DERMATOPHYTOSIS
Many studies have reported a statistically significantly higher frequency of dermatophyte infection with main risk factors including age, male sex, obesity duration of diabetes, type II DM, and levels of blood glucose. Tinea pedis and onychomycosis were the most common type of infections seen in these studies. The most frequently isolated fungi were *Trichophyton mentagrophytes* and *Trichophyton rubrum*.16,17 Onychomycosis can cause hypertrophic and deformed nails that may damage adjacent skin and their pressure can result in decubitus ulceration of neighboring fingers or nail beds. Combination of systemic treatment with itraconazole, terbinafine, and atraumatic chemical ablation with subsequent local treatment is required.18–22

ZYGOMYCETES INFECTION
Hyperglycemia can allow usually nonpathogenic organisms to establish infection and gangrene in traumatized areas. Diabetics with leg ulcers, open wounds, or surgical incisions not responding to therapy may have either primary or complicating phycomycetes infections. Diagnosis is confirmed by culture and by histologic demonstrations of fungal elements invading vascular channels. Treatment consists of debridement of all necrotic tissue, administering intravenous amphotericin B, correction of acid-based imbalance, and control of hyperglycemia.12

RHINOCEREBRAL MUCORMYCOSIS
This is caused by zygomycetes. It presents with headache, fever, lethargy, nasal congestion, and facial/ocular pain and swelling. Later, the patient develops unilateral proptosis, ophthalmoplegia, and palate or nasocutaneous necrosis. Approximately 75% to 80% of all such cases occur in patients with DM.23 It is imperative to draw attention to the facts that it is invariably associated with ketoacidosis, that it is severe, and that therapeutic success is related to prompt recognition and correction of ketoacidosis.

LICHEN PLANUS
The incidence of diabetes in lichen planus (LP) ranges from 28% to 36%.24,25 The reported rates vary from 0.55% to 5.76% of diabetics having clinical and less often histologic evidence of oral lichen planus (OLP).26 LP is characterized by pruritic, flat-topped, violaceous papules over the flexor aspects of the forearm, wrists, lower leg, and lower part of the back. Mucous membranes of the oral
cavity and genitalia are involved in two thirds of patients. In past studies, the prevalence of OLP was 5.76% in type 1 DM patients, 2.83% in type II DM patients, and 1.82% in controls. When LP is associated with glucose intolerance, however, no particular human leukocyte antigen (HLA) phenotype is found.

**VITILIGO**

Vitiligo is an acquired idiopathic depigmentation of the skin characterized by ivory/chalky white macules. It is associated with both NIDDM and IDDM. Vitiligo has a high incidence in patients with DM, ranging from 9% to 16%. Researchers found that 4.8% of diabetics have vitiligo, while a few reports have demonstrated a high incidence of DM in the families of patients with vitiligo. Both diabetes and vitiligo are considered to be of autoimmune origin, and a common risk factor is familial predisposition. Both are associated with HLA-DR3 and HLA-DR4.

**PSORIASIS**

Psoriasis, a chronic inflammatory skin disorder, is characterized by a variety of immunologic and inflammatory changes and may similarly predispose patients for disorders such as type II diabetes, arterial hypertension, hyperlipidemia, and coronary heart disease. There have been various recent studies confirming the association between DM and psoriasis. A few other studies have reported an incidence of diabetes as high as 16% to 27.9% in patients with psoriasis.

**PRURITUS**

The relationship between generalized pruritus and DM is debatable. Most of the studies are inconclusive; however, a couple of studies have shown an incidence of 14% to 20%. Diabetic anhidrosis and oligohidrosis may contribute to xerosis. Pruritus in diabetics is usually intense and localized, and may result in prurigo nodularis. Pruritus vulvae is significantly more common in diabetics, mostly associated with candida infection, followed by other causes such as neurodermatitis or contact allergic/irritant dermatitis. Localized pruritus is also common in the perineal area and lower extremities.

**CUTANEOUS PORPHYRIAS**

Diabetes has been reported among patients with most forms of hepatic porphyria, including acute intermittent porphyria, variegated porphyria, and porphyria cutanea tarda (PCT). The cutaneous manifestations include bullae on light-exposed areas, excess skin fragility, hypertrichosis, melanosis, scarring alopecia, and scleroderma-like plaques.

Histologically, there is a subepidermal bulla with a sparse underlying inflammatory infiltrate. Immunoglobulins, especially immunoglobulin G, and complement deposits have been demonstrated at the dermoepidermal junction and around superficial blood vessels.

The diagnosis is confirmed by a marked elevation of urinary uroporphyrin levels, with a less-pronounced increase in coproporphyrins. Serum ferritin as well as hepatocellular iron stores are increased.

**SKIN TAGS**

Skin tags, or acrochordons, are small exophytic growths of skin that have a predilection for the neck, axillae, and eyelids of middle-aged patients. They are 1 mm to 1 cm in diameter and are either skin or brownish colored. The male to female ratio is 1:2. The correlation between diabetes and skin tags varies from 26.38% to 72.34%. The plausible mechanism for evolution of skin tags in diabetic patients is hyperinsulinemia, which elevates serum concentration of free insulin-like growth factor 1, while reducing insulin-like growth factor–binding protein 3. These endocrine shifts alter cellular proliferation and growth, which may manifest as skin tags.

**NAIL CHANGES**

**Infection**

*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Proteus vulgaris* are the prime culprits. Acute paronychia involving proximal and/or lateral nail folds may result in partial or total matrix destruction, followed by a permanent abnormality of the nail plate. Onycholysis and greenish black discoloration of the nail caused by *Pseudomonas* colonization are the
other features. Fungal infection initiates chronic paronychia, resulting in invasion of the nail plate leading to onychomycosis.

**Vascular Lesions**

Beau's lines develop as a result of occasional spasms in digital arteries, which may produce a period of relative ischemia in the nail matrix, resulting in a reduction or cessation of nail growth and transverse depression across the nail plate(s). Onychauxis, hypertrophic thickening, darkening, and surface irregularity may be caused by vascular insufficiency. *Pterygium*, a result of arterial spasm, leads to fusion of the undersurface of the proximal nail fold to the underlying matrix and nail bed epithelium. *Pterygium inversum unguis*, epithelium of the hyponychium, and distal nail bed remains attached to the undersurface of the nail plate. Proximal nail fold capillary microscopic changes may show dilated small vessels in the form of isolated homogenous enlargement of the venular limbs. Other vascular features such as tortuosity, hemorrhages, and ischemic areas have been seen in DM. Splinter hemorrhages of arterial emboli may occlude terminal digital arteries and result in hemorrhage distal to their impaction. Yellow discoloration of the nails is a result of vascular impairment. This may occur in all of the nails but most commonly on the distal aspect of the nail of the hallux seen in half of diabetics.7

**Miscellaneous Nail Changes**

Additional nail changes include Rosenau's depression (small pitted craters on the surface of the nail plate), onychocryptosis (ingrown toenails), pincer nail deformity (overcurvature of the nail plate), onychomadesis (where the nail plate separates from the nail bed at a proximal site and then proceeds distally), and leukonychia (white areas on the nail plate).53

**Oral Lesions**

Angular stomatitis, gingival tenderness, xerostomia, burning mouth, acute gingival abscesses, subgingival perforation, and heavy supragingival deposits of tartar are a few manifestations of oral lesions.12

**Pigmented Purpuric Dermatosis**

Pigmented purpuric dermatosis results from red blood cell extravasation of the superficial vascular plexus. It is characterized by the presence of patches of orange to tan pigmentation, and "Cayenne pepper" spots on the shins (Figure 2).54 Approximately half of these patients have associated diabetic dermopathy. This condition may be a marker for microangiopathy in patients with diabetes.15

**Hemochromatosis**

This is a clinical disorder referred to as bronze diabetes, with a classical triad of diabetes, hepatic cirrhosis, and hyperpigmentation. Other features may be cardiac disease, joint involvement, and hypogonadism. Excessive iron accumulation in the liver, pancreas, and heart damages these organs.12,13 The incidence of frank diabetes in patients with hemochromatosis ranges from 14% to 78%. A proposed mechanism for diabetes in this disease is the development of cirrhosis, which may interfere with a hepatic factor that enhances peripheral glucose utilization.12 Skin manifestations of liver failure are present in the form of palmar erythema, loss of hair, purpura, and spider telangiectasias.13 Histopathologically, Perls' stain shows hemosiderin deposits around the blood vessels and sweat glands. Heavy metal deposits of various types stimulate melanin transfer from melanocytes to keratinocytes. This causes a general increase in epidermal melanization, suggesting that hyperpigmentation is not caused by iron but by melanin.12

**Lipodystrophy**

**Lawrence-Seip Syndrome**

Lawrence-Seip syndrome (total lipoatrophy) may either be congenital or acquired. In both, there is complete loss of adipose tissue,
hepatomegaly, and hyperlipidemia.\textsuperscript{55} Diabetes usually develops after the first decade of life and is insulin-resistant and nonketotic. Cutaneous abnormalities include acanthosis nigricans, generalized hypertrichosis, and curly scalp hair. In the congenital form, inheritance is usually autosomal recessive; such children are sometimes products of a consanguineous marriage. The acquired form may develop after bacterial infections, such as pertussis, or after viral infections. Women are affected more commonly than men. Partial lipodystrophy is an insidious symmetrical loss of facial fat tissue that may spread to affect the arms and upper part of the trunk. In some cases, there may be coincidental hypertrophy of subcutaneous fat of the lower part of the body.

**BULLOUS PEMPHIGOID**

Bullous pemphigoid is a chronic blistering dermatosis characterized by subepidermal separation within the lamina lucida of the epidermal basement membrane zone (Figure 3). In two studies investigating the association between bullous pemphigoid and DM, the incidence of bullous pemphigoid was found to be 41% and 20%, respectively.\textsuperscript{56,57} The proposed mechanism for increased association is that diabetics have a lower threshold than healthy individuals for suction-induced blister since autoimmune mechanisms are active in both bullous pemphigoid and type 1 DM. The other theory is that glucosylated skin collagen, which increases during nonenzymatic glucosylation of collagen in diabetics, is capable of inducing the production of autoantibodies with specificity directed against the modified collagen.

**KAPOSI’S SARCOMA/MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA**

Kaposi's sarcoma (KS)/multiple idiopathic hemorrhagic sarcoma is a neoplasm that usually begins on the lower part of the legs as multiple, purple macules, nodules, and/or plaques, and is seen most often in elderly Jewish and Italian men. Later, other areas of skin, mucous membranes, and internal organs may be involved. The occurrence of DM has been studied in the older, more classic group of patients with this disease, in whom the incidence varies from 27% to 46% in various studies. KS seen in the acquired immunodeficiency syndrome bears no relation to diabetes.\textsuperscript{7-12}

**WERNER SYNDROME**

Premature aging affects tissues. Werner syndrome develops in the first or second decade of life and is characterized by short stature, premature graying of the hair, alopecia, cataract, skin atrophy, hyperkeratosis, and sharpening of the nose. Indolent ulcers occur on the feet and ankles. In these cases, diabetes ranges from 33% to 44.4% and is characterized by mild degree, absence of ketosis, relative insulin insensitivity, and a tendency for the fasting blood sugar level to be within normal limits.\textsuperscript{57,58}

**GLUCAGONOMA SYNDROME**

First described by Becker in 1942, this syndrome is usually caused by tumors of the alpha cell-glucagon–secreting portion of the pancreas. It manifests itself with four major components: (1) hypersecretion of glucagon; (2) diabetes, usually mild (85% of patients have diabetes or at least abnormal glucose tolerance), but there is neither associated ketoacidosis nor does the diabetes in these patients result in the usual degenerative changes; (3) weight loss; and, (4) necrolytic migratory erythema. This chronic fluctuating dermatosis is characterized by an annular and figurative erythema that forms bullae and erosions. It is mainly seen in the intertrigenous and periorificial regions and on the extremities. Painful glossitis, intermittent diarrhea, mood changes, and thrombosis have also been reported.\textsuperscript{7,13}

**LIPOID PROTEINOSIS**

This is a recessively inherited disease characterized by hyalin deposits in the skin and the mucous membranes. Papules, bullae, pustules, hyperkeratotic areas, and scars involve the skin. Characteristic yellow, ivory, waxy papules have a predilection for the dorsal aspect of the neck, hands, fingers, and free margins of the eyelids. Abnormalities in glucose tolerance among patients with lipid proteinosis have been reported.\textsuperscript{12}

**CLEAR CELL SYRINGOMA**

Clear cell syringoma is clinically similar to syringoma but differs in two features. It has a histologic preponderance of clear cells and frequent coexistence of DM. This may be the result of phosphorylase deficiency secondary to elevated glucose levels in diabetics that in turn results in the formation of the clear cells.\textsuperscript{7}
DERMATITIS HERPETIFORMIS
The HLA associations such as HLA, DR3, and DRW2 of dermatitis herpetiformis and insulin-dependent diabetes may be a possible explanation of the two diseases appearing together more frequently than expected.7

HAIR DISORDERS
Diffuse thinning of the scalp hair is not unusual in uncontrolled diabetes, and fine lanugo hair on the back and arms may be seen in undernourished diabetic patients. Achard–Thiers syndrome, characterized by obesity, hirsutism, hypertension, and diabetes31 is another entity. Alopecia areata, totalis, and universalis (Figure 4), a unique manifestation of NIDDM, has recently been reported.59

CUTANEOUS REACTION TO DIABETIC THERAPY
First-generation sulfonylureas such as chlorpropamide and tolbutamide are most commonly associated with hypersensitivity-related cutaneous manifestations. They may develop in 1% to 5% of patients within the first 1 to 2 months of treatment. The most common is a maculopapular eruption, but morbilliform eruption, erythema, or urticarial lesions may also be seen. They often disappear with discontinuation of therapy. Photosensitive reactions, lichenoid lesions, and rosacea-like eruptions are also seen.3 Generalized pruritus may herald a diffuse exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome with marked mucous membrane involvement, or toxic epidermal necrolysis.13,60

Chlorpropamide may cause a disulfiram-like reaction consisting of marked flushing, headache, tachycardia, and shortness of breath beginning 15 minutes after alcohol consumption and gradually resolving over the following hour.61 This distinct entity occurs in one third of type II diabetes patients taking this drug and it is inherited as an autosomal-dominant trait.12

Cutaneous reactions such as erythema, exanthems, photosensitivity, pruritus, and urticaria have been reported with increasing use of second-generation sulfonylureas such as glyburide, glipizide, and glimepride. Similar reactions have also been reported with metformin.61

INSULIN CUTANEOUS REACTIONS
The incidence of insulin reaction varies from 10% to 56%, which may be immediate local, immediate general, delayed, or biphasic and occurs within the first month of insulin therapy.13 Allergic reactions may be caused by reaction to impurities in the insulin preparation consisting of beef or pork proteins, to the insulin molecule itself, or to additional polypeptides, preservatives, or additives. Use of the newer monocomponent porcine insulins and purified human insulins has made these skin side effects very rare, with an incidence of 0.1% to 0.2%.61

Insulin-induced lipoatrophy and lipohypertrophy is jointly referred to as lipodystrophy. It occurs at the site of injection or occasionally at distant sites. It presents as a depressed circumscribed area of skin, possibly reflecting a localized immune reaction to the insulin with associated loss of subcutaneous fat.27 This reaction is more common in women in areas of substantial fat deposition.13 Lipohypertrophy presents as soft dermal nodules, clinically resembling lipomas, at the site of frequent injections. It may be a response to the lipogenic action of insulin. Chronically injected sites become hypoesthetic, and this results in a delayed absorption rate.

DIABETIC FOOT
Lower extremity complications are common in diabetic patients and include neuropathy, ulceration, infection, and peripheral arterial disease. The term diabetic foot is used to include all cutaneous manifestations in the foot that occur as a result of the above complications.47 Proper evaluation of the diabetic foot identifies peripheral neuropathy (60% to 70%), peripheral ischemic vascular disease (15% to 20%), and combined clinically significant neuropathy and vascular disease (15% to 20%) as the cause of ulcerations60 (Figure 5A and 5B).

ISCHEMIA
Ischemia results from premature peripheral vascular insufficiency secondary to atherosclerosis of large and medium vessels and microangiopathy. Clinically, the skin shows atrophic changes with cool, shiny skin, dystrophic nails, and hair loss. This may progress to ulceration and gangrene commencing at the tips of the toes.47
There is an increased frequency of soft tissue infections of the lower extremities in diabetics. A mixture of organisms in the infected tissue is usually found and nonclostridial gas gangrene can occur. Maceration between the fourth and fifth toe is common, leading to marked bacterial and fungal colonization.

**Neuropathy**

The peripheral neuropathy in diabetes is thought to be caused by microangiopathy, affecting the intraneural blood vessels. In the early stages of neuropathy, the foot is frequently warm with good peripheral circulation. Numbness and pain may be present in a glove and stocking distribution prior to the loss of sensation. The neuropathy may result in blisters and ulcers developing over pressure areas usually as a result of painless trauma. Callus or hypohidrosis from autonomic neuropathy. The characteristic lesion in diabetic neuropathy is the perforating plantar ulcer or melum perforans. A small ulcer can belie considerable deep tissue destruction and even osteomyelitis. Ulcers are typically circular and punched out (Figure 6) and associated with callus and concomitant loss of temperature and pain sensation and absence of ankle reflexes. Neuropathic joint disease can cause painless disorganized Charcot-type joints. The foot has accelerated plantar arches and hammer toes. Topical treatment must include the debridement of the ulcer with removal of necrotic tissue. Stimulants of granulation tissue-like membranes, benzyl peroxide, or absorbent dressings may be used. Neurotrophic ulcers require redistribution of weight of the metatarsal heads with special orthopedic shoes. Amputation is indicated when vascular flow is inadequate or cannot be restored by modern surgical procedures.

**REFERENCES**


**CORE CURRICULUM REVIEW QUESTIONS**

Noninsulin Dependent, Type II Diabetes Mellitus Related Dermatoses: Parts I, II, and III

Instructions: For each of the following numbered questions, choose the most appropriate lettered response.

1) What percentage of patients having necrobiosis lipoidica diabeticorum without diabetes may eventually develop diabetes mellitus?
   a. 20%
   b. 50%
   c. 60%
   d. 90%
   e. 100%

2) What percentage of patients with necrobiosis lipoidica diabeticorum might undergo spontaneous remission?
   a. 13%–19%
   b. 33%–49%
   c. 43%–59%
   d. 20%–30%
   e. 50%–70%

3) What is the mean age of presentation of necrobiosis lipoidica diabeticorum in insulin dependent diabetics?
   a. 22 years
   b. 34 years
   c. 12 years
   d. 50 years
   e. 40 years

4) The term diabetic dermopathy was coined by:
   a. Melin.
   b. Nils Tornblom.
   c. Binkley.
   d. T. Colcott Fox.
   e. M. Oppenheim.

5) Which of the following cutaneous manifestations has been reported to occur following hepatitis B and Bacille Calmette-Guérin vaccination?
   a. Necrobiosis lipoidica
   b. Granuloma annulare
   c. Diabetic dermopathy
   d. Diabetic bullae
   e. Scleredema

6) What are the characteristic sites for presentation of diabetic bullae?
   a. Head and neck
   b. Back
   c. Hands and forearms
   d. Chest
   e. Oral mucosa

7) Which of the following is a histopathological feature of bullous diabeticorum?
   a. Linear or thready pattern of immunofluorescence
   b. Intraepidermal cleft
   c. Caterpillar cells
   d. Eosinophilic spongiosis
   e. Neutrophilic infiltration of dermal papillae

8) Diabetic cheiroarthropathy is characterized by:
   a. waxy skin and limitation of movements at joints.
   b. arthritis.
   c. joint effusion.
   d. commonly involving the feet.
   e. synovitis.

9) Scleredema adutorum is characterized by:
   a. Marked decrease in dermal thickness.
   b. involvement of hands and feet.
   c. correlating with nephropathy and retinopathy.
   d. swollen collagen bundles separated by wide, clear spaces.
   e. occurring only in diabetes.

10) The pathological basis of rubeosis faciei is likely to be:
   a. microangiopathy.
   b. neuropathy.
   c. hypersensitivity reaction.
d. streptococcal infection.
e. photo-allergic reaction.

11) How many patients with type II diabetes develop acanthosis nigricans by the 5th decade?
a. 10%
b. 20%
c. 70%
d. 50%
e. 80%

12) The most common causative organism for malignant external otitis is:
a. *Pseudomonas aeruginosa*
b. *Staphylococcus aureus*
c. *Streptococcus pyogens*
d. *Klebsiella granulomatis*
e. *Corynebacterium*

13) What is the incidence of diabetes in lichen planus?
a. 28%–36%
b. 10%–15%
c. 44%–53%
d. 1%–8%
e. 60%–80%

14) Skin tags are attributed to:
a. vascular endothelial growth factor.
b. tissue growth factor.

ANSWERS TO THE CORE CURRICULUM REVIEW QUESTIONS:

1) d
2) a
3) a
4) c
5) b
6) d
7) c
8) a
9) d
10) a
11) d
12) a
13) a
14) d
15) c
16) b

HISTORICAL DIAGNOSIS & TREATMENT: SCLERODERMA (continued from page 365)

SYNONYMS: DERMATOCSEROSIS; SCLEREMA; SCLEROMA; SCLERIASIS; HIDE BOUND DISEASE

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. The evolution of the patches may be quite insidious or preceded or accompanied by moderate burning pain or pruritis. Neighboring plaques may coalesce and sometimes enclose islands of normal skin. In all cases the integument feels thick and is often leathery and so bound down to the deeper structures that it cannot be pinched up in folds. In the diffuse form the progressive thickening and shrinking of the skin may greatly interfere with the function and nutrition of the parts beneath. On a limb the muscles may atrophy and the joints become ankylosed. In the condition termed sclerodactyly the hands and fingers are rendered stiff, immobile and useless. When the integument of the chest is involved respiration may be greatly interfered with. On the face the natural folds disappear, movements of the mouth and eyelids are much inhibited and the face assumes an expressionless and cadaveric appearance. When the condition is very extensive it usually causes marasmus and death. In some cases after months or years the infiltration disappears gradually and leaves the skin thin, dry, wrinkled and parchment like. The more common circumscribed variety, also known as morphea, is usually slower in its development and more prone to recover in time and leave either a scar like atrophy or merely depressions caused by loss of subcutaneous structures, or no traces at all. New patches may develop while others disappear. Sometimes the disease limits itself chiefly to one side of the face and produces a more or less marked facial hemiatrophy. The course of scleroderma is variable, there may be periods of improvement and recrudescence and the disease may become arrested at any stage. The etiology is obscure. The disease occurs three times as frequently in women as in men and is most common in youth and middle age.

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.
We are all familiar with the stinging sensation of disinfecting our hands with alcohol-based hand rubs (ABHRs). It is an open secret that we doctors and other health care personnel do not like using them, because we have a lingering suspicion that if they are really doing their job of killing germs, they are probably doing nasty things to our skin in the process.

In an interesting study on this subject, nurses’ perceptions of adverse effects of conventional hygienic handwashing vs alcohol-based hand rubs were surveyed by a self-administered multicenter questionnaire study. The majority (69.5%) of nurses considered alcoholic disinfection to be more damaging than handwashing by ordinary soap products. The prevalence of hand dermatitis was 13.4% by self-diagnosis and 22.4% by symptom-based questions.

DISCUSSION

Preventing nosocomial infections is high on the list of health care priorities worldwide, and complying with the “Clear Care is Safer Care” campaign is one of the main concerns of the World Health Organization.

The aim of this paper is to analyze the dermatologic aspects of ABHRs and help put to rest the confusion surrounding any possible deleterious effects they have been alleged to have on skin during handwashing.

Skin tolerance to ABHRs or classic handwashing with mild soap and water of the hands of workers in health care facilities was evaluated in a recent prospective multicenter study in France. That study was conducted in a large population in 9 health care facilities that comprised 1932 assessments and took into account numerous individual and environmental risk factors. A univariate analysis showed that the use of an ABHR appeared to cause less dryness and less irritation than regular hand soap. This trend in favor of ABHRs was confirmed by a multivariate analysis, which appeared to show that ABHRs even offered protection against their occurrence. The authors found that the greater the frequency of handwashing with soap, the greater the risk of dryness or irritation, while the risk of dryness and irritation was relatively stable at low (3–5 times daily), average (6–10 times daily), or frequent (11–20 times daily) ABHR use. Interestingly, members of the staff who used an ABHR very frequently (>20 times daily) enjoyed a distinct protective effect.

This large, well-designed, qualitative, and convincing French study serves to support previous investigations that yielded similar findings. Two of them had been published 5 years earlier. One of them was conducted in Germany, and it measured the biological response of regular human skin to ABHRs and detergents in repetitive patch testing and wash testing on 45 volunteers. The ABHR preparations were associated with minimal irritation comparable to the application of water alone. On the other hand, sodium lauryl sulfate (SLS), produced a stronger barrier disruption, erythema, and dryness. There was no additional irritation with the combined use of SLS and disinfectants. In contrast, there was a decrease in barrier disruption and erythema induced by the combined application of SLS followed by ABHR compared with the use of SLS alone. That study thus showed that the combination of washing and disinfection appears to have a protective advantage compared with washing alone.

A large American study published in the same year showed similar results. The authors carried out single and repetitive patch testing with 60% to 100% alcohols, a positive control (SLS), and negative controls. Wash tests were also performed with 80% ethanol and 0.5% SLS on forearms with each agent alone and with both agents in a tandem design. The results showed no significant change in skin barrier or erythema induced by...
the alcohols in the patch tests, whereas skin hydration decreased significantly. Application of alcohols to previously irritated skin did not show a stronger skin barrier disruption than application of SLS alone. Wash tests demonstrated that the application of alcohol caused significantly less skin irritation than washing with a detergent. Surprisingly, all the evaluated skin physiological parameters were less impaired by the combination of SLS with ethanol compared with SLS alone. This suggested that the application of ethanol after handwashing may reduce irritant skin changes caused by washing, meaning that ethanol use after skin washing had a protective effect. The authors’ rationale and explanation for this apparent paradox of the protective effect of alcohol was that it was caused by a washout of detergent molecules left on and in the stratum corneum and which may lead to prolonged skin irritation. The importance of these studies is that alcohols used in ABHRs did not induce further skin irritation but may have even reduced the irritation caused by detergents.

Interestingly, a protective role of ABHRs was demonstrated in a study performed more than 20 years ago. It should be noted that the researchers were associated with the Dermal Research Department of the S. C. Johnson & Son, Inc Company. They evaluated the effects of an antimicrobial hand gel that contained 60% ethanol plus emollients on the condition of the skin, when the gel was used as a supplement to handwashing. Volunteers washed their hands with a bar soap 10 times per day for 5 days. Between washings, one hand was treated with 1.0 mL of the gel, while the other hand was untreated. The final results revealed that the gel-treated hands exhibited significantly lower photographic scores for the major signs of dry and irritated skin, ie, cracking, scaling, and erythema. The gel treatment also helped to maintain normal skin hydration levels, as measured by transepidermal water loss and skin impedance. These authors concluded that an alcohol gel with the appropriate emollients can help eliminate a major deterrent to handwashing among health care personnel by reducing soap-induced irritation.

Two smaller studies, performed by another group, had come to similar conclusions. In one of them, a detergent, a disinfectant, or alternating disinfectants and detergents were applied twice every 10 minutes for 1 hour to the ventral surfaces of the arms and forearms of 17 volunteers. The alcohol-based disinfectant caused less visible skin irritation and less skin-barrier disruption than the detergent. The alternate use of a detergent and a disinfectant caused less irritation than detergent alone, and a possible interaction between the two irritants was not indicated. The other study by the same group and performed on 15 volunteers for 2 days yielded the same results: an alcohol-based disinfectant or the alternate use of a disinfectant and a detergent caused less skin irritation than detergent alone.

In an additional study, 50 staff members working full time in a critical care unit followed two randomly assigned hand hygiene regimens for 4 consecutive weeks. Participants using a waterless hand rub containing 61% ethanol with emollients showed significant improvements in Hand Skin Assessment scores and in Visual Skin Scaling scores compared with participants who used a 2% chlorhexidine gluconate-containing traditional antiseptic wash.

Finally, irritation and dryness of 32 nurses’ hands were evaluated by self-assessment and visual assessment in another prospective randomized trial with a crossover design. The ABHR regimen was well tolerated and did not result in skin irritation or dryness. In contrast, skin irritation and dryness increased significantly when nurses washed their hands with the hospital-supplied soap product.

CONCLUSIONS

The aim of the present report has been to dispel the concern that ABHR damages, dries, and irritates the skin more than handwashing with ordinary soap. Health care workers tend to believe that alcohol is harmful for their skin, mainly due to the stinging and burning sensations caused by ABHRs on intact skin and especially on damaged areas of the skin.

All of the publications we cite here support the general consensus that not only are ABHRs better tolerated, less irritating, and less damaging to the skin than handwashing, but they can even reduce the irritation caused by handwashing, probably by eliminating residual detergent remnants. Awareness of these findings might serve the Clear Care is Safer Care campaign.

REFERENCES


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A 34-year-old non-pregnant woman noted a mildly pruritic skin lesion on her right breast for 1 week following an episode of coryza, malaise, and low-grade fever of 3 days duration. The latter symptoms subsided without any treatment. Ketoconazole cream prescribed by her family physician did not resolve the breast eruption after 1 week, so was stopped. A week later, multiple skin lesions erupted suddenly on her right chest wall starting near the herald patch in midaxillary line and spread distally until the midback. She then consulted the authors. She denied a history of abrasion or trauma to the affected areas. Travel, contact, sexual, and drug histories were unremarkable. She categorically denied past or family history of eczema, psoriasis, contact dermatitis, and drug eruptions. On examination, the initial lesion was an annular and well-demarcated erythematous plaque on her right breast in the upper outer quadrant. Multiple small oval scaly plaques were noted, extending distally along the ribs to the midline on her back, not crossing the midline, predominantly over the distribution of right T1 dermatome (Figure 1). Peripheral collarette scaling was noted (Figure 2). A few scattered small lesions were also noted in the vicinity of this dermatome. Three isolated small plaques were also present on the trunk, one in the supramammary area and the other two on the abdomen and back, respectively. Palmoplantar and mucosal surfaces were uninvolved. The rest of the skin and systemic examination revealed no abnormalities. Complete blood cell counts, fasting glucose, and urinalysis were normal. Venereal Disease Research Laboratory (VDRL) results were nonreactive and human immunodeficiency virus (HIV) antibodies were negative. Repeat testing of VDRL in serial dilutions and HIV antibodies after 3 months were also nonreactive and negative, respectively. Scrapings from the initial large lesion and subsequent smaller eruptions did not show any evidence of fungal infection on potassium hydroxide smear examination. The patient declined skin biopsy; however, we thought that the most diagnostic label for this condition was pityriasis rosea. Hence, we treated her with triamcinolone acetonide ointment 0.025% to be applied twice daily and desloratadine tablet 5 mg daily for 10 days. The patient demonstrated complete resolution, leaving postinflammatory hypopigmentation. There was no recurrence until 1 year after complete remission.

Pityriasis rosea (PR) typically affects the trunk and proximal regions of the extremities. The eruption following a herald patch demonstrates orientation along Langer’s cleavage lines. While a classical presentation is easily diagnosed clinically, atypical variants often pose diagnostic difficulties.1-3 Although skin biopsy may sort out differentiation from other conditions, the biopsy findings are very often nonspecific. The patient may decline skin biopsy. In such situations, the diagnosis is made with the clinician’s judgment. Sometimes, the diagnosis may be retrospective. In our experience, meticulous history and regular follow-up, preferably with the same specialist, for a significant period after resolution guides us to an appropriate diagnosis. We believe that PR is largely a clinical diagnosis. A recent Cochrane review does not recommend insistence on skin biopsy when the diagnosis of PR seems clinically compatible.4 Differential diagnoses including tinea corporis, secondary syphilis, erythema annulare centrifugum, erythema chronicum migrans, pityriasis lichenoides, psoriasis, eczema, contact dermatitis, and drug-induced PR were unlikely in our patient.

Considering a prodrome of upper respiratory infection, the clinical course of a typical herald patch followed by smaller secondary plaques with peripheral collarette scales, and complete resolution during a span of 3 weeks, we believe this case fulfills the diagnostic criteria and deserves a diagnostic label of PR.1 It was striking to note that the eruptions in our patient clinically progressed in a dermatomal pattern.

The atypical variants of PR are classified on the basis of morphology and distribution of the majority of secondary eruptions following a herald plaque. Atypical presentations are known in
at least 20% of patients with PR.\textsuperscript{5} We retrospectively believe that segmental or dermatomal PR was an appropriate diagnostic label for our patient. Several unusual variants of PR are reported in the literature, including unilateral, inverse, vesicular, papular, purpuric, hemorrhagic, erythema multiforme-like, urti-
carial, and those involving mucosae, palms, soles, flexures, and the face.\textsuperscript{3} In his review of atypical forms described by several workers, Klauder mentioned different anatomical locations of localized and unilateral PR.\textsuperscript{6} It may be likely that some of the patients described in this contribution may have had a scope to be studied as segmental variant. Untanned skin affected by PR was described earlier.\textsuperscript{7} This does not convince us of the likely cause of eruptions in our patient, however, as the lesions were present only on one side. Klauder was also not convinced regarding this concept.\textsuperscript{8}

The cause of such a strange and predominant distribution along the neural segment(s) is quite intriguing. We specifically sought history of linear trauma preceding the onset of secondary lesions to rule out Köebner phenomenon. Neurologic and immunologic responses in context to papulosquamous diseases such as psoriasis are known, indicating upregulation of neuropeptides and increased levels of nerve growth factor.\textsuperscript{9} It remains to be elucidated whether such activity also exists in PR and whether it has any bearing on its clinical presentation.

The discovery of dermatomal distribution in herpes zoster was highly pivotal in our present understanding of reactivation of dormant varicella-zoster virus in the dorsal root or autonomic ganglion.\textsuperscript{10} Slight overlap in the adjoining dermatome is a rare phenomenon documented even in immunocompetent patients with herpes zoster, a disease hallmarked for segmental distribution.\textsuperscript{11,12} This may offer some explanation for the eruptions in the adjoining dermatome in our patient.

A possibility that PR could sometimes be segmental is alluded to in a recent epidemiologic study.\textsuperscript{13} To the best of our knowledge, only one case of PR-like eruptions on the arms following a vague dermatomal distribution as a result of the drug imatinib mesylate is reported on PubMed.\textsuperscript{14} We believe that dermatomal PR was never formally documented in the literature, as we searched the strings segmental, dermatomal, and zosteriform pityriasis rosea on PubMed in the English literature for finding the relevant publications.
CONCLUSIONS
To the best of our knowledge, dermatomal PR, segmental PR, and zosteriform PR are all unreported clinical variants of PR in PubMed. The case is presented here for its interesting feature and extreme rarity in clinical practice.

Acknowledgement: Dr Steven Emmet, Solan Beach, CA conducted the literature search.

REFERENCES
8. Klauder J. Does tanned skin prevent eruption of pityriasis rosea. AMA Arch Derm. 1957;76:200–205.
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CASE STUDY

Neutrophilic Dermatosis Caused by Azathioprine

Mark C. Valentine, MD; John S. Walsh, MD

An 89-year-old woman came to the office because of a pruritic eruption involving her trunk and limbs, present for a number of years and only partially relieved by topical triamcinolone. She had been evaluated by another dermatologist 9 years previously for an eruption of several months' duration on the arms, back, and legs. At that time, the eruption consisted of irregularly shaped, red to violaceous papules averaging 5 mm in diameter and was accompanied by lacy white buccal mucosal changes suggestive of lichen planus. Skin biopsy was said to be "quite typical for lichen planus" at that time. She was treated with clobetasol with a fairly good response. Another dermatologist evaluated her itching and diagnosed atopic eczema 15 months prior to seeing me. Since that time, she had been applying triamcinolone, but her itching was growing progressively more severe. She had stopped her hydrochlorothiazide 1 week previously in case it was causing her itching. Her medical history was significant for diabetes and hypertension. Her systemic medications were metformin, pioglitazone, lovastatin, atenolol, and hydrochlorothiazide. She had a history of allergies to penicillin, demeclocycline, and chlorotetracycline. Her physical findings on initial evaluation consisted of a widespread eruption of excoriated 3- to 6-mm reddish papules on the back, arms, abdomen, and legs, sparing the face and hands. No blisters or lichenoid lesions were noted. Because of the intractable nature of the itching, blood was drawn for epidermal antibody testing, and she was instructed to stay off the hydrochlorothiazide for an additional 2 weeks. Blood testing was positive for elevated levels of immunoglobulin G bullous pemphigoid 180 and 230 antibodies, and there was strongly positive indirect immunofluorescence for immunoglobulin G against monkey esophagus and human split skin substrates, typical for bullous pemphigoid. Skin biopsy was not performed. Because of the appearance and distribution of her skin lesions, it was concluded that she had a nonbullous variant of pemphigoid and that she did not fit the usual description of lichen planus pemphigoides. She was placed on topical clobetasol and prednisone at an initial dosage of 20 mg every other morning. Only when the dose was increased to 30 mg every other day did her eruption resolve, in the ninth week of treatment. By then, she was complaining of severe insomnia and had some facial Cushingoid changes, so she was started on azathioprine 50 mg daily as a steroid-sparing agent. Thiopurine methyltransferase genotyping was normal. She missed her 2-week follow-up visit and went to the emergency department 18 days after starting azathioprine complaining of flank and abdominal pain and some weakness. Workup there, including computed tomography of the abdomen revealed only low-grade fever and hypokalemia. She was discharged and showed up in my office the following day with a new eruption of skin lesions on her hands. She had been off azathioprine for 4 days at that time. Skin findings now consisted of succulent dusky red-violet papules and plaques, some studied with small pustules, limited to the dorsal hands, wrists, and fingers (Figure 1). Skin biopsy showed an epidermis with mild spongiosis and focal overlying neutrophilic scale/crust. In the superficial to mid-dermis there was a dense perivascular and interstitial predominantly neutrophilic inflammatory infiltrate (Figure 2). Occasional eosinophils were observed. Vessels were dilated and lined by prominent endothelial cells. There were extravasated erythrocytes, neutrophilic debris, and prominent papillary dermal edema. Diagnostic findings of a necrotizing vasculitis were not present. There was exocytosis of neutrophils into the overlying epidermis. Results from special stains for bacteria and fungi were negative. It was determined that the biopsy represented a neutrophilic dermatosis such as Sweet syndrome or neutrophilic dermatosis of the dorsal hands. One week after the biopsy was obtained, the new dermatitis improved by 60%, with the patient off azathioprine and taking prednisone 30 mg every other day. The prednisone was reduced to 20 mg every other day, and there was only faint residual erythema on her hands after another 3 weeks. By that time, her original eruption consisted of only a few subtle papules on the torso with minimal itch.

Sweet syndrome was originally described as “acute febrile neutrophilic dermatosis” in 1964. A variant that is limited to the dorsal hands was described in 1995, originally termed pustular vasculitis of the hands. The condition was subsequently described in a number of other patients, and most recent reports have favored the terminology neutrophilic dermatosis of the dorsal hands (NDDH). Both the generalized and local forms are reliably responsive to treatment with...
systemic corticosteroids. While most cases of NDDH are of unknown cause, some patients have had associated hematologic disorders, ulcerative colitis, or solid tumors. Based on the lack of reports, NDDH caused by drug hypersensitivity seems to be a rare event.

Generalized Sweet syndrome has a longer list of associated medical conditions and may be triggered by hypersensitivity to multiple medications, including some antibiotics. Several cases of Sweet syndrome have been reported in patients undergoing treatment with azathioprine, in some instances also accompanied by drug fever. Researchers reviewed 67 cases of azathioprine hypersensitivity, with 49% of cases exhibiting cutaneous manifestations. The majority of these were consistent with a neutrophilic dermatosis. With rare exceptions, these patients have been under treatment for inflammatory bowel disease (IBD). Confusion may arise in patients with IBD for two reasons. First, spontaneous dermatoses, especially pyoderma gangrenosum and erythema nodosum, but also Sweet syndrome, may occur in patients with IBD, so the eruption may be attributed to the IBD and not to azathioprine. Second, some of the associated systemic symptoms of azathioprine hypersensitivity such as fever, weakness, and diarrhea may easily mislead the clinician to suspect a flare of IBD or infection, rather than azathioprine as the cause.

In most reported cases, the skin condition resolved promptly after discontinuation of azathioprine, but the azathioprine dose was actually increased in one case and the rash resolved. In some cases, the etiology of the rash was confirmed by recrudescence of neutrophilic dermatosis when the patient was rechallenged with azathioprine.

Azathioprine is a well-recognized cause of hypersensitivity reactions, ranging from a maculopapular rash to systemic illness with fever, pain, weakness, and sometimes evidence of visceral involvement including hepatitis or pancreatitis. These symptoms generally arise in the first 2 to 3 weeks of therapy. A case series from France described 5 patients, all with IBD, with erythema nodosum-like and pustular eruptions caused by azathioprine. The authors point out that patients with Crohn’s disease seem to be uniquely susceptible to azathioprine hypersensitivity and cite a report that presents evidence associating a specific inosine triphosphate pyrophosphatase gene polymorphism with azathioprine hypersensitivity in this population.

The present case differs from most previously reported patients with azathioprine-induced neutrophilic dermatosis because there was no associated IBD and the eruption was localized to the hands. NDDH should be added to the list of potential hypersensitivity reactions to azathioprine.

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To the Editor:

William Charles Wells, MD (1757–1817), rates a footnote in the history of evolutionary thought—he published a theory of natural selection decades before Darwin and Wallace. His theory is based on severely flawed data; thus, Wells may be the patron saint for those who correctly expound grand and correct theories based on bad data.

Wells was an American who was educated in South Carolina and Edinburgh and a royalist who left the United States in 1784.\(^1\) A recognized scientist, he was awarded the Rumford Medal from the Royal Society for his research on dew. In 1813, Wells presented a paper at the Royal Society on what he thought was a “white English woman with regions of negro skin.”\(^2\) Excerpts from his very detailed clinical description include the following:

- “lesion observed at her birth.”
- “fair female of white race of mankind” except for “the blackness of part of her skin.”
- “parts covered by the black skin are, the left shoulder, arm, fore-arm and hand…but are not universally black.”
- “The black skin, whenever it is contiguous to the white, terminated very abruptly, so that its boundary may be distinctly traced.”
- “Palm of her hand and inside of her fingers are black, whereas these parts in a negro are only a tawny hue.”
- Cuticular lines in the black arm appeared everywhere stronger to the sight than similar lines of a black man.”
- “Nails of her black fingers…darker also than those of a negro’s hand.”
- “On the black fore-arm are about a dozen hard substances, the largest the size of a common pea. Some very black…one or two reddish black…readily bled when punctured by a needle.”
- “A number of very black hairs…three quarters of an inch long.”

With this evidence, I suggest his patient had a giant congenital nevus. The differential diagnosis could include dermal melanocytic hamartoma and an X-linked genodermatosis with mosaicism. Based on this patient, Wells expounded the hypothesis that the human races are selected by their abilities to survive and propagate in different environments. This patient was briefly mentioned by others after its initial publication, but Wells’ hypothesis was not discussed until Darwin addressed it in the fourth edition of *The Origin of the Species*.\(^3\) Wells’ theory on the origin of races within a species was not truly revolutionary for its time, and this is suggested as the reason why Wells did not enter the evolutionary pantheon.\(^3\) In addition, evolution was only one idea within Wells’ varied intellectual career.

The case, although dramatic, was not referenced in 18th-century compendiums of rare conditions or dermatology texts (Personal observations).

Wells carefully described the lesions and even conducted clinical experiments inspecting the epidermis after blistering. He compared his patient with the skin of two other “Negroes” and was impressed by similarities rather than differences between the patients. Detailed skin microscopic histology, not yet invented, would have identified the lesion but may have prevented Wells from developing his concept of natural selection. Physicians are often presented with the wonders of nature and should be encouraged to use those opportunities for profound thinking.

Disclosure: “Negro” and “race” are used in the current manuscript as used in Wells’ publication.\(^2\)

**REFERENCES**


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Propranolol as a Novel Addition to Anti–Kaposi Sarcoma Armamentarium: A Hypothesis

To the Editor:

The serendipitous efficacy of propranolol for the treatment of hemangioma was described for the first time in 2008. Since then, there have been several studies that highlighted its impressive efficacy. In this short paper, the aim is to advise our colleagues about the antiangiogenic effect of propranolol in order to encourage research on the use of this agent in the treatment of Kaposi sarcoma (KS), which is a vascular lesion of low-grade malignant potential.

Angiogenesis, a process of construction of new blood capillaries, is crucial for tumor progression and metastasis. Recent studies have identified a number of molecules and signaling pathways that underlie angiogenesis in KS and clarified the pivotal role of the vascular endothelial growth factor (VEGF) family of proteins and their receptors in tumor development. Additionally, fibroblast growth factor (FGF-2) plays a pathogenetic role in KS, not only by promoting angiogenesis, but also by conferring a transformed phenotype on KS cells. Matrix metalloproteinases (MMPs) are associated with KS tumorigenesis and may contribute to the mechanism of KS invasive growth. Notably, MMPs 2 and 9 have been associated with different phases of angiogenesis and can contribute to angiogenesis by disrupting the vessel basement membrane and other extracellular matrix barriers and enabling endothelial cell migration through the surrounding tissues.

Propranolol is a nonselective β-blocker that interferes with endothelial cells, vascular tone, and angiogenesis and induces apoptosis in proliferating endothelial cells, resulting in tumor regression. On the other hand, propranolol causes the blockade of proangiogenic signals by down-regulation of angiogenic factors such as VEGF, FGF-2, MMP-2, and MMP-9 and results in the arrest of growth of hemangiomas.

Taken altogether, given the ability of propranolol to interfere with several essential steps of neovascularization and its decrease of several related molecules and signaling pathways such as VEGF, FGF-2, MMP-2, MMP-9 and induction of apoptosis, it could open up a novel therapeutic opportunity for treatment of KS. Our short paper justifies and encourages the conduction of clinical trials on this subject.

REFERENCES

To the Editor:
The rosette sign represents a dermatoscopic structure seen exclusively with polarized light examination. It is characterized by the presence of 4 white globules symmetrically arranged, creating a square, with a configuration similar to a 4-leaf clover. It is possible to be located in the center of the follicular openings, and it may correspond histologically to a hyperkeratotic area with orthokeratosis or parakeratosis (flag sign).

In the literature, there is only one report to date that demonstrates the rosettes in actinic keratosis, lichenoid keratosis, and squamous cell carcinoma over actinic keratosis. We present 4 other dermatoses in which the authors had the opportunity to observe the presence of rosettes: flat seborrheic keratosis (Figure 1), pigmented (Figure 2) and nonpigmented basal cell carcinoma (Figure 3), and melanoma (Figure 4). In all of these lesions, contact dermatoscopy with polarized light was performed, and the diagnosis was confirmed by histopathology.

We report these findings to demonstrate the rosette sign in different conditions other than those already described, in addition to stimulating practitioners to identify one more interesting dermatoscopic finding. Only with a larger number of cases the confirmation of the importance of this new structure will be possible.

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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 glucocorticosteroid 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 systematically at relatively low dosage levels. Systemic 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) in this HPA axis study were different from the subject population (mild to moderate atopic dermatitis) and the dosing regimen (two 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 to 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:

Apply a thin layer to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin areas two times daily for atopic dermatitis in patients 3 months of age and older. Safety of Locoid Lipocream in pediatric patients has not been established beyond 4 weeks of use.

Rub in gently. Avoid contact with the eyes. Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician. Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings. Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician. If no improvement is seen within 2 weeks, contact your physician. Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

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.

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