EDITORIAL
Bed Bugs Revisited
Lavery and Parish

ORIGINAL CONTRIBUTIONS
High Frequency of Psoriasis in Relatives in a Turkish Multiple Sclerosis Cohort
Dogan, Atakan, Karne, and Karabudak

Advances in Topical Delivery Systems in Acne: New Solutions to Address Concentration Dependent Irritation and Dryness
Ceilley

REVIEWS
The Tzanck Smear Test: Rediscovery of a Practical Diagnostic Tool
Durdu, Sekin, and Baba

Fatigue in Psoriasis With Arthritis
Carneiro, Chaves, Verardino, Drummond, Ramos-e-Silva, and Carneiro

CORE CURRICULUM
Nail Biology, Morphologic Changes, and Clinical Ramifications: Part I
Sehgal, Aggarwal, Srivastava, and Chatterjee

DEPARTMENTS
NEW THERAPY UPDATE
Veltin Gel
(Clindamycin Phosphate 1.2% and Tretinoin 0.025%)
Abramovits, Oquendo, and Gupta

PERILS OF DERMATOPATHOLOGY
Why Immunofluorescence?
Husain, Rojas, Maghari, and Lambert

CONGRESS REPORT
Scratching the Surface: The History of Skin, Its Diseases and Their Treatment—History of Medicine Unit, University of Birmingham, October 29–30, 2010 [Parallel Publication]
Wynter

CASE STUDIES
Longitudinal Erythronychia: The Value of Cosmetic Alterations in Nail Findings
Rasid, Torres-Cabala, and Chon

A Case of Cinderella: Erythema Dyschromicum Perstans (Ashy Dermatosis or Dermatosis Cinecienta)
Muñoz and Chang

Bullous-Hemorrhagic Darier Disease
Sánchez-Salas, Aranibar, Torres, and Giusa

BOOK REVIEW
Dermatologic Complications With Body Art: Tattoos, Piercings, and Permanent Make-Up
Reviewed by Parish
**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%
Rx only
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.

Dry skin of mild to moderate severity was the most frequently reported (≥ 1%) treatment related adverse event. Erythema, scaling, dryness, burning/stinging were also seen during treatment.

DRUG INTERACTIONS

Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in preparing 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, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion.

In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed. No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g. retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to sunlight or artificial irradiation sources.

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

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₁ males and females, or growth, development and reproductive function of F₂ offspring.

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

• This product is for external use only.

Marketed by:
GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA

Manufactured by:
Galdema Production Canada Inc., Baie d’Urfé, QC, H9X 3S4 Canada
Made in Canada.
GALDERMA is a registered trademark.
PS1503-0
Revised: March 2010


Galderma is a registered trademark. ©2010 Galderma Laboratories, L.P.
Galderma Laboratories, L.P.
14501 W. Freeway
Fort Worth, TX 76177
diff-113 Printed in USA 09/10
www.diff.com/NCP

Committed to the future of dermatology
6th ANNUAL EDUCATIONAL CONFERENCE
March 4-5, 2011 | Nashville, Tennessee

A weekend of educational learning and training to grow your knowledge of lasers, light sources, and the cosmetic industry.

Industry Workshops | Lectures | Exhibits
Friday night Welcome Reception sponsored by DUSA

Complete Brochure and Registration Form available at http://www.tnlasersociety.com

TSLMS
Tennessee Society for Laser Medicine and Surgery, Inc.

For more information call (615) 460-1650 or email wilma.cooley@tnmed.org

Conference Workshops:
Total Body Rejuvenation - sponsored by Syneron / Candela
Keys to a Successful Aesthetic Practice with the Latest in Laser Hair Removal and CO2 Fractional Laser Resurfacing - sponsored by Lumenis

Featured Lectures:
Nonablative and Ablative Fractional Resurfacing
Cellulite and Body Shaping Devices
Laser Lipo, Lipolysis, and Liposuction of the Neck, Trunk, and Extremities
Vascular and Pigment Laser Update
The Treatment of Melasma
Lasers in Skin of Color
Complications with Lasers and Light
Toxin and Filler Update – 2011
Combining Fillers and Minimally Invasive Surgery
My Most Unusual Laser Case
...and more

Tennessee Society for Laser Medicine and Surgery, Inc.
# TABLE OF CONTENTS

## EDITORIAL

**Bed Bugs Revisited** ......................................................................................................................................... 6  
*Michael Joseph Lavery; Lawrence Charles Parish, MD, MD (Hon)*

## ORIGINAL CONTRIBUTIONS

**High Frequency of Psoriasis in Relatives in a Turkish Multiple Sclerosis Cohort** ................................. 11  
*Sibel Dogan, MD; Nilgün Atakan, MD; Asli Kurne, MD; Rana Karabudak, MD*

**Advances in Topical Delivery Systems in Acne: New Solutions to Address Concentration Dependent Irritation and Dryness** ................................................ 15  
*Roger I. Ceilley, MD*

## REVIEWS

**The Tzanck Smear Test: Rediscovery of a Practical Diagnostic Tool** ......................................................... 23  
*Murat Durdu, MD; Deniz Seçkin, MD; Mete Baba, MD  
Self-Test Review Questions (p. 32)*

**Fatigue in Psoriasis With Arthritis** ................................................................................................................. 34  
*Claudio Carneiro, MD; Mario Chaves, MD; Gustavo Verardino, MD; Alexandre Drummond, MD; Marcia Ramos-e-Silva, MD, PhD;  
Sueli Carneiro, MD, PhD*

## CORE CURRICULUM

**Nail Biology, Morphologic Changes, and Clinical Ramifications: Part I** ...................................................... 39  
*Virendra N. Sehgal, MD; Ashok K. Aggarwal, MD; Govind Srivastava, MD; Kingsuk Chatterjee, MBBS*

## DEPARTMENTS

**New Therapy Update**  
*William Abramovits, MD; Aditya K. Gupta, MD, Section Editors*

**Veltin Gel (Clindamycin Phosphate 1.2% and Tretinoin 0.025%)** ................................................................. 49  
*William Abramovits, MD; Marcial Oquendo, MD; Aditya K. Gupta, MD*

**Perils of Dermatopathology**  
*W. Clark Lambert, MD, PhD, Section Editor*

**Why Immunofluorescence?** ........................................................................................................................... 52  
*Zain Husain, BS; Javier Rojas, MD; Amin Maghari, MD; W. Clark Lambert, MD, PhD*

**Congress Report**  
*Marcia Ramos-e-Silva, MD, PhD, Section Editor*

**Scratching the Surface: The History of Skin, Its Diseases and Their Treatment—History of Medicine Unit, University of Birmingham, October 29–30, 2010 [Parallel Publication]** .............................................. 56  
*Rebecca Wynter, MPhil, PhD*
CASE STUDIES

Vesna Petronic-Rosic, MD, MSc, Section Editor

Longitudinal Erythronychia: The Value of Cosmetic Alterations in Nail Findings ............................................... 60
Rashid M. Rashid, MD, PhD; Carlos Torres-Cabala, MD; Susan Chon, MD

A Case of Cinderella: Erythema Dyschromicum Perstans (Ashy Dermatosis or Dermatosis Cincicentia) ............ 63
Claudia Muñoz, MD, MPH; Anne Lynn S. Chang, MD

Bullous-Hemorrhagic Darier Disease ............................................................................................................. 65
María Pilar Sánchez-Salas, MD; Francisco Javier García Latasa de Aranibar, MD; Rosa Oncín Torres, MD; Paula Gambó Grasa, MD

BOOK REVIEW

Noah S. Scheinfeld, MD, JD, Section Editor

Dermatologic Complications With Body Art: Tattoos, Piercings, and Permanent Make-Up ................................ 68
Reviewed by Lawrence Charles Parish, MD, MD (Hon)
EDITORIAL

Bed Bugs Revisited
Michael Joseph Lavery; Lawrence Charles Parish, MD, MD (Hon)

Night night, sleep tight
Don't let the bed bugs bite
If they do, squeeze them tight
And they won't bite another night
—Irish bedtime verse

CONTRIBUTING FACTORS

The folklore that bed bugs are present due to poor hygiene and sanitation is still true, but lack of cleanliness does not account for reports from homes with good housekeepers or even from luxury hotels. When dichlorodiphenyltrichloroethane (DDT) was used, some observers even considered the use of insecticides as creating the presence of bed bugs. This is erroneous, as the insecticide forced the bed bugs out from their hiding places in mattresses, upholstered furniture, and the crevices in plaster walls.

Could increased air travel be contributing to the problem? People can move from infested areas quickly, bringing bed bugs with them in their luggage; therefore, suitcases are best kept on stands and away from the floor. Moreover, recent treatments may be less effective, due to the development of resistance and the delayed mechanism of action in the newer agents. DDT was insecticidal, but its ban in 1972 due to its effects on the food chain and possible link to cancer resulted in fewer bed bug deaths. In addition, some bed bugs have undergone mutations, resulting in certain treatments that work in some states and not in others, eg, bed bugs in Florida are 264 times less resistant to 1% deltamethrin than are New York bed bugs.

ENTOMOLOGY

Bed bugs belong to the family Cimicidae and are homeothermic ectoparasites, feeding primarily on mammals but also on poultry and rodents. The most common genus causing the current problems is Cimex lectularius. Other forms include Cimex hemipterus (mainly in the tropics) and Leptocimex bouleti (mainly in South America and West Africa).
The butterfly has wings of gold,
The fiery wings of flame,
The bed bug has no wings at all,
But he gets there just the same9

Bed bugs are reddish brown, flat, oval-shaped, wingless, typically measure 4 to 7 mm, are big enough to be seen, and are small enough to enter through cracks in the wall or under doorways; therefore, their spread is not totally confined to the attachment to clothing and luggage (Figure 1). Common nesting areas are those where there is minimal light, including behind paintings, under ripped wallpaper or posters, near couches, around the bed, in the mattress, on the bed board, on the night stand, or even outside the house (eg, cars, bus shelters, hospitals, nursing homes, public transport systems), anywhere it is well hidden, dark, and close to a carbon dioxide (CO2) source. They usually remain clustered together and near the victim, because they are wingless6 and attracted to the exhaled CO2 (too high a level of CO2 can be fatal).10

Bed bugs can live for about a year without eating,11 if the surrounding conditions are adequate. In a laboratory, they are known to survive for up to 4 years and even for more than 18 months without any food.1 The optimum temperature for temperate bed bugs is 79°F and for tropical bed bugs 97°F, but after 2 weeks at 104°F (with no air conditioning), temperate bed bugs are effectively dead, and they cannot produce viable offspring (M. T. Siva-Jothy, personal communication, August 12, 2010).

CLINICAL FEATURES
Signs of bed bug bites can take several days to occur, with up to 50% of individuals, showing no reaction.2 The telltale sign of a bed bug bite is a red macular wheal in clusters of 3: breakfast, lunch, and dinner on exposed areas (mainly face, arms, hands, and legs) (Figure 2). There is itching, sometimes severe enough to cause the victim to excoriate the involved areas, leaving crusts and possibly leading to superimposed pyoderma. These bites may cause bleeding, and continual scratching can lead to infection.6 Other signs of bed bug infestation include blood on the mattress, dead bed bugs and/or fecal material, and a sweet musty odor coming from the ventral stink glands of the bed bug.8

Bed bugs usually begin feeding on their prey around an hour before dawn, using their proboscis to attach to the skin—usually the face, arms, or legs—but any exposed skin can be affected. Once the bed bug has bitten, it injects its saliva, which contains an anesthetic that numbs the area and an anticoagulant, which eases the flow of blood from humans to the bug through the proboscis more easily.11 Feeding lasts between 3 and 12 minutes, upon which the bed bug returns to its nesting area to mate, lay eggs, or digest its recent meal. The amount of blood drawn varies but can be 6 times its own weight.12 Some nights, a patient can sustain more than 100 bites.6

TREATMENT
Just as there is the trio of breakfast, lunch, and dinner, so intervention should include another threesome: symptomatic relief, fumigation, and prevention. Relief can be accomplished with topical steroids. Fumigation is needed, as bed bugs quickly reproduce with thousands of progeny in just a few weeks.2 Such insecticides used include deltamethrin, permethrin, and pyrethrins, as well as newer agents such as chlorfenapyr or hydroprene.12 Washing bed clothing, cleaning drapes and upholstery, and repairing torn wallpaper and disreputable plaster are useful preventive measures.

Were it not for the expense, trained dogs are able to detect the bed bug odor and thus their hiding places.13 Studying the female organ spermalege could result in a new antibiotic for human therapy (M. T. Siva-Jothy, personal communication, August 12, 2010).

CONCLUSIONS
Bed bugs are currently an irritation, but their worldwide increase in incidence is worrisome. Unsanitary conditions are no longer
the only associated factor, with increase in travel and resistance to drug treatments playing a role. Vigilance and fumigation on the slightest provocation are advised. Although bed bugs cannot be exterminated from this earth, their numbers can be controlled by even the simplest of measures to prevent a full-blown pandemic. Prevention is better than cure.

Once bitten, twice shy!

REFERENCES


HISTORICAL DIAGNOSIS & TREATMENT

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

DIAGNOSIS: In a fully developed case there is little likelihood of confusion, though in its early stages the disease can be distinguished from papular urtica only after long observation. Generalized eczema does not spare the flexures and is protean and much less obstinate. Scabies affects the hands and penis. In pediculosis corporis the duration of the disease, the distribution of the lesions, the long parallel scratch marks and the presence of the parasites make the differential diagnosis easy.

TREATMENT: There are no specific remedies. As a rule the most that can be accomplished is to mitigate the severe itching. Cannabis indica and potassium bromide are helpful at times. Frequent warm baths with sapo mol lis followed by inunctions with a two to five per cent betanaphthol salve, unguentum sulphuris, unguentum sulphuris compositum, N. F., or a simple emollient ointment prove very beneficial in some cases.
Introducing VELTIN Gel—A New Topical Treatment for Patients 12 Years or Older With Acne Vulgaris

Once-daily application in the evening

VELTIN Gel

Combines the acne-fighting properties of tretinoin and clindamycin
Contains tretinoin, solubilized in an aqueous-based gel
Combats inflammatory and noninflammatory acne

Important Safety Information for VELTIN Gel

VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
Observed local treatment-related adverse reactions (≥1%) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased
VELTIN Gel should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. VELTIN Gel should be used with caution in patients receiving such agents
VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
It is not known whether either clindamycin or tretinoin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Due to possible serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug. Exercise caution if administering VELTIN Gel to a nursing woman
The efficacy and safety have not been established in pediatric patients below the age of 12 years
VELTIN Gel is not for oral, ophthalmic, or intravaginal use

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

6 ADVERSE REACTIONS
6.1 Adverse Reactions in Clinical Studies
The safety data reflect exposure to VEL TIN 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 VEL TIN Gel were application site reactions, including dryness (6%), irritation (5%), exfoliation (5%), erythema (4%), pruritus (2%), and dermatitis (1%). Sunburn (1%) was also reported. Incidence of skin reactions peaked at week 2 and then gradually decreased.

Local skin reactions were actively assessed at baseline and at the end of 12 weeks of treatment in patients exposed to VEL TIN Gel. At baseline (N=476), local skin reactions included erythema (24%), scaling (8%), dryness (11%), burning (8%), and itching (17%). At 12 weeks of treatment (N=409), local skin reactions included erythema (21%), scaling (19%), dryness (22%), burning (13%), and itching (15%). During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

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

7.2 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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C. There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A limited teratology study performed in Sprague-Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a daily dose of 2 mg/kg (three times greater than the maximum recommended clinical dose based on body surface area comparison) three times per week for up to 2 years 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 effects 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 have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to fetus is not known.

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

8.4 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.]

13 NONCLINICAL TOXICOLOGY
13.1 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 as clindamycin phosphate in the VELTIN Gel vehicle (32 mg/kg/day, 13 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenesis.

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 amylose. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 µg (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenzo[α]anthracene (DMBA).

In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoic-phorbol 13-acetate or mezerein for up to 20 weeks. Topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas per mouse. However, papillomas resistant to topical tretinoin suppression were at higher risk for pre-malignant progression. Tretinoin has been shown to enhance photoco-carcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photoco-carcinogenic 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.
Psoriasis is a chronic, recurrent, inflammatory skin disorder that has been recently accepted as an autoimmune disease. The presence of similar pathophysiologic mechanisms within autoimmune diseases has motivated investigators to search for a common genetic background, association, and coexistence between these diseases. Multiple sclerosis (MS), which is accepted as a model T cell–mediated autoimmune disease, has been the subject of several studies showing the associations with various autoimmune diseases. Families with MS members have also been investigated, and different patterns of autoimmune diseases have been found in different populations. Recent studies show that psoriasis is one of the autoimmune diseases that occur in MS patients’ families with a higher frequency. In this study, we investigated the familial frequency of psoriasis in a Turkish multiple sclerosis cohort compared with a similar sex- and age-matched control group.

MATERIALS AND METHODS
The records of 127 patients (78 women and 49 men; ratio, 1.59:1) with definite MS were included in this study between 2006 and 2007. All of the patients were diagnosed and followed up in the neurology department of Hacettepe University. The patients were contacted by phone and were asked whether any of their first- and/or second-degree relatives had psoriasis. The control group consisted of 125 patients (77 women and 48 men; ratio, 1.6:1) who were admitted to the internal diseases outpatient clinic of the same university.

Records of MS patients included age, symptoms and signs at onset of MS, functional neurologic systems, and disability scoring with the expanded disability status scale of the last visit. Information on a family history of psoriasis within MS patients was obtained from phone contacts made with the patients themselves. Full biological relatives, including first- (parent, sibling, child) and second-degree relatives (grandparents, uncles/aunts, nephews/nieces) were considered.

STATISTICAL ANALYSIS
Contingency tables were analyzed by Fisher exact test and chi-square test. Frequency and descriptive analysis was made on SPSS 11.0 (SPSS Inc, Chicago, IL).

RESULTS
Demographic characteristics of MS and control groups are given in Table I. There were no significant differences between the groups with regard to age and sex. Eight relatives of MS patients had psoriasis, whereas only one relative had psoriasis in the control group. Although a higher frequency of psoriasis is found in MS patients’ relatives, a statistically significant increased risk of psoriasis was not obtained ($P > .05$). All of the psoriatic relatives had chronic plaque-type psoriasis.

The relatives with psoriasis in MS and control groups are shown in Table II. Most relatives with psoriasis in the MS population were fathers ($n=2$) and brothers ($n=2$), but this frequency was not significant with respect to other relatives who were a mother ($n=1$), sister ($n=1$), nephew ($n=1$), and niece ($n=1$) ($P > .05$).

The mean age of MS onset of patients who had a relative with psoriasis was 31.8 years, while the patients without psoriatic relatives had
a mean onset age of 32.3 years. There was no statistically significant difference in age of onset when MS patients were compared according to psoriasis history in relatives ($P > .05$).

The symptoms and signs at onset of MS patients with and without psoriatic relatives are compared in Table III. There were no significant differences between patient groups with respect to signs and symptoms at onset.

**DISCUSSION**

In this study, although not statistically significant, a higher frequency of psoriasis was found in relatives of MS patients. An increased risk for psoriasis in MS patients and their relatives could not be defined. The prevalence of psoriasis in an otherwise healthy Turkish population has been estimated to be 1% to 2% in previous reports; therefore, the psoriasis prevalence of 6.2% within the relatives of MS patients in our study was strikingly engrossing. We believe that there could have been false-negative family histories, resulting in a probable higher frequency of psoriasis in MS families, because the data were retrospectively collected by phone.

Three of the MS patients had psoriasis themselves. Their psoriasis onset ages were 15, 20, and 41 years and MS onset ages were 22, 35, and 42 years, respectively. All of the patients who had psoriasis themselves were diagnosed in the dermatology department between 2005 and 2007. The small number of patients with coexistent psoriasis and MS inhibited the evaluation of disease interaction on prognosis for each other. In our opinion, studies and individual cases should be strongly supported to be reported to understand more adequately these relationships.

In some studies, MS patients with a relative with psoriasis were found to have a younger age of onset. In our study, we found no difference of age at onset between MS patients with and without psoriatic relatives. This feature was also not evaluated as a predictor of MS disability because the duration and number of attacks of MS patient groups were not homogenous when divided according to psoriasis family history.

Psoriasis is accepted as an autoimmune T cell–mediated disorder. Like other autoimmune diseases, the associated major histocompatibility complex alleles have begun to be expressed for psoriasis. Activated T cells produce systemic inflammatory cytokines, including principally interferon gamma. Interferon gamma particularly induces ectopic class II major histocompatibility complex expression on keratinocytes and activated cytotoxic T cells. This pathomechanism supports the probability of self-intolerance in

<table>
<thead>
<tr>
<th>Relative</th>
<th>No.</th>
<th>Percentage</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>2</td>
<td>25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mother</td>
<td>1</td>
<td>12.5</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Brother</td>
<td>2</td>
<td>12.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sister</td>
<td>1</td>
<td>25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nephew</td>
<td>1</td>
<td>12.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Niece</td>
<td>1</td>
<td>12.5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
psoriasis, which seems to be the main keystone of autoimmunity. Although not fully proved, it was shown that the autoimmunity in psoriasis could be adopted by means of immune pathomechanisms, when a patient developed psoriasis after receiving syngeneic bone marrow from a psoriatic donor. In view of the evidence of autoimmunity in psoriasis, the higher frequency of psoriasis in MS patients’ relatives may be the outcome of a complex heterogenic background of autoimmunity.

CONCLUSIONS

Coexistence of psoriasis with autoimmune diseases supports the upcoming evidence of psoriasis’ own autoimmune nature. The underlying self-reactivity remains to be unknown in many autoimmune diseases, making the coexistence more crucial to define and investigate. The predictivity of these associations on disease morbidity and/or mortality requires more investigation consisting of higher numbers of patients.

REFERENCES


TRICHOMEGALY

Medication reported to cause eyelash growth

<table>
<thead>
<tr>
<th>Medication</th>
<th>Eyelash Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomid</td>
<td>Loniten</td>
</tr>
<tr>
<td>Cosopt</td>
<td>Lumigan</td>
</tr>
<tr>
<td>Cortisone-like</td>
<td>Neoral</td>
</tr>
<tr>
<td>Dilantin</td>
<td>Rogaine</td>
</tr>
<tr>
<td>Erbitux</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Litt, JZ. Curious, Odd, Rare, and Abnormal Reactions to Medications. Fort Lee, NJ: Barricade Books; 2009:164.
The power to calm inflammatory acne
- Inflammation is an important aspect in the pathophysiology of acne.
- Much laboratory and clinical studies document the anti-inflammatory effects of minocycline.

Complementary T³ Calming Wipes
Soothing and alcohol-free — part of a complete approach to acne treatment

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 *in vitro* study
  — The majority of tetracycline-resistant *P. acnes* were cross-resistant to doxycycline — but sensitive to minocycline.³

The only pelletized form of Minocycline available...

MINOCIN®
minocycline HCl  pellet-filled capsules

A dual approach to acne care
For more information, go to www.minocin-kit.com

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 effects 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.

**References:**

*In vitro activity does not necessarily correlate to in vivo activity.*
Developing effective topical dermatologic formulations is challenging, yet key, to many issues in acne treatment. Formulation influences the dosage regimen; it affects efficacy and tolerability and is interactive with compliance. In creating high-performance topicals, we must consider two formulations. The primary formulation is delivered to the patient, but once it is applied to the skin, its components (especially if there is water in the formulation) begin to evaporate. Some begin to penetrate the skin, blending with the skin’s natural hydrolipidic film, resulting in the secondary formulation. It is often from this changed formulation that the drug is delivered, and the problems of irritation occur.

**MYTHS**

There are a number of myths surrounding formulation development. A great vehicle is not great for all drugs or skin conditions. Optimal vehicles have to be customized for the active ingredient. There is a view that all gels are drying, resulting from many years ago when the initial gels used in dermatology were alcohol and acetone based. Today, there are very few remaining alcohol gels (e.g., Retin-A® gel). Another aspect is whether penetration enhancers can be put into any formulation. Penetration enhancers are drug specific and formulation sensitive. Finally, methylparaben, propylparaben, and propylene glycol have been considered by some as inappropriate in topical formulations. This is not the case: methylparaben and propylparaben are the most widely used preservatives, and sensitivity reactions are low and irritation at low concentrations is rare. Propylene glycol is also a useful multifunctional ingredient.

Therapeutic options for acne have changed little over the years, but there has been much progress in their delivery and application of therapeutic modalities, increasing both the effectiveness, as well as patient tolerability and acceptance. An in-depth understanding of the pathophysiologic mechanisms has lead to the increased use of combination therapy; however, side effects associated with various topical antiacne agents and the undesirable physicochemical characteristics of certain important agents, such as tretinoin and benzoyl peroxide (BPO), can affect their utility and patient compliance.

**WHAT IS AN EFFECTIVE FORMULATION?**

A better understanding of the physicochemical effects of both active ingredients and vehicles has led to the introduction of new products with enhanced efficacy, tolerability, and cosmetic acceptability.

An effective topical formulation must satisfy a number of key criteria:

1. Provide a stable chemical environment to accommodate multiple compounds that may have different, if not incompatible, physicochemical characteristics.
2. Enhance penetration of the active ingredients into the extremely lipophilic pilosebaceous unit.

3. Contain concentrations of active ingredients that, in combination with excipients, are effective and well tolerated.

4. Contain excipients that are not drying or irritating, but are occluding or moisturizing, which, in combination, can modulate the release of the product at the treatment site.

5. Be cosmetically acceptable and easy to apply.

**THERAPEUTIC OPTIONS**

Current evidence suggests that acne is the result of a combination of increased sebum production and follicular hyperkeratinization, compounded by the host responses to the pro-inflammatory activities of *Propionibacterium acnes*. Combination therapy, targeting the multiple components of acne, should provide better patient outcomes and is now commonplace; however, concentration- and formulation-dependent skin irritation and dryness can limit utility especially with the use of retinoids, BPO, and some formulation excipients.

Topical retinoids are one of the cornerstones of acne therapy and are recommended as first-line therapy for all but the most severe forms. They are used as monotherapy in mild comedonal acne and in combination with BPO and antimicrobials (topical or oral) for inflammatory acne.

---

**Table. Degree of Bothersomeness Caused by Fixed-Combination Products Containing 5% Benzoyl Peroxide**

<table>
<thead>
<tr>
<th>Degree of Bothersomeness</th>
<th>Dry Skin, %</th>
<th>Redness, %</th>
<th>Flaky/Peeling Skin, %</th>
<th>Itchy Skin, %</th>
<th>Irritated Skin, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
<td>14</td>
<td>10</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Mild</td>
<td>26</td>
<td>30</td>
<td>29</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>34</td>
<td>36</td>
<td>34</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Severe</td>
<td>34</td>
<td>20</td>
<td>27</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

Patients were asked to rate how bothersome each of those side effects were while using two clindamycin/benzoyl peroxide 5% marketed products (1 meaning the effects were not at all bothersome and 10 meaning they were extremely bothersome). Scores are grouped into mild (1–3), moderate (4–7), and severe (8–10).

---

**Figure 1.** Mean cumulative irritation score with varying benzoyl peroxide (BPO) concentrations. Reproduced with permission from Bucks et al.17

---

**Figure 1.** Mean cumulative irritation score with varying benzoyl peroxide (BPO) concentrations. Reproduced with permission from Bucks et al.17
Retinoids normalize the abnormal follicular desquamation associated with acne, which facilitates penetration of other antiacne agents and prevents obstruction of the pilosebaceous orifice. As a result, they can be both comedolytic and anticomedogenic, having been shown to reduce the formation of microcomedones and comedones. Retinoids also have direct and indirect anti-inflammatory effects, presumably from their actions on toll-like receptors and cytokine production.

A major drawback of retinoids is the potential to cause irritation, a side effect that is generally dose dependent. Irritation, exfoliation, dryness, and scaling with retinoid therapy is particularly common during the initial 3 to 4 weeks of treatment. Irritation can also be a limiting factor for treatment adherence in many patients.

In addition to retinoids, two topical acne medications commonly used in fixed-combination formulations are clindamycin and BPO. Clindamycin diminishes signs by reducing the levels of P. acnes and may decrease inflammation. BPO is also safe and effective, with its efficacy being maintained over many years of use and the distinct advantage of not being associated with antimicrobial resistance. In addition, BPO has keratolytic and anticomedogenic effects. As with the retinoids, the primary limitation of BPO in certain patients is concentration-dependent (and potentially formulation-dependent) skin dryness and irritation.

Surfactants, preservatives, and high levels of organic solvents often used in combination with BPO or for solubilizing retinoids are potential irritants. Alcohol and surfactants disrupt membrane lipid bilayers of the epidermal barrier. Preservatives are also sensitizing. In addition, the first-generation tretinoin products, including all the generics that followed, were solubilized formulated into a formulation containing significant levels of isopropyl myristate or alcohol. The use of these products is associated with a “burst” in penetration of tretinoin, when the medication is applied to the epidermis, causing dryness and peeling that can advance to unwanted scaling and redness.

**RESOLUTION**

Novel drug delivery strategies play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a concomitant reduction in their side effects.
Recognizing the impact of skin irritation and dryness on successful acne management is important.

In a recent survey of 200 patients with acne who had used fixed-combination products containing 5% BPO and 1% clindamycin for 6 months, 56% to 68% reported being bothered by dry skin, redness, flaky/peeling skin, or even irritation (Table). As a result, patients adopted a variety of coping mechanisms including spot treatment (33%), intermittent use (32%), or discontinuation (10%). A number of patients switched to another product, and many (41%) applied moisturizers to counteract the redness and dryness.

High concentrations of BPO (≥5%) are known to result in skin irritation that may limit patient adherence. Two commonly used fixed-combination products, containing 5% BPO and clindamycin, may be moderately irritating, but there is a meaningful reduction in irritation scores when the concentration is reduced from 5% to 2.5%. By extrapolating this information, one could create an ideal fixed-combination acne product that would be used once daily, contain a low concentration of BPO (<5%), be stable, and be formulated in a vehicle, enhancing BPO bioavailability and minimizing irritation.

**ACANYA® GEL**

A unique formulation of BPO 2.5% with clindamycin phosphate 1.2% (Acanya gel; Coria Laboratories, Aliso Viejo, CA) is a once-daily, fixed-combination acne product to combine a low concentration (2.5%) of microdispersed BPO particles, delivered in a hydrogel with a nonirritating excipient, acting as both a humectant and a penetration enhancer.

The aqueous gel formulation BPO 2.5%/clindamycin phosphate 1.2% achieves stability between two otherwise incompatible active ingredients: solubilized clindamycin phosphate and a microsuspension of BPO. Low amounts of propylene glycol act as a humectant-type moisturizer and effective delivery solvent for the BPO, following application to the skin, and allows for good bioavailability without compromising cosmetic elegance. In addition, the uniformly distributed suspended micronized particles further minimize irritation compared with solubilized BPO.
A 21-day cumulative irritation study showed that reducing the BPO concentration from 5% to 2.5% in a series of clindamycin/BPO fixed combinations with common vehicle reduced irritation by 33% (Figure 1). In addition, this gel was shown in an in vitro percutaneous absorption study to have comparable bioavailability with other marketed fixed combinations where the concentration of BPO was higher (5%) (Figure 2).

The gel was studied for the once-daily treatment of moderate to severe acne in more than 2800 patients. Unlike many previous studies on fixed-combination products, almost 19% of patients had severe acne, based on Evaluator Global Severity Score. By week 12, the median percent reduction in inflammatory lesions with 2.5% BPO/clindamycin phosphate 1.2% was 64%, compared with a 54% reduction with clindamycin phosphate (1.2%), 55% reduction with BPO 2.5%, and 34% reduction with vehicle (P<.001) (Figure 3). Median percent reductions in noninflammatory lesions and total lesions were 49%, 40%, 41%, and 26% and 52%, 45%, 46%, and 27%, respectively. Of significance, cutaneous tolerability was excellent. Mean scores for erythema, scaling, itching, burning, and stinging at each postbaseline visit were <1 (1 = mild) and comparable with active ingredients and vehicle (Figure 4).

**ATRALIN® GEL**

Atralin gel (tretinoin 0.05%; Coria Laboratories, Aliso Viejo, CA) uses a low concentration of dispersed controlled-release micronized particles of tretinoin in a moisturizing hydrogel vehicle to avoid localized hot spots of high tretinoin concentration. Also, the gel formulation contains excipients that are commonly found in skin-hydration and moisturizer products (soluble collagen, sodium hyaluronate, and glycerin). In addition to minimizing irritation, it maximizes efficacy. This was addressed by ensuring that the particles were very small to target follicular...

**Figure 4.** Cutaneous tolerability of 2.5% benzoyl peroxide (BPO)/1.2% clindamycin phosphate compared with vehicle. Black rectangle = clindamycin/BPO 2.5%; yellow rectangle = vehicle. All scores were ≤0.3, where a score of 1 = mild. Mean scores (scale 0 [none] – 3 [severe]). Adapted from Thiboutot et al with permission from the American Academy of Dermatology.

**Figure 5.** Deposition of micronized particles of tretinoin in tretinoin gel 0.05%.
penetration and direct uptake into the sebum through the follicular opening (Figure 5).

Tolerability of Atralin gel is excellent. Analyses of the combined studies demonstrate a low incidence of skin-related adverse events (AEs) after treatment with tretinoin gel 0.05%; 70% of patients reported no skin-related AEs.21 The most commonly reported skin-related AE within the tretinoin gel 0.05% group was dry skin (16%). This is in comparison with the higher-strength tretinoin 0.1% microsphere, where the overall incidence of skin-related AEs was 52% (P<.001 vs 0.05% tretinoin) and dry skin occurred in 30% of patients (Figure 6). In addition, peeling/scaling/flaking skin was reported by 30% of patients treated with tretinoin 0.1% microsphere (compared with only 12% taking tretinoin gel 0.05%) and erythema in 18% of patients (compared with 7% taking tretinoin gel 0.05%).

Skin-related AEs generally resolved within the first 4 weeks of treatment and were similar to baseline at week 12; furthermore, the incidence rates observed with tretinoin gel 0.05% in the combined analysis were 50% to 75% lower than those rates reported in the literature for other marketed tretinoin formulations containing half the concentration of tretinoin gel (ie, 0.025%).22,23

CONCLUSIONS
Developing topical formulations in dermatology is challenging but necessary if patient outcomes are to be improved. A better understanding of the pathophysiology of acne has helped to consolidate our views on the best treatment options; however, retinoids and fixed-combination products containing BPO can cause dose-dependent and formulation-dependent irritation and dryness, limiting use in some patients and resulting in a number of coping mechanisms. Recent advances in formulation technology have permitted the development of products that are both effective and well tolerated.

Acknowledgement and disclosure: Brian Bulley, MSc, assisted in the development of this manuscript. Dr Ceilley is a consultant for Coria Laboratories, Aliso Viejo, CA.

REFERENCES
5 Ghali F, Kang S, Leyden J, et al. Changing the face of acne...


We improve your looks with our formulas... and now our look is improved too, with DNA FOCUSED SKINCARE

DISTRIBUTED BY: AXIA MEDICAL SOLUTIONS
CALL 866-494-4466 for information or samples
Cytology is a diagnostic method based on the investigation of characteristics of individual cells. Morphologic features of cells change in various diseases. Cytology examines these alterations for the early diagnosis and treatment of diseases. This diagnostic method has been used for the diagnosis of diseases of various systems since the mid-19th century. For dermatologic diseases, cytology was first used by Arnault Tzanck in 1947. To date, the Tzanck smear test has been used in the diagnosis of various erosive-vesiculobullous and nodular lesions, including many tumors. The sampling methods for Tzanck smears and the cytologic findings of a broad range of skin diseases that could provide a rapid diagnosis are described. (SKINmed. 2011;9:23–32)

The Tzanck smear test is a simple, rapid, valuable, and cost-effective diagnostic method based on the investigation of characteristics of individual cells. In this method, materials are obtained by various techniques and then transferred to a glass slide. Slides can be stained with various dyes and then are examined under a light microscope. To date, cytology has mostly been used in the diagnosis of various erosive-vesiculobullous and nodular lesions, including many tumors. The sampling methods for Tzanck smears and the cytologic findings of a broad range of skin diseases that could provide a rapid diagnosis are described. (SKINmed. 2011;9:23–32)
### Major Indications for a Tzanck Smear Test With Relevant Main Findings

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Cytologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous infections</strong></td>
<td></td>
</tr>
<tr>
<td>Cutaneous infections</td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Bullous impetigo</td>
<td>Dyskeratotic acantholytic cells, abundant neutrophils, and clusters of cocci(^1)</td>
</tr>
<tr>
<td>SSSS</td>
<td>Dyskeratotic acantholytic cells, absence of abundant neutrophils, and cocci(^6)</td>
</tr>
<tr>
<td>Mycobacterial infections</td>
<td>Negative images of mycobacteria, acid-fast bacilli(^7)</td>
</tr>
<tr>
<td>Bacillary angiomatosis</td>
<td>Clumps of coccobacilli of <em>Bartonella henselae</em> in Warthin-Starry–stained smears(^8)</td>
</tr>
<tr>
<td>Fungal infections</td>
<td></td>
</tr>
<tr>
<td>Dermatophytic infections</td>
<td>Hyphae and spores(^9)</td>
</tr>
<tr>
<td>Candidiosis</td>
<td>Pseudohyphae and spores(^9)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>Septate hyphae with 45-degree angle branching and/or aspergillus heads(^9)</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>Ribbon-like, nonseptate, thin-walled hyphae(^9)</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Broad-based budding spores(^10)</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Spherical, oval, or cigar-shaped yeasts and asteroid bodies(^11)</td>
</tr>
<tr>
<td>Viral infections</td>
<td></td>
</tr>
<tr>
<td>Herpetic infections</td>
<td>Acantholytic cells, multinucleated giant cells, and eosinophilic inclusion bodies(^1)</td>
</tr>
<tr>
<td>Hand, foot, and mouth disease</td>
<td>Syncytial nuclei, absence of acantholytic cells(^1)</td>
</tr>
<tr>
<td>Human papillomavirus infections</td>
<td>Koliocytes(^12)</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Intracytoplasmic inclusion bodies (&quot;Henderson-Patterson’s bodies&quot;)(^1)</td>
</tr>
<tr>
<td>Miller’s nodule and orf</td>
<td>Intracytoplasmic inclusion bodies (&quot;Guarnieri’s bodies&quot;)(^13)</td>
</tr>
<tr>
<td>Parasitic infestations</td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Ellipsoid-shaped Leishman-Donovan bodies(^1)</td>
</tr>
<tr>
<td>Demodicosis</td>
<td>More than 5 Demodex mites/cm(^2)</td>
</tr>
<tr>
<td>Scabies</td>
<td><em>Sarcoptes scabiei</em> with 4 pairs of legs and multiple dorsal cuticular spines(^14)</td>
</tr>
<tr>
<td>Cutaneous amoebiasis</td>
<td>Trophozoites of <em>Entamoeba histolytica</em>(^15)</td>
</tr>
<tr>
<td>Immunobullous disorders</td>
<td></td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Acantholytic cells with direct immunofluorescence positivity(^12)</td>
</tr>
<tr>
<td>Other autoimmune bullous diseases</td>
<td>Nonspecific(^12)</td>
</tr>
<tr>
<td>Erythema multiforme, TEN</td>
<td>Apoptotic and necrotic cells, absence of acantholytic cells(^16)</td>
</tr>
<tr>
<td>Genodermatoses</td>
<td></td>
</tr>
<tr>
<td>Hailey-Hailey disease</td>
<td>Acantholytic cells without direct immunofluorescence positivity(^16)</td>
</tr>
<tr>
<td>Darier’s disease</td>
<td>Acantholytic cells, corps ronds, grains(^1)</td>
</tr>
<tr>
<td>Spongiotic dermatitis</td>
<td>Presence of more than 10 tadpole cells at ×100 magnification(^17)</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>Tadpole cells and lymphocytes(^18)</td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>Tadpole cells and polymorphonuclear leukocytes(^18)</td>
</tr>
</tbody>
</table>

*Table continued on adjacent page*
with a swab. Ulcerated lesions are gently cleaned to remove the excess tissue. If the ulcerated lesion has a crust, it is removed with sterile forceps. The base of the ulcer is then scraped by the blunt end of a scalpel (Figure 1M and 1N). Touch smear preparation is usually used for some of the infectious and neoplastic skin diseases. For a touch smear, the ulcerated tissue is touched to the glass slides, or the biopsy material is held by forceps and touched on the glass slides at several points without causing undue pressure or lateral movement (Figure 1O).²³,²⁵

**Staining of Samples**

The most commonly used stain is May-Grünwald-Giemsa (MGG) (Bio-optica, Milan, Italy).¹ The others include Wright, Diff-Quick, Papanicolaou, and hematoxylin and eosin (H&E) stains. Smears can be quickly stained by the MGG (20–25 seconds) and Diff-Quick (2 minutes) stains. The Papanicolaou stain is especially used to demonstrate viral inclusion bodies for the diagnosis of warts and other viral infections.⁹

Immediate alcohol fixation is required for both Papanicolaou and H&E stains. For other staining methods, specimens should be stained as soon as they have been air-dried. If not, excessive drying results in cellular swelling and loss of nuclear details; however, cytoplasmic and background details are protected.⁹,¹⁰

If necessary, other staining methods such as Gram staining for bacterial infections, acid-fast staining for mycobacterial infections, methylene blue or toluidine blue stainings for mastocytosis, and periodic acid-Schiff (PAS) or Gomorri’s methenamine silver (GMS) stainings for deep fungal infections can be used.⁷,¹⁰ If a Tzanck smear test shows only acantholytic cells, direct immunofluorescence study on smears can be additionally performed.²⁶
Cytologic Findings

Cutaneous Infections
Cytology can be the first diagnostic tool for detection of various bacterial, fungal, viral, and parasitic agents. Presence of abundant macrophages, neutrophils, or multinucleated giant cells with or without granuloma formation should alarm the cytologist about the possibility of an infectious process.10

Bacterial Infections
Most bacterial agents can be detected by using routine cytologic stains, but some bacteria need to be identified by additional stains such as acid-fast (Mycobacteria and Nocardia species) or Warthin-Starry (Bartonella henselae and spirochetes) stains. Cytology reveals morphologic type of bacteria such as bacilli or cocci. Besides, most bacteria can be classified as Gram-positive or Gram-negative by Gram staining. Gram-positive bacteria appear purple or deep blue, whereas Gram-negative bacteria appear red or pink.9

Bullous impetigo. Cytologic features are highly sensitive (92%) and specific (100%) for bullous impetigo.16 Scruping smear of bullous impetigo lesions shows acantholytic cells, abundant neutrophils, and clusters of cocci. Some of the acantholytic cells are dyskeratotic. Gram-stained specimens reveal clusters of Gram-positive cocci. By contrast, cocci are not observed in staphylococcal scalded skin syndrome (SSSS), because this disease is caused by an exfoliative toxin of Staphylococcus aureus that causes an infection in a distinct area.6,13

Tuberculosis. Mycobacteria cannot be identified by routine cytologic stainings; therefore, unstained bacilli are observed as “negative images” or “ghost bacilli.” Acid-fast staining discloses pink or red bacilli. Presence of these acid-fast–positive bacilli is highly probable in lesions that show caseation necrosis with or without granulomas.27

Leprosy. Interpretation of cytologic findings is probably most difficult in leprosy due to the variable morphology of Mycobacterium leprae. Acid-fast bacilli can appear in rod-shaped, fragmented, or granular forms. The bacilli are easily detected in patients with lepromatous leprosy; however, they are very few in number in tuberculoid leprosy. In reactional leprosy, smears show numerous foamy macrophages with “negative” images of M leprae.28

Fungal Infections
Potassium hydroxide (KOH) is usually used for the identification of superficial fungal infections. The fungal elements of those infections can also be detected in Papanicolaou, Giemsa, or methylene blue–stained smears. Some deep fungi can be identified according to the morphologic characteristics of their hyphae on direct microscopic examinations or stained smears (Table).9 In suspected cases, confirmatory stains such as GMS and PAS can be performed.10

Viral Infections
Viruses cannot be detected by examining smears under a light microscope, but their cytopathic effects can be observed.9,10

Herpesvirus infections. The most specific but difficult to find cytologic features of herpetic infections are nuclear changes, namely prominent eosinophilic inclusion bodies (Cowdry A nuclei) resembling “eggs in a basket.” For detection of these nuclear changes, Papanicolaou and Romanowsky stains are the most...
valuable cytologic stains. The specificity of acantholytic and multinucleated giant cells (Figure 2A) for herpetic infections has been reported to be 100%. Acantholytic cells are large round keratinocytes with hyperchromatic nuclei and scanty basophilic cytoplasm. The basophilic staining is peripherally deeper on the cell membrane ("mourning-edged" cells) leading to a perinuclear halo. Due to cytopathic effects of herpes virus, multinucleated giant cells contain ≥3 syncytial nuclei, and they sometimes swell enormously to a diameter of 60 to 80 μm (ballooning degeneration). Presences of acantholytic and multinucleated giant cells in herpetic infections have been reported between 53.1% and 86%. These differences are related to the types and duration of the lesions. Positivity of those cells is decreased after 3 days and much higher in vesicles than pustules. Cytologically, differentiation between herpes simplex and varicella zoster virus infections can be made by direct immunofluorescence examination using monoclonal antibodies against herpes simplex virus and varicella zoster virus.

Hand, foot, and mouth disease. Coxsackie virus induces syncytial nuclei in epithelial cells and causes vesicles and aphthous lesions (Figure 2B). The size of each nucleus in giant cells is uniform. The number of nuclei is less than that in herpetic infections. Papainicolau staining may disclose intracytoplasmic inclusion bodies. In contrast to herpetic infections, acantholytic cells are not observed in hand, foot, and mouth disease.

Human papillomavirus infections. Cytology is useful in oral or genital warts, but it may be difficult to obtain adequate materials from cutaneous lesions. Cytologic evidence of human papillomavirus infections includes koilocytes with basophilic nucleus and punched-out perinuclear halo surrounded by a dense peripheral cytoplasm. Small eosinophilic inclusion bodies may seldom be observed in both cytospin and nucleus. All these features can be more easily seen in specimens stained with Papanicolaou stain than with other stains.

Molluscum contagiosum. Unlike other DNA viruses, the Molluscum contagiosum virus replicates in the cytoplasm of keratinocytes, leading to oval, large (30–35 μm), deeply basophilic intracytoplasmic inclusion bodies, the so-called molluscum bodies or Henderson-Patterson bodies (Figure 2C). It is difficult to observe the nuclei of infected cells.

Milker’s nodule and orf. Milker’s nodule and orf, caused by the Parapoxviruses, induce round or oval cytoplasmic eosinophilic inclusion bodies in keratinocytes known as “Guarnieri’s bodies,” which are usually surrounded by a clear halo (Figure 2D). There are also a variable number of acantholytic cells, necrotic keratinocytes, and inflammatory cells in the background.

Parasitic Infections

Leishmaniasis. A diagnostic finding for cutaneous leishmaniasis is ellipsoid-shaped parasites with a 2- to 4-μm, eccentric nucleus and paranuclear kinetoplast in the cytoplasm of macrophages and giant cells, also in granulomas or extracellular background. A large number of parasites within the cytoplasm of macrophages appear in a “swarm of bees” formation. Positive findings of parasites have been reported to be between 30% and 82.6%. These differences are related to the duration of lesions, the smear method, and the presence of secondary bacterial infections. Positive results of parasites are especially high in the first 6 months of infection; afterwards, it declines. The longer the duration of the disease, the higher the possibility of the presence of granulomas and multinucleated (Langhans type and/or foreign body type) giant cells in the lesions.

Demodicosis, scabies, and cutaneous amebiasis. Demodex mites are between 0.3 mm and 0.4 mm and live in hair follicles of mammals. They have 4 pairs of short legs and cross-striations on the abdomen. Demodicosis is not usually included in the differential diagnoses of dermatologists or the diagnosis is frequently masked by other skin diseases. The diagnosis of demodicosis needs both compatible clinical features and the presence of a high density of mites (>5 mites/cm²). Standardized skin surface biopsy is a better diagnostic tool for demodicosis than direct microscopic examination of fresh secretions from sebaceous glands. Definitive diagnosis of scabies is made...
The Tzanck Smear Test

by microscopic identification of *Sarcoptes scabiei* (KOH examination) in skin scrapings taken from the burrows or vesicles. This mite has 4 pairs of legs, multiple cuticular spines, and measures 0.3 mm.14 Direct specimens or PAS and acid phosphatase–stained specimens in cases with doubtful direct specimens show trophozoites of *Entamoeba histolytica* (15–40 μm) with finger-shaped pseudopods.15,25

IMMUNOBULLOUS DISORDERS

**Pemphigus**

Pemphigus is characterized by numerous single or loosely adherent clumps of acantholytic cells with rounded or ovoid, mostly smooth, or occasionally serrated surface. The most distinctive features of those cells are the presence of a large hyperchromatic, usually centrally situated, nucleus and pronounced nucleoli.38 The cytoplasm is scanty, usually basophilic and darker at the periphery (“mourning-edged” cells) (Figure 3A).1 Tadpole cells are usually few in number, but more than 10 tadpole cells (at ×100 magnification) are observed in pemphigus herpetiformis.16 In chronic cases, multinucleated giant histiocytes can rarely be seen. These multinucleated giant histiocytes frequently phagocytize the acantholytic cells (Figure 3B).39 Inflammatory cells are mainly neutrophilic and eosinophilic. “Sertoli’s rosette cells” consist of an epithelial cell at the center surrounded by a ring of leukocytes, and “streptocytes” are the chains of white blood cells (Figure 3C).6 Direct immunofluorescence or immunohistochemistry studies in smear show the typical immunoreactant deposition around the acantholytic cells and increase the specificity of the Tzanck smear test for pemphigus (Figure 3D).26,38

Acantholysis is a typical finding in the pemphigus group of autoimmune bullous diseases; however, it can also be observed in other skin disorders. The specificity of acantholytic cells for pemphigus has been found to be 43.4%.36 Based on the cytopathic findings, an algorithmic approach to acantholytic dermatoses has previously been proposed.16

**Erythema Multiforme**

Cytology reveals necrotic epithelial cells, leukocytes, and fibrin filaments.1 Nuclear pyknosis, karyorrhexis, and fragmentation of keratinocytes may be present in early lesions.16 A Tzanck smear may also be a rapid test to distinguish toxic epidermal necrolysis from SSSS. Toxic epidermal necrolysis shows necrotic cuboidal basal cells and leukocytes, whereas SSSS specimens reveal large, superficial squamous cells and dyskeratotic acantholytic cells without inflammatory cells and cocci.19

**Genodermatoses**

**Hailey-Hailey Disease**

Cytology of Hailey-Hailey disease is characterized by numerous acantholytic cells that mostly show round and uniformly hypertrophic nucleus and basophilic cytoplasm. Occasionally, dyskeratotic cells with pyknotic nucleus may also be seen.12 Unlike the pemphigus group, direct immunofluorescence test on smears is negative.16

**Darier’s Disease**

Cytologic findings of Darier’s disease are diagnostic. Similar to histopathologic examination, cytology reveals dyskeratotic acantholytic cells, “corps ronds,” and “grains.” Corps ronds are pyknotic keratinocytes with a round-shaped and hyaline, acidophilic cytoplasm, and a pyknotic nucleus surrounded by a clear halo. The grains are the end-product of the corps ronds. The nuclei of grains are ovoid and are surrounded by a homogeneous dyskeratotic material.1,13

**Spongiotic Dermatitis**

In spongiotic dermatitis, the nuclei of keratinocytes that form the wall of spongiform vesicles are pushed to one side due to the pressure of intraepidermal edema, and the cytoplasm takes the form of a tail (tadpole cells). The presence of tadpole cells in cytopathologic examination usually refers to contact dermatitis. Tadpole cells, however, may also be observed in many other skin diseases. It has been reported that the presence of more than 10 tadpole cells at ×100 magnification is 83% sensitive and 100% specific for spongiotic dermatitis.17 Lymphocytes are the predominant cells in the majority (84%) of allergic contact dermatitis cases, whereas polymorphonuclear leukocytes outnumber the lymphocytes in most (82%) irritant contact dermatitis cases.16

---

Figure 3. A normal keratinocyte (red arrow) and an acantholytic cell (black arrow) (A); acantholytic cells phagocytized by a multinucleated giant cell (arrows) (B); “Sertoli’s rosette cells,” an epithelial cell at the center surrounded by a ring of leukocytes (arrow) (C); and immunoglobulin G deposition around the acantholytic cell (arrow) (D) in pemphigus. May-Grünwald-Giemsa stain, magnification ×1000 (A–C); direct immunofluorescence examination, magnification ×1000 (D).
Granulomatous Diseases

Characteristic cytologic findings of granulomatous dermatitis are granuloma formation and multinucleated giant cells of Langhans, foreign body, and/or Touton types (Figure 4A). Cytology may also reveal various infectious agents (Figure 4B–4H). Furthermore, Touton-type giant cells in juvenile xanthogranuloma (Figure 4I), a foreign body in foreign body granuloma (Figure 4J), necrobioitic material in necrobiosis lipoidica (Figure 4K), and mucinous material in granuloma annulare (Figure 4L) can also be observed. An algorithmic approach to granulomatous dermatitis based on cytologic findings has been previously proposed.7

Neonatal Pustular Diseases

The Tzanck smear test is helpful in the differential diagnosis of neonatal pustular diseases. In both acropustulosis of infancy and transient neonatal pustular melanosis, abundant neutrophils and few eosinophils are observed. A Tzanck smear of pustules in erythema toxicum neonatorum, however, reveals a dense accumulation of eosinophils. All 3 dermatoses show neither bacteria nor fungal agents.19

Tumoral Lesions

Benign Tumoral Lesions

Mastocytoma. The Tzanck smear test is useful for rapid diagnosis of mastocytoma in children. Cytology shows abundant polygonal, triangular, or round mast cells (15–20 μm) with metachromatically stained granules (0.2–0.5 μm). Granules are stained basophilic with MGG, while stained reddish purple with methylene blue (Figure 5A).6

Sebaceous hyperplasia. Scraping smear shows clusters of large foamy sebaceous cells with abundant cytoplasm (Figure 5B). Unlike sebaceous carcinoma, cellular atypia is absent. Lipid staining is positive.5

Seborrheic keratosis. Cytologically, a seborrheic keratosis shows hyperkeratosis, basaloid cells, and horny cystic areas filled with keratin (Figure 5C). Pigment granules are observed in both nucleated and enucleated keratinocytes and also in the background. If lesions are flat or ulcerated, they may be mistaken for basal cell carcinoma (BCC).6

Melanocytic nevi. Cytologic examination presents epidermal and dermal type melanocytic cells (Figure 5D); however, cytologic differentiation of the benign nevoid cells from the malignant ones may be difficult.20

Malignant Tumors

The Tzanck smear test is useful in differentiating BCC from other skin tumors such as squamous cell carcinoma (SCC) and melanoma.5 For this reason, it could make a great contribution to preoperative surgical planning. The Tzanck smear test can also be used for the investigation of a possible recurrence of a previously treated neoplasm and for the follow-up of patients with chronic dermatoses in whom the development of a malignancy is possible. Furthermore, a previous study showed the effectiveness of a Tzanck smear test for intraoperative surgical margin control in the treatment of well-demarcated BCC.40

Basal cell carcinoma. Clusters of basaloid cells are the most characteristic cytologic pattern for BCC (Figure 6A). This cytologic finding has high sensitivity (97%) and specificity (86%) for BCC.41 Basaloid cells are uniform in size, elongated, and have a central oval nucleus usually without nucleoli and scanty, poorly defined basophilic cytoplasm. Nuclear dysplasia1,12 and clusters of spindle-shaped cells5 may rarely be seen. Furthermore, the adenoid type shows small dark basaloid cells in pseudoglandular arrangement, and the spaces between the cells are filled with a myxoid substance. Keratotic-type BCC reveals keratin structures and atypical keratinocytes, whereas
pigmented BCC shows melanin granules in the macrophages and epithelial cell groups and in the background.22

**Squamous cell carcinoma.** The characteristic feature is cytologic atypia of keratinocytes, namely, poikilocaryosis, poikilocytosis, nuclear contour irregularity, prominent nucleoli, nuclear molding, and mitosis (Figure 6B). In very poorly differentiated tumors, bizarre nuclei, multinucleated giant cells, and spindle-shaped keratinocytes may also be observed.5,12 In contrast to BCC, SCC does not show adherent clusters of small cells.1 These cytologic findings of SCC are sometimes difficult to differentiate from those of keratoacanthoma and Bowen's disease.5,12 Thus, histopathologic examination should be made for the definitive diagnosis.6

**Melanoma.** Cytologically, melanoma is characterized by the presence of large pleomorphic cells that may be epitheloid, spindle-shaped, rounded or mixed-type (Figure 6C). Binucleated or multinucleated cells are frequently present. Pathognomonic features are binucleated melanocytes with two symmetric and convergent nuclei ("fly-eye" nuclei).6 The nucleus may be irregular and include a large eosinophilic nucleolus. Well-defined punched-out intranuclear inclusions are characteristic of melanoma.12 Melanin granules may be found in the pale basophilic cytoplasm of cells, melanophages, and in the background.3 Cytologic diagnosis of amelanotic melanoma is difficult because the tumors can be mistaken for metastatic carcinoma. Recently, with the advances in immunohistochemical staining techniques, correct diagnosis is possible in the majority of cases with amelanotic melanoma. Immunohistochemically, S-100 staining is more sensitive but less specific, and HMB-45 staining is less sensitive but more specific.42

**Cutaneous lymphoma.** Patch lesions of mycosis fungoides show nonspecific features, while plaques and tumors show abundant, noncohesive, atypical lymphocytes with cerebriform nuclei (Figure 6D).12 Papanicolaou staining discloses folds or irregular nuclear membranes of nuclei. A scanty cytoplasm surrounds a round nucleus, but the cytoplasm is generally abundant and the nuclei show high mitotic activity in cells of anaplastic large cell lymphoma. Classification of lymphocytes can be made by performing an immunohistochemical study on smears.22

**Paget's disease.** Cytology helps to make an early diagnosis of Paget's disease. It reveals isolated or clusters of Paget's cells that have round to ovoid eccentric nuclei, dense chromatin, and prominent nucleoli. Cytoplasm contains microvacuoles, mucine, and occasionally granular melanin.1

**Kaposi's sarcoma.** Cytologic examination of lesions in Kaposi's sarcoma shows single or cohesive bundles of cigar-shaped spindle cells with occasional single prominent nucleolus (Figure 6E). The cytoplasm of the tumor cells are indefinite and basophilic. These cells are positive for CD31 and CD34.22

**Miscellaneous**

Cytology has also been used for the diagnosis of various cutaneous malignant tumors such as metastatic carcinoma, Merkel cell carcinoma, sebaceous carcinoma, and histiocytosis. It is of utmost importance that the immunohistochemical study is performed for the cytologic diagnosis of the above-mentioned diseases (Figure 6F).5,12,22 because cytologic diagnosis of tumoral lesions can sometimes be difficult due to overlapping cytologic features of certain tumors and tumor-like conditions.22

**CONCLUSIONS**

The Tzanck smear test can be used not only in the diagnosis but also in the treatment and follow-up of many skin diseases. The studies reporting the diagnostic value of a Tzanck smear test in erosive-vesiculobullous lesions are limited in the literature.16-18,29 Further cytologic studies are needed for granulomatous and tumor diseases. Diagnostic efficacy and utility of the Tzanck smear test can be increased by performing histochemical, immunohistochemical, or immunofluorescence studies when needed. If the Tzanck smear test is performed in a laboratory in some countries, such as in the United States, Canada, or Australia, it may be essential to comply with the certain laboratory quality regulations and accreditation standards. We believe that the value of cytology will be better understood in the future by more frequently using the Tzanck smear test in daily dermatology practice.
REFERENCES


SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

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

1) “Corps ronds” and “grains,” seen on Tzanck smear test of a characteristic lesion, are indicative of:
   a. bullous pemphigoid  
   b. Darier disease  
   c. erythema multiforme  
   d. Hailey-Hailey disease (benign familial Pemphigus)  
   e. pemphigus vulgaris  
   f. None of the above

2) Which of the following, seen on Tzanck smear test, is consistent with herpesvirus infection but not Coxsackie virus infection?
   a. Acantholytic cells.  
   b. Characteristic inclusions.  
   c. Multinucleated epidermal giant cells.  
   d. Visualization of characteristic changes using the Papanicolaou stain.  
   e. Visualization of characteristic changes using the Romanowsky stain.

3) Of the following, a Touton-type giant cell, seen on Tzanck smear test, is most characteristic of:
   a. foreign body granuloma  
   b. granuloma annulare  
   c. juvenile xanthogranuloma  
   d. necrobiosis lipoidica  
   e. None of the above

4) A dense accumulation of eosinophils, seen on Tzanck smear test of a characteristic lesion, is most indicative of:
   a. acropustulosis of infancy  
   b. erythema toxicum neonatorum  
   c. transient neonatal pustular melanosis  
   d. All of the above  
   e. None of the above

5) Which of the following, seen on Tzanck smear test of a characteristic lesion, are characteristic of toxic epidermal necrolysis (TEN) but not staphylococcal scalded skin syndrome (SSSS)?
   a. Dyskeratotic acantholytic cells without cocci.  
   b. Epidermal giant cells with hyperchromatic, molded nuclei.  
   c. Large superficial squamous cells.  
   d. Leukocytes.  
   e. Necrotic cuboidal basal cells.

From the Departments of Pathology and Dermatology, UMDNJ-New Jersey Medical School, Newark, NJ
Address for Correspondence: W. Clark Lambert, MD, PhD, Room C520 MSB, UMDNJ-NJMS, 185 South Orange Avenue, Newark, NJ 07101 • E-mail: lamberwc@umdnj.edu

SKINmed. 2011;9:23–32 32 The Tzanck Smear Test
Available soon...

0.0375%

A New Tretinoin Therapy
From Triax Pharmaceuticals
Skin is a universal, recurrent, chronic, and systemic inflammatory disease that affects about 2% of the world's population. It is polygenic, with unquestionable genetic predisposition, and it is influenced by environmental factors. Joint involvement appears in 40% of patients, and the most common is the asymmetric oligo/polyarticular form. The articular disease has a variable evolution, but, in 20% of patients, it is intense, debilitating, and disabling. Among the several systemic manifestations of the disease, as well as its association with the metabolic syndrome, fatigue in psoriasis patients has recently drawn great interest.3

In clinical practice, fatigue has frequently been described by patients with chronic diseases. It is the most common symptom reported by cancer patients and is almost omnipresent among patients with other chronic diseases. It may be influenced by factors such as disease activity, medication, age, sex, and duration of the symptoms.4–6

Fatigue encompasses a multidimensional expression that influences on a physical, emotional, and cognitive level, even on the social aspects of life.6,7 It frequently coexists and interacts with other factors, including mood disturbances, anemia, infections, fever, pain, sleep, and stress, making its assessment complex.7,8 The importance and relation between fatigue and quality of life were researched and documented among various diseases such as cancers, multiple sclerosis, systemic lupus erythematosus, chronic viral diseases including acquired immune deficiency syndrome, chronic kidney disease, chronic liver disease, and rheumatoid arthritis.6–10

Fatigué

In Dorland’s Illustrated Medical Dictionary, fatigue is defined as “a state of increased discomfort and decreased efficiency resulting from prolonged or excessive exertion” and “loss of power or capacity to respond to stimulation.”11

Acute fatigue affects healthy individuals, including sport participants such as speed racers, short-distance swimmers, and speed cyclists. It arises due to the exaggerated energetic substrate in a low-oxygen intake environment and thus results in low performance.6 Another type of fatigue occurs in marathon runners, resistance swimmers, tour cyclists, and long-shift heavy task workers, where the energy production is made in an aerobic manner, at a high performance rate, and where the cardiorespiratory conditions are fundamental. There are types of fatigue associated with chronic diseases, infectious diseases, psychiatric disorders, and exogenous intoxication, in which the manifestations may be acute or chronic and often overshadow the manifestations of the main disease.6 Certain medications such as methotrexate, used for treatment of psoriasis, may present an inexplicable tiredness as an adverse effect, which the patients may refer to as fatigue.1 Besides these fatigue types, there are others in which no physical or mental disease may be identified, forming a nosologic entity currently referred to as chronic fatigue syndrome, to which chapters of medical books are dedicated.8

The original fatigue sites may be divided in two areas: one whose compounds are peripheral and another where they are central. Peripheral mechanisms are scientifically grounded and result from the failure in

---

**ABSTRACT**

Patients have frequently described fatigue in association with chronic diseases, including cancer and a host of neurologic, metabolic, and psychiatric diseases. Fatigue can be influenced by factors such as the activity of the disease, medication, age, sex, and duration of symptoms. It presents a multidimensional influence with expression on physical, emotional, cognitive, and even social aspects of life. Fatigue also coexists and often interacts with other factors, including disturbance of mood, anemia, infections, fever, pain, sleep, and stress, making its evaluation complex. Psoriasis is a systemic inflammatory and chronic disease that can be widespread and recurrent. Patients with psoriatic arthritis have reduced physical activity (associated with pain, inflammation of joints, muscle hypotrophy, reduced muscular strength, and resistance), reduction of self-esteem, and depression and reduction of quality of life, leading to common somatic manifestations such as fatigue and sleep disturbances. (SKINmed. 2011;9:34–37)

---

**Fatigue in Psoriasis With Arthritis**

Claudio Carneiro, MD; Mario Chaves, MD; Gustavo Verardino, MD; Alessandra Drummond, MD; Marcia Ramos-e-Silva, MD, PhD; Sueli Carneiro, MD, PhD

**ABSTRACT**

In clinical practice, fatigue has frequently been described by patients with chronic diseases. It is the most common symptom reported by cancer patients and is almost omnipresent among patients with other chronic diseases. It may be influenced by factors such as disease activity, medication, age, sex, and duration of the symptoms.4–6

Fatigue encompasses a multidimensional expression that influences on a physical, emotional, and cognitive level, even on the social aspects of life.6,7 It frequently coexists and interacts with other factors, including mood disturbances, anemia, infections, fever, pain, sleep, and stress, making its assessment complex.7,8 The importance and relation between fatigue and quality of life were researched and documented among various diseases such as cancers, multiple sclerosis, systemic lupus erythematosus, chronic viral diseases including acquired immune deficiency syndrome, chronic kidney disease, chronic liver disease, and rheumatoid arthritis.6–10

---

From the Sector of Dermatology and Post-Graduation Course in Dermatology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Address for Correspondence: Marcia Ramos-e-Silva, MD, PhD, Rua Dona Mariana 143/C-32, 22280-020, Rio de Janeiro, Brazil • E-mail: ramos.e.silva@dermato.med.br

SKINmed. 2011;9:34–37 © 2011 Pulse Marketing & Communications, LLC
PHYSIOPATHOLOGY OF FATIGUE

In humans, fatigue is more central than peripheral and more psychological than physiological; nevertheless, it is very difficult to quantify such facts. During very intense exercising, physical fatigue can arise in a short span of time, while less intense exercises may be extended before exhaustion voids the muscular work. The determining factor in the appearance of effort fatigue is the voluntary muscular activity, in which the “feeding” substrate is progressively reduced by exhaustion due to accumulation of metabolites and lack of regulating mechanisms.6

Multiple factors accelerate the appearance of fatigue, which include heat, humidity, altitude, and muscular fitness. Other factors delay fatigue, such as pleasure, rhythm, motivation, knowledge of the steps of a task to be performed, and physical fitness. Sex and age also interfere in the establishment of fatigue.9,24

Chronic fatigue may appear following long-term activities without sufficient rest for recovery or as a sensation of tiredness that is not justified as cause from physical exercise.12

The endoplasmatic reticulum of muscular fibers (sarcoplasmatic reticulum) stocks Ca2+ ions and has Ca volt-dependent channels. Myosin has the capacity to hydrolyze ATP, which is enhanced by the Ca2+ ions and inhibited by the Mg++ ions, and its maximum activity occurs in a pH of 6.4. Actin also requires presence of Mg++ and Ca2+.25

It may be concluded that the alterations in proteins; the sarcolem; Mg++, Ca2+, and KCl quantities; pH; and energy production (mitochondria, glycogen, phosphocreatine, and ATP) interfere with muscular contraction and may thus cause fatigue.26

From a neuromagic point of view, fatigue is studied together with lassitude. Fatigue would be weariness or exhaustion due to physical or mental effort, while lassitude has a more restrictive meaning, tending more to be a lack of capacity to remain physically or mentally active.26

The intolerance to exercise (tiredness from small efforts) and fatigue are common manifestations of myopathic diseases, in which the muscles are primarily weakened, as occurs in myasthenia gravis, muscular atrophy, post-polioymelitis syndrome, in some glycogen storage diseases, and mitochondrial myopathies. Fatigue is a frequent complaint in multiple sclerosis. Patients with a neurologic disease characterized by unresting muscular activity, such as in Parkinson disease, athetosis, and Huntington chorea, complain about fatigue.27

The reduction of productivity and work capacity caused by fatigue was studied by industrial psychologists. In these studies, the importance of physical or mental motivational factors was clearly demonstrated.14,30 Real muscular weakness cannot be detected in most individuals who complain about fatigue. The individual affected by fatigue is unable to handle complex problems and tends to be less reasonable. The worker affected by fatigue cannot provide the
necessary support to his family and often turns into the tyrant who returns at night to join the family. Inferiority complexes may surface. In neurologic and psychiatric departments, anxiety and depression are frequently diagnosed in fatigued patients.23

Most patients who seek medical help due to unexplained chronic fatigue present some kind of psychiatric disorder. The most frequent symptoms are unrest, irritability, anxiety, depression, migraine, insomnia, drowsiness, and reduction in appetite and libido.31,32

CLINICAL ASPECTS OF FATIGUE
Fatigue may be acute (<1 month) or chronic (>1 month). In the acute form, the most easily identified causes prevail.22

Almost all chronic diseases may be associated with fatigue. The differential diagnosis includes infections, anemia, neoplastic diseases, connective tissue diseases, endocrinopathy, neurologic diseases, chronic kidney diseases, chronic liver diseases, metabolic diseases and tonic disorders, sleep disorders, psychiatric diseases, and many others.27–29

Chronic fatigue syndrome is the current name of the disorder characterized by severe disabling fatigue accompanied by other physical, constitutional, and neurophysiologic complaints. The frequency is higher among women (2:1), and patients are aged between 25 and 45 years, although children and elderly patients have also been diagnosed.27–29,33

Cases may occur in isolation or in groups. Famous outbreaks include those in Los Angeles County Hospital (1934), Royal Free Hospital in London (1955), and Incline Village in Nevada (1985). The etiology of such outbreaks, although suggestive of an infectious etiology or other environmental factors, were not established.27,33,34

Chronic fatigue is very common and occurs in up to 20% of the patients in general emergency clinics. The chronic fatigue syndrome is far less common and affects between 100 to 300 per 100,000 individuals in the United States.33,34

The pathogenesis of chronic fatigue syndrome is controversial and the attempted explanations include post-infectious and post-viral states (Epstein-Barr virus, retrovirus, or enterovirus), immunologic disorders, somatic worrying, or depression. Antibodies against some of those viruses have already been detected at a high rate among chronic fatigue syndrome patients, but the subsequent studies failed to confirm any relation.27–29,33

FATIGUE AND PSORIASIC ARTHRITIS
Diseases with immune characteristics frequently include fatigue among its symptoms. Psoriasis is one of the most common dermatologic/rheumatologic diseases and bears immunogenetic information (HLA Cw6, HLA B13, HLA B17, B27, B57) in its physiopathology; however, the study on the incidence or prevalence of fatigue in psoriatic arthritis or psoriasis patients was not found in the literature.23,35

The presence of a psychiatric disorder in patients with skin diseases, or resulting from them, is well known. Depression and anxiety symptoms are frequent in psoriasis and/or psoriatic arthritis patients, possibly influencing fatigue symptoms.34 Psychiatric comorbidity in skin disease patients may reach 25% and keeps a greater correlation with the quality of life score than with the clinical gravity attributed by the doctor. The presence of psychiatric comorbidity may be responsible, among other factors, for a greater perception of symptoms, including fatigue.1,36

In rheumatoid arthritis, for example, fatigue is a relatively common symptom, affecting 90% of patients and, for half of them, is the most upsetting aspect of the disease.37

Patients with rheumatoid arthritis intensively affected by fatigue perceive their fatigue as frustrating or exhausting, while those not intensively affected see fatigue as a normal phenomenon.37,38 The intensity of fatigue has been linked to age, pain, depressive thoughts, worries, and sleep disorders.38 Fatigue in rheumatoid arthritis, therefore, is more related to physical factors, depression, and psychosocial factors than to inflammation. Only a small percentage of patients with rheumatoid arthritis can be classified as being clinically depressed.39

Likewise, as in rheumatoid arthritis, patients with psoriatic arthritis also experience a decrease in physical activity (due to pain, articular inflammation, muscle hypotrophy, reduction of strength, and muscular resistance), reduction of self-esteem, and often depression and reduction in the quality of life, which leads to common somatic manifestations such as fatigue and sleep disorders.39 In addition, patients with psoriasis excessively worry about their disease and are distrustful about the treatments. Patients with such profiles are the ones who most complain about pain, pruritus, and fatigue.40

The severity of psoriasis used to be assessed only by the extension of the dermatitis, leaving aside the assessment of fatigue, the quality of life and anxiety, and depression symptoms. Psoriasis, however, can provoke disabling and life-threatening disease.40 These effects include stress, embarrassment, stigmata, and physical discomfort. With time, the patient’s emotional compromise grows, in detriment to his/her social involvement and drop in productivity in school or work, as well as the loss in self-esteem. Systematic analysis revealed fatigue as superior and different to normal tiredness, and patients believe that it is linked to the disease’s activity, bare sleep, tension of the articular components, and lack of well-being. It is considered more important than the articular symptoms.40

CONCLUSIONS
Fatigue is therefore a symptom of great relevance that has to be measured and assessed in arthritis patients, including patients with psoriasis.
REFERENCES


The nail is a dermal appendage formed through the interaction of mesoderm and ectoderm. The nails serve to protect the terminal phalanx and fingertip from traumatic impact and provide counter-pressure to the pulp that is essential to the tactile sensation involving the fingers. Nails are used for fine manipulations, scratching, protection, and beautification of the hand.

Nails are a window to the interior of the body and provide important clues to an underlying disorder. They are often subjected to trauma such as biting, chewing, breaking, or splitting and exposed to the external environment. The desire for beautiful nails is a universal phenomenon. The problem of nail trauma has increased with procedures for adorning nails such as cleaning with a brush or removing cuticles with clippers and pushers, leading to secondary infections. The most common allergens are found in nail cosmetics such as nail enamel, artificial sculptured nails, and preformed plastic tips. Contact dermatitis of the nail unit is not an unusual event. It may present as onychodystrophy, onycholysis, paronychia, or dermatitis.

Abnormalities of the nail may serve as an important clue to cutaneous disease and may provide information about disease or toxic exposures that occurred several months in the past. A complete examination of the nail, therefore, should include the shape, symmetry, and color of the nail plate, nail fold, cuticle, and nail bed. Deposits under the nail plate and changes in gross appearance, color, or shape of the nail unit should be evaluated.

**NAIL BIOLOGY**

**Anatomy**

The nail plate is the permanent component of the nail matrix. Its normal appearance and growth depends on the integrity of several constituents: the surrounding tissues or perionychium and the bony phalanx that contribute to the nail apparatus. The nail is proximally inserted in an invagination practically parallel to the upper surface of the skin and laterally in the lateral nail groove. This pocket-like invagination has a roof, the proximal nail fold, and a floor, the matrix from which the nail is derived. The germinal matrix forms the bulk of the nail unit. The proximal element forms the superficial one third of the nail, whereas the distal element provides its deeper two thirds. The ventral surface of the proximal nail fold closely adheres to the nail for a short distance and forms a gradually desquamating tissue. The cuticle is made of the stratum corneum of the proximal nail fold. The cuticle seals and therefore protects the ungual cul-de-sac. The nail plate is bordered by the proximal nail fold, which is continuous with the similarly structured lateral nail folds on each side. The nail bed extends from the lunula to the hyponychium. The nail bed presents parallel longitudinal rete ridges. This area has a firm attachment to the nail plate, and nail avulsion produces a denudation of the nail bed. Colorless but translucent, the highly vascular connective tissue containing glomus organs renders a pink color to the nail (Figure 1).

**Developmental Anatomy**

Individual digits are discernible from the 8th week of gestation. Rudimentary nails appear by the 9th week. Nail field with the...
matrix primordium underlying the proximal nail fold is well formed by 13th week. The nail plate emerges from beneath the proximal nail fold during the 14th week, the nail plate covers almost the whole nail bed by the 17th week, and the nail unit and finger grow in tandem in the 20th week of gestation.5

The nail apparatus develops and matures from the primitive epidermis between the 9th and 20th weeks of intra-uterine life. At the 20th week, the matrix cells show a postnatal type of cell division, differentiation, and keratinization, then the nail plate begins to move more distally. The nail bed at this stage loses its granular layer.5

The nail apparatus develops and matures from the primitive epidermis between the 9th and 20th weeks of intra-uterine life. At the 20th week, the matrix cells show a postnatal type of cell division, differentiation, and keratinization, then the nail plate begins to move more distally. The nail bed at this stage loses its granular layer.

**Physiology**

Man has recognized the importance of nails in their finer functions and in their existence as an extension of aesthetic beauty. Adorning, painting, polishing, sculpturing, and using preformed plastic tips have all found places in nail cosmetics, and such practice is at least as old as human civilization.6 While the desire for beautiful nails is a universal phenomenon, the more humans manipulate their nails, the more profound the attendant complications.6 The structure of claws and hooves and their evolutionary relationship to humans has recently been reviewed.

In generalized integumentary diseases, such as psoriasis, the nail apparatus, hair follicle, and epidermis are affected. The main function of the nail apparatus is to produce a strong, relatively inflexible, keratinous nail plate over the dorsal surface of the end of each digit. The nail plate acts as a protective covering for the fingertip. The flat nail plate, by exerting counterpressure over the volar skin and the pulp, allows precision and delicacy in many subtle functions of the fingers.7

The rectangular nail plate is the largest structure, resting on and firmly adherent to the nail bed. Approximately one quarter of the nail is covered by the proximal nail fold, and a narrow margin of the sides of the nail plate is occluded by the lateral nail folds. Underlying the proximal part of the nail is the half-moon lunule (white lunula). It is most prominent on the thumb and great toe and is partially/completely concealed by the proximal nail fold of other digits. The reason for the white color is unknown. The natural shape of the free margin of the nail is the same as the contour of the distal border of the lunula.

The nail plate distal to the lunula appears pink from its translucency, allowing for the redness of the vascular nail bed to be seen through it. The lateral nail fold and the adjacent tissue lateral to the nail fold is also termed the nail wall.

The definition of the nail matrix appears debatable.8 It is considered to be a localized region beneath the proximal nail, which produces the major part of the normal nail plate, the “germinal matrix.” The matrix can be subdivided into dorsal, intermediate, and ventral sections, contributing by a lamellar fashion to the formation of the nail plate.

The nail plate may appear thick up to 30% as it passes from the distal margin of the lunula to the end of the nail bed. This is not associated with an increase in cell numbers, yet it may represent compaction of the nail caused by distal tip trauma and may not be associated with nail bed or plate production.9

**Nail Abnormalities**

**Morphology**

This situation may change with disease, where the nail bed changes its histologic appearance to gain a granular layer10 and may contribute a “false nail” of cornified epithelium to the undersurface of the nail. At the point of separation of the nail plate from the nail bed, the proximal part of the hyponychium may be modified as the solehorn. Solenhorn is a central thickened structure with a dermal core, typically found on the toe of elderly persons, often associated with vascular anomalies. On close examination, apart from white proximal lunula and distal pink nail, another narrow, barely perceptible onychodermal band has been described. Perhaps, its significance is that it has a blood supply different from the main body of the nail bed. It becomes more prominent in diseases such as acrocyanosis. If the tip of the finger is pressed firmly, the band and an area just proximal to it blanch, and if the pressure is repeated several times the band reddens.

Many changes in color have been described in the onychodermal band in health and disease. Its structural significance lies in the attachment of the nail plate and the nail bed. In psoriasis, separation of the nail plate from the nail bed may become progressive if there is a breach in the onychodermal band.

The matrix is devoid of the granular layer, and cells may differentiate with an expression of trichocyte hard keratin as they become incorporated into the nail plate, alongside normal epithelial keratins.11,12 During the process, the nuclei may be retained and such retained nuclei

---

**Figure 1.** Nail structure depicting its anatomic components.
are called Pertinax bodies. Electron microscopic studies have shown that the other detail cytologic changes seen in the matrix epithelium are essentially the same as seen in the epidermis. Matrix melanocytes in the nail are different from those elsewhere by their failure to produce melanin in the normal circumstances in white persons. This can change, with melanotic streaks presenting in local inflammatory, nevoid, or neoplastic disease.

The nail bed epidermis is only 2- to 3-cells thick, having no granular layer. The transitional zone from living keratinocytes to dead ones in the ventral nail plate cell is abrupt, occurring in the space of one horizontal cell layer. The loss of the overlying nail results in the development of a granular layer, which is otherwise present only in disease states. The nail plate comprises 3 horizontal layers, namely: (1) a thin dorsal lamina, (2) the thicker intermediate layer, and (3) a ventral lamina arising from the nail bed.

A transition between flattened cells dorsally and thicker cells ventrally can be demonstrated at high magnification, while the contents of each cell appear to show a uniform fine granularity similar to a hair cuticle. The nail plate flexibility owes itself to significant amounts of phospholipids, mainly in the dorsal and intermediate layer. The nail bed dermal collagen is vertically oriented, being directly attached to the phalange periosteum and the epidermal basal lamina.

**Biochemical Changes in Nail Abnormalities**

The nail plate is rich in calcium, as phosphate in the form of hydroxyapatite crystals, and is intracellularly bound to phospholipids. Nail keratin analysis essentially shows the same fractions as that of hair: fibrillar, low-sulfur protein; globular, high-sulfur protein; matrix protein; and high glycine-tyrosine–rich matrix protein.

Nail amino acid analysis in contrast to hair analysis reveals higher cysteine, glutamic acid, and serine values but lower tyrosine values. Immunohistochemically trichocyte keratins have been detected within the epithelial structures of the nail unit. In the nail, it demonstrates a well-demarcated supra-basal region corresponding to the matrix. The distribution of the keratins in the nail bed and matrix has resulted in further understanding the molecular basis of pachyonychia congenita, where the various nail manifestations are found to correlate well with mutations within the keratin genes and corresponding phenotypes. The nails are prone to develop onychoschizia or lamellar splitting in children younger than 5 years. The subungual area, as a whole, in old age may show thickening of blood vessel walls with vascular elastic tissue fragmentation.

The nail plate often shows irregularities in the proximal nail-generative region and thickening of the nail bed blood vessels (Pertinax bodies). As the nail growth becomes inversely proportional to age, the larger corneocytes seen in older age relate to the slower rate of growth of nail plates.

Koilonychia, most commonly associated with iron deficiency, may be persistent in some children with a deficiency of cysteine-rich keratin. In dermatoses, such as psoriasis and dermatophyte infection, nail bed hyperkeratosis may push the nail up distally to produce a spoon shaped nail.

Occupational koilonychias result from permanent wave solutions in hairdressers or from softening of the nail with oil in mechanics. While onychomadesis or nail loss has been associated with local dermatoses such as bullous disorders and paronychia, it may manifest as a feature of generalized dermatoses such as toxic epidermal necrolysis.
and a rapid-onset pustular psoriasis. Scarring in lichen planus and that following toxic epidermal necrolysis may result in onychomadesis. Retinoids and large doses of cloxacillin and cephaloridine have been known to cause temporary nail loss. In epidermolysis bullosa, nail loss can be part of an inherited structural defect. Alopecia unguium or onychoptosis defluvium is a periodic, atraumatic, familial, noninflammatory nail loss, associated with dental amelogenesis imperfecta. Onycholysis is the distal and/or lateral separation of the nail from the nail bed.24 Psoriatic onycholysis is typically distal with variable lateral involvement, and used as reference point for other forms of onycholysis. “Oil spots” or a “salmon patch” appearance of the nail is due to the accumulation of shed squames, sequestrated debris, glycoprotein exudates, and air in the nail bed. The border of the onycholysis appears in the nail bed as reddish brown from the underlying inflammatory changes (Figure 2).

The diminished adherence of nail to nail bed could be primary and/or secondary to trauma, fungal infection, eczema, or photo-onycholysis.24,25 It is opined that onycholysis is one of the commonest nail signs.26 Minor trauma sustained in some occupations could cause secondary onycholysis. Contact reactions may be because of use of nail cosmetics or immersion of hands in soap and water resulting in reputed trauma. Psoriasis, fungal infections, and dermatitis are also regarded as fairly common causes of onycholysis.24 Photo-onycholysis has been reported to occur during treatment with psoralsens, demethylchlortetracycline, and doxycycline.27 A winged appearance of nail occurs when a central fibrotic band proximally divides a nail into two.28 This condition has since been termed pterygium (Figure 3). The background and sequence of events of pterygium29 are enumerated:

1. Pterygium formation is preceded by an inflammatory destructive process.
2. Fusion between the nail fold and the underlying nail bed are prominent.
3. The fibrotic band, then, obstructs the normal nail growth.
4. Superficial abnormal blood vessels are apparent.
5. Skin markings are absent.

The preceding changes are well documented in lichen planus and its variants and that following trauma. While longitudinal groove(s) running across the whole or part of the nails’ longitudinal axis, of the thumb in particular, may be normal, they can still be easily distinguished from pterygium, which prominently stands on the nail surface and in which full thickness of the nails is involved.28 Dystrophia unguium mediana canalisformis is an entity first described in 192830 where the nail is split, usually in the midline, with a “fir tree”-like appearance of ridges angled backward. It has been attributed to a definite history of trauma in some patients and to oral retinoids31 in others.

Transverse grooves, involving either full or partial thickness of the nails, may be caused by exogenous/endogenous factors. An account of transverse ridging of thumbnails was first described in 1966.32 They may occur on isolated diseased digits as a result of trauma, inflammation, or neurologic events. They may be generalized, reflecting a systemic event, coronary artery disease, measles, mumps, or pneumonia. The transverse grooves resulting from endogenous cause(s) are often referred to as Beau’s lines (Figure 4). Zinc deficiency has also been associated with the condition. Accordingly, Beau’s lines can be used as a useful clinical marker. The margin of the line matching well with the proximal nail fold and the distance of the groove from the nail fold represents the time elapsed since the growth disturbance. Depth and the width of the groove are proportional with duration and severity of the disease.33 Foci of parakeratosis, reflecting an isolated nail malformation in psoriasis, are cardinal.24 Clinically, they appear as punctate erosions on
the surface of the nails called pitting (Figure 5). The number, size, and pattern of nail pits are often taken into account in differentiating between psoriasis and alopecia areata. Fewer, larger, and randomly placed “pits” characterize psoriasis, while a large number of small, uniform, shallow pits arranged classically in a “cross-hatched” pattern are indicative of alopecia areata (Figure 6), which might not always be the case. When numerous, pitting may appear randomly distributed on the nail surface or may show a geometric pattern. In the latter, there may be rippling or a grid of pits. Trachyonychia is a result of extensive pitting combined with other surface irregularities. Elkonyxis is defined as an isolated large pit due to a localized full thickness defect in the nail plate. Elkonyxis can result from a nail trauma or may be associated with Reiter disease or psoriasis.

The term twenty-nail dystrophy (TND) in children was coined in 1977. TND is characterized by a pattern of changes affecting all the nails. The term trachyonychia (from the Greek ἕκασσος, meaning rough), described in 1979, is well suited to convey the clinical appearance of the affected nails. TND syndrome is classified into two groups: (1) loss of luster in all nails identified by vertical, striated sand paper, and (2) shiny nails.

The French term sand-blasted nails was coined in 1978, wherein detailed examination was performed on trachyonychia in TND. TND was found to be associated with congenital etiology, autoimmunity, ichthyosis vulgaris, alopecia areata, vitiligo, lichen planus, and hematologic disorders.

In a recent overview of TND/trachyonychia, it was concluded that the lesions are fairly representative and are characterized by alternating elevation and depression (ridging) and/or pitting, lack of luster, roughening likened to sand paper, splitting, muddy grayish white color, and prominent dystrophy (Figure 7). The diagnosis of TND should primarily be made on the onset in infancy/childhood, occasionally in adults, and confirmed by cardinal clinical features and microscopic pathology. Earlier, the role of longitudinal nail biopsy was emphasized in diagnosing TND.

Common skin diseases such as psoriasis, lichen planus, alopecia areata, and TND often manifest in nail changes. Nail changes are seen in 12% of psoriasis patients, where 1% to 2% of the general population is affected with psoriasis. A pathologic basis of nail changes was later defined in psoriasis, where location such as the cutaneous surface of the proximal nail fold, undersurface of the proximal nail fold, nail matrix, nail bed, and the hyponychium sites of inflammatory and hyperkeratotic papule may be considered the mainstay. In addition, erythematous, scaly papules and plaques seen on the cutaneous surface of the proximal nail fold and hyponychium appeared similar to psoriasis elsewhere on the skin. Accordingly, the lesions in these locations do not produce changes in the nail plate. The undersurface of the proximal nail fold, when involved in psoriasis, causes a separation of the proximal nail fold from the nail plate. This separation may cause a paronychia, the characteristic features of which are erythematous, inflamed proximal nail fold, ragged or absent cuticle,
and chronicity perpetuated by maceration and overgrowth of yeast under the proximal nail fold (Figure 8).

The psoriasis lesions of the matrix can occur both in the proximal and distal matrix. The proximal matrix contributes orthokeratotic keratin to the dorsal nail plate, while the distal matrix to the ventral nails plate. A cluster of abnormal parakeratotic cells are produced in psoriasis, and the clinical features depend on the matrix area affected. Accordingly, if the proximal matrix is involved, the parakeratotic cells are carried to the dorsal nail plate up to a certain distance and are suddenly lost, producing a depression or pit (marking the prior location of the parakeratotic cells), the hallmark of psoriatic nail disease. When the central or distal matrix is involved, the parakeratotic cells remain trapped within the nail plate, producing opaque white reflections when examined under light. Involvement of the nail bed results in an erythematous macule visible through a translucent nail plate. Glycoproteins produced from psoriasis accumulate beneath the nail plate and clinically present as a yellowish nail bed macule that earned the connotation “oil drop sign.” Splinter hemorrhages, onycholysis, mounds of keratinous debris, and complete dystrophy are other worthwhile features. In addition, complete dystrophy characterizes severe psoriasis or acrodermatitis continua of Hallopeau. The severity of nail disease could be well correlated to severe skin disease(s) and advanced psoriatic arthritis. Beau’s lines may be associated with pustular psoriasis. Other less common nail changes include nail fold telangiectasias, red lunulae, punctate red spots in the lunula, transverse leukonychia, leukonychia punctata, half-and-half nail, koilonychia, and onychoschizia.

A multicenter study compared the prevalence of onychomycosis in psoriatic nails with that of nonpsoriatic nails. The study found that a positive family history; location of lesions on the elbows, knees, gluteal clefts, and scalp; and nail pitting help to confirm the diagnosis of psoriasis. A positive potassium hydroxide preparation/fungal culture may help establish the diagnosis of onychomycosis. In addition, the evaluation of the clinical pattern of nail abnormality in onychomycosis manifesting either as distal and lateral subungual onychomycosis (DLSO) (Figure 8A), candida onychomycosis (Figure 8B), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO) (Figure 8C), or total dystrophic (destructive) onychomycosis (TDO) may be helpful. The presence of tinea pedis facilitates the diagnosis of onychomycosis.

Coexistence of psoriasis and secondary onychomycosis is intriguing. A study of 561 patients with psoriasis found that 47% had nail changes, of whom 27% were positive for mycelia spore on potassium hydroxide mount. Nail plate pitting, a hallmark of psoriasis, may also be seen in alopecia areata, pityriasis rubra pilaris, and Reiter disease. There were certain clinical differences in pits of psoriasis and alopecia areata, their briefs are outlined in the Table. Deeper and more irregular pits, similar to those of psoriasis could also be seen in pityriasis rubra pilaris. In children, nail lichen planus may occur as an isolated finding.

Several clinical variations, depending on the location of lichenoid inflammatory infiltrate, may be seen in lichen planus of the nails. Primarily, lichen planus affects the nail matrix and may result in: (1) onychorrhexis, recognized by nail plate thinning, ridging and fissuring. (2) Trachyonychia, a rough sand paper appearance of the surface.

Figure 8. (A) Distal and lateral subungual onychomycosis, (B) candida onychomycosis, and (C) proximal subungual onychomycosis, mycelia, and spores may be demonstrated on potassium hydroxide mount.
of the nail plate, gray opacity, and brittle/split nails. The nail plate might be thrown into folds and may result in complete nail atrophy.

(3) Pterygium, a chief association of lichen planus following intense lichenoid infiltrate encompassing the proximal nail fold, the nail matrix, and the nail bed. The cul-de-sac under the proximal nail fold may shorten, the nail plate may progressively result in thinning, and finally the proximal nail fold may fuse with the matrix and the proximal nail bed, thus dividing the nail plate into two lateral sections (Figure 9).

Pterygium is pathognomonic of nail lichen planus; however, it could also be a feature of nail patella syndrome. Trauma, peripheral vascular diseases, Raynaud’s phenomenon, radiotherapy, infection, and immunobullous diseases may be the other causes.

Alopecia areata could too involve one, multiple, or all 20 nails. Pitting of the nails was reported in 21.9% of patients with alopecia areata. The probable nature of pitting, vis-a-vis psoriasis, has already been mentioned (vide supra). Nail plate pitting and trachyonychia were considered to be characteristic of alopecia areata, while other studies found trachyonychia in only 3.65% of patients with alopecia areata, and in 15.4% patients with alopecia universalis. Another opinion was that alopecia areata could affect only the matrix and the spotty absence of gray opacity and brittle/split nails. The acute onset of alopecia areata has also been described to be associated with nail plate shedding (onychomadesis). Nail pitting is a prominent finding in psoriasis, alopecia areata, dermatitis, HLA-B27 inheritance, diabetes mellitus, and occupational trauma.

Acknowledgement: Asha Singh, MS, PhD, Professor and Head of the Anatomy Department, SGT Dental College, Gurgaon, reviewed the section on nail biology. The final text (parts I and II) was reviewed by Prashant Verma, MD, Senior Resident, Department of Dermatology and STD, University College of Medical Sciences and Associated Guru Teg Bahadur Hospital, Shadnagar, Delhi.

REFERENCES

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

Once-daily application in the evening

VELTIN Gel

- Combines the acne-fighting properties of tretinoin and clindamycin
- Contains tretinoin, solubilized in an aqueous-based gel
- Combats inflammatory and noninflammatory acne

Important Safety Information for VELTIN Gel

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea occurs. Severe colitis has occurred following oral or parenteral clindamycin administration. Severe colitis may result in death
- Avoid exposure to sunlight and sunlamps when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Daily use of sunscreen products and protective apparel are recommended. Weather extremes (eg, wind and cold) also may be irritating to patients using VELTIN Gel
- Observed local treatment-related adverse reactions (≥1%) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of 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.
5.1 Colitis

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

8.3 Nursing Mothers

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

8.4 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.]

13 NONCLINICAL TOXICOLOGY

13.1 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 chromosomal aberration assay.

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

Tretinoin: In two independent mouse studies where tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years no carcinogenicity was observed, with maximum effects of dermal amyloidoses. However, in a dermal carcinogenicity study in mice, tretinoin applied at a dose of 5.1 mg (1.4 times the recommended clinical dose based on body surface area comparison) three times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz[a]anthracene (DMBA).

In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol 13-acetate or mezeorin 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 photocarcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photocarcinogenic 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.

17 PATIENT COUNSELING INFORMATION [See FDA-approved Patient Labeling]

17.1 Instructions for Use

At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips). Patients should be advised not to use more than a pea sized amount to cover the face and not to apply more often than once daily (at bedtime) as this will not make for faster results and may increase irritation.

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

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

17.2 Skin Irritation

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

17.3 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 consulted.

STIEFEL and STIEFEL Design are registered trademarks of Stiefel Laboratories, Inc. VELTIN is a trademark of Astellas Pharma Europe B.V.
DESCRIPTION

Veltin gel (clindamycin phosphate and tretinoin), 1.2%/0.025%, is a fixed combination of two solubilized active ingredients in an aqueous-based gel. It is manufactured by Stiefel Laboratories, Inc (Research Triangle Park, NC), a GSK company. Veltin gel was approved by the US Food and Drug Administration on July 16, 2010.1,2

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate).

The chemical name for tretinoin is all-trans 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid family of compounds.

Veltin gel contains the following inactive ingredients: butylated hydroxytoluene, carbomer 940, anhydrous citric acid, edetate disodium, methylparaben, laureth 4, propylene glycol, tromethamine, and purified water.

MECHANISM OF ACTION

Clindamycin binds to the 50S ribosomal subunit of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis.

Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, it stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

CLINICAL PHARMACOLOGY

Clindamycin has been shown to have in vitro activity against Propionibacterium acnes, a bacterium that has been associated with acne vulgaris; however, the clinical significance of this activity against P acnes was not examined in clinical studies with Veltin gel. P acnes resistance to clindamycin has been documented, often in association with erythromycin resistance.

Topical tretinoin is used in the treatment of mild to moderate acne and on skin that has been damaged by excessive sun exposure. Tretinoin causes an increase in cell turnover and death, which reduces the number of cell layers in the skin. This rapid turnover may prevent new acne lesions from forming.

CLINICAL STUDIES

Three randomized, double-blind, multicenter, 12-week studies compared the combination product clindamycin 1%—tretinoin 0.025% gel with clindamycin gel 1%, tretinoin gel 0.025%, and vehicle gel in almost 3900 patients 12 years and older with acne. One trial used the Veltin formulation, while the other two trials used an older, slightly different formulation (Velac). Study medications were applied once daily in the evening in all trials. Efficacy was assessed at weeks 2, 4, 8, and 12. The co-primary end points were the mean absolute change from baseline to week 12 in 2 of 3 (total, inflammatory, and noninflammatory) lesion counts and the proportion of patients with at least a 2-grade improvement in Investigator’s Static Global Assessment (ISGA) score (a 0–5 scale) from baseline to week 12.1,3–5

EFFICACY

Based on assessment of the co-primary end points, the newer formulation was found to be superior to the comparator in terms of change in ISGA score and in the absolute reduction in at least 2 of 3 lesion counts (total, inflammatory, or noninflammatory).
The median time to 50% reduction in total lesion count was significantly faster with clindamycin–tretinoin gel (8 weeks) than with clindamycin gel alone (12 weeks), tretinoin gel alone (12 weeks), or vehicle (median time not reached at study completion) \( (P<.0001) \). The proportion of patients who achieved an ISGA score of 0 or 1 at 12 weeks was significantly higher in the clindamycin–tretinoin gel group (37%) compared with clindamycin gel alone (27%), tretinoin gel alone (25%), or vehicle gel (14%) \( (P \leq .0001) \).

Comparing baseline with week 12 data, the combination clindamycin–tretinoin gel was superior to the other study medications in terms of decreasing the ISGA score to clear/almost clear and in decreasing the number of total lesions and inflammatory lesions. In one trial, the combination clindamycin–tretinoin gel was similar to the tretinoin gel in the reduction of noninflammatory lesions, while the other two trials found clindamycin–tretinoin superior to the other 3 arms of this end point.

In the combined analysis of all studies, clindamycin–tretinoin gel was significantly better than clindamycin 1% gel, tretinoin 0.025% gel, and vehicle gel in reducing total inflammatory and noninflammatory lesions after 12 weeks of treatment \( (P \leq .0043) \).

### ADVERSE REACTIONS

The completion rate from one of the studies was 1446 of 1649 patients (88%). The most common reason for study discontinuation was withdrawn consent (n=76) and lost to follow-up (n=73). Few patients withdrew due to adverse events (n=11), noncompliance (n=10), or lack of efficacy (n=7).

The safety data from the combined studies reflect exposure to clindamycin–tretinoin in 1104 patients 12 years or older with acne vulgaris. Patients were treated once daily in the evening for 12 weeks. Adverse reactions that were reported in ≥1% of patients treated with the combination gel are presented in the Table.

Local skin reactions included erythema, scaling, dryness, burning, and itching. During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter.

### SAFETY

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. If significant diarrhea occurs, treatment would be discontinued.4

Exposure to sunlight, including sunlamps, should be avoided during the use of tretinoin, and patients with sunburn should be advised not to use the product until fully recovered due to heightened susceptibility to sunlight as a result of the use of treatment.1

This treatment should not be used in combination with erythromycin-containing products due to possible antagonism to the clindamycin component. In vitro studies have shown antagonism between these 2 antimicrobials. The clinical significance of this in vitro antagonism is not known. Clindamycin has been shown to have neuromuscular-blocking effects that may enhance the action of other neuromuscular-blocking agents; therefore, it should be used with caution in patients receiving such agents.

This combination gel falls under Pregnancy Category C. There are no well-controlled studies in pregnant women treated with clindamycin–tretinoin. A limited 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. 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. Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates, and

| Table. Adverse Events \(^a\) in Patients According to Treatment |
|---------------------|------------------|------------------|------------------|------------------|
| ADVERSE EVENT, NO. (%) | CLINDAMYcin–TretinoiN Gel (N=1104) | CLINDAMYcin Gel 1% (N=1091) | TretinoiN Gel 0.025% (N=1084) | Vehicle Gel (N=552) |
| Dryness | 140 (13) | 38 (3) | 141 (13) | 17 (3) |
| Desquamation | 64 (6) | 12 (1) | 62 (6) | 3 (1) |
| Burning | 50 (5) | 4 (<1) | 57 (5) | 5 (1) |
| Erythema | 50 (5) | 2 (<1) | 56 (5) | 2 (<1) |
| Pruritus | 40 (4) | 6 (1) | 39 (4) | 3 (1) |
| Sunburn | 26 (2) | 7 (1) | 23 (2) | 6 (1) |
| Irritation | 11 (1) | 6 (1) | 7 (1) | 3 (1) |

\(^a\)All adverse events at application site.
SKINmed. 2011;9:49–51

Veltin Gel

has also been shown to enhance photocarcinogenicity in studies involving UV radiation exposure.

Safety and effectiveness of clindamycin–tretinoin in pediatric patients younger than 12 years have not been established nor has it been established in patients 65 years and older.

INDICATIONS AND ADMINISTRATION

Veltin (clindamycin phosphate and tretinoin) gel, 1.2%/0.025% is a yellow, opaque topical gel indicated for the treatment of acne vulgaris in patients 12 years and older. The gel should be applied once daily in the evening, gently rubbing the medication to lightly cover the entire affected area. Approximately a pea-sized amount will be needed for each application. The eyes, lips, and mucous membranes should be avoided. It is not for oral, ophthalmic, or intravaginal use. Because it is a combination of clindamycin–tretinoin, it is contraindicated in patients with regional enteritis, ulcerative colitis, or a history of antibiotic-associated colitis.1,2

Each gram of Veltin gel contains, as dispensed, 10 mg (1%) clindamycin as clindamycin phosphate and 0.25 mg (0.025%) tretinoin solubilized in an aqueous-based gel. The tube sizes for this product are 30 g and 60 g.

CONCLUSIONS

This gel (Veltin) represents an alternative to another topical formulation (Ziana; Medicis, Scottsdale, AZ)6 that differs mainly in the vehicle and in the way the tretinoin is released from it. No head-to-head studies allow us to recommend one brand over the other based on superiority of effectiveness vis a vis side effects. We find the use of these combinations useful to provide a once-a-day treatment paradigm for acne that utilizes 3 molecules with different modes of action (with benzoyl peroxide in the form of a wash, for example) hopefully to optimize compliance and success.

REFERENCES

1 Veltin (clindamycin phosphate 1.2% and tretinoin 0.025%) gel [package insert]. Research Triangle Park, NC: Stiefel Laboratories, Inc; 2006.
6 Ziana (clindamycin phosphate 1.2% and tretinoin 0.025%) gel [package insert]. Scottsdale, AZ. Medicis: The Dermatology Company; 2006.

FORMULARY OF DR GEORGE C. ANDREWS

**Bleach**

- Bismuth oxychloride ointment
- Mercury bichloride grains v
- Bismuth oxychloride ounces ii
- Lanolin anhydrous ounces ii
- Aqua rosae ointment q. s. ounces xvi
- Oil jasmine drops xxx

Add mercury bichloride to oil and i ounce of alcohol. Melt all other ingredients, and when sufficiently cold, slowly add the oil solution.

Submitted by Douglas D. Altchek, MD, New York, NY
Immunofluorescence (IF) was first developed in 1941 when Coons identified pneumococci using a direct fluorescent method. This was followed by indirect IF, which added greater specificity and signal amplification. In 1979, immunohistochemistry (IHC) was developed with the introduction of horseradish peroxidase and peroxidase antiperoxidase. This was soon followed by the use of the avidin and biotin complex in the early 1980s. IHC provided more sensitive results than IF and quickly began replacing its predecessor in the laboratory setting, begging the question, why do we still use immunofluorescence?

CURRENT USE

IHC and IF are important laboratory techniques used in current dermatopathology. They are simple, rapid, and relatively inexpensive diagnostic methods with numerous applications. The development of new antibodies, improvements in detection of antigens, and automated processing systems have enhanced their diagnostic utility. Each technique has its own inherent strengths and weaknesses, which should be understood to ensure their proper and optimal use in diagnostics.

IMMUNOHISTOCHEMISTRY

IHC is a technique used to localize antigens in cells of a tissue section using monoclonal antibodies to bind to specific antigens in the tissues and using a method of visualizing this antigen-antibody complex such as linked peroxidase enzyme (Figure 1 and Figure 2). IHC allows the investigator to localize a given protein within the tissue examined. IHC has numerous applications in dermatopathology including the detection of markers associated with neural and neuroendocrine neoplasms, soft tissue neoplasms, infectious diseases, melanocytic proliferations, vascular proliferations, and epidermal and appendageal neoplasms. Melanocytic staining is garnering great interest for both diagnostic and prognostic value. Two general models are used: direct and indirect methods. The direct method is a one-step staining process and uses a labeled antibody that reacts directly with the antigen in tissue sections. It is relatively simple and quick, but there can be poor sensitivity due to minimal signal amplification. The indirect method uses an unlabeled primary antibody specific for the tissue antigen and a labeled secondary antibody, which reacts with the primary antibody. Signal amplification via several secondary antibody reactions with different antigenic sites on the primary antibody provides higher sensitivity than direct IHC. In addition, it allows the secondary antibody to be used with various primary antibodies raised in the same species. The secondary antibody can be labeled with an enzyme to visualize the reaction, often seen as a brown stain. Formalin-fixed paraffin-embedded (FFPE) tissue specimens generally use a biotinylated secondary antibody followed by an avidin-biotin peroxidase complex and development with a soluble chromogenic substrate. This allows for high sensitivity and reliable detection of specific antigens and can be automated for labeling, imaging, and scoring. IHC also allows the investigator to view cytologic details and tissue architecture. In addition, the preparations are permanent and relatively light insensitive. Although IHC is a valuable diagnostic tool, there are several limitations with its use. First, only one protein can be detected at a time, since multiple color approaches combining peroxidase with other development systems are inadequate and cannot be used to co-localize two antigens within the same subcellular compartment. Another limitation is that the resolution of antigen localization is limited due to the chromogenic substrate precipitate and the thickness of the sections imaged in the light microscope. Lastly, chromogenic systems easily saturate, which restricts semiquantitative analysis.

IMMUNOFLUORESCENCE

IF is a technique used to visualize a specific protein or antigen in cells or tissue sections by binding a specific antibody chemi-
Why Immunofluorescence?

Figure 1. Diffuse nonspecific anti-immunoglobulin M immune reaction in adnexa and adipose tissue of the deep dermis.

Figure 2. Anti-immunoglobulin M immune reaction primarily localized to the vessel walls.

Figure 3. Anti-immunoglobulin M immunofluorescence indicates antigen-antibody immune-complex deposition in vessel walls.

cally conjugated with a fluorescent dye (Figure 3). Fluorescence is a phenomenon in which a substance absorbs light or other electromagnetic radiation of a different wavelength and emits light, usually of a longer wavelength and lower energy than the absorbed radiation. The dyes chosen for IF are excited by light of one wavelength, usually blue or green, and emit light of a different wavelength in the visible spectrum. The most common fluorescent dyes are fluorescein, which emits green light; Texas Red and Peridin chlorophyll protein, which emit red light; and rhodamine and phycoerythrin, which emit orange/red light.5 By using selective filters, only the light coming from the dye or fluorochrome used is detected in the fluorescence microscope. This technique can be used to detect the distribution of any protein, and if different fluorochromes are attached to different antibodies, multiple proteins can be identified within the same cell or tissue section.

IF is a standard procedure for diagnosis of immune-mediated dermatologic diseases such as immunobullous disease and is also useful in connective tissue diseases, oral inflammatory diseases, and vaculitis.6 Similar to IHC, there are direct and indirect IF methods. In practice, direct IF is often used to detect presence of autoantibodies, immunoglobulin A (IgA), IgG, IgM, complement, and fibrin, whereas indirect IF is performed to detect circulating autoantibodies directed against an antigen in the skin.6 IF-stained samples are then examined under a fluorescence or confocal microscope. There are several advantages of IF over standard immunostaining. It allows for the simultaneous visualization of multiple antigens, even in the same subcellular compartment. There is also higher resolution because fluorophores are directly conjugated to the antibody. IF also gives quantitative
signals for analysis. However, IF is not usually used in FFPE specimens because there is a perception that paraffin sections are not suitable for fluorescence microscopy because of excessive background autofluorescence. This would make high-quality IF imaging difficult. In addition, the fluorescence tends to decrease with time, making it difficult to review IF-stained specimens at a later time. Experts have proposed a new method for high-resolution IF labeling of FFPE tissues, which combines antigen retrieval, indirect IF, and confocal laser scanning microscopy. This limits autofluorescence and allows investigators to study co-expression of multiple markers and to detect subcellular antigen localization within tissue samples.

**CONCLUSIONS**

IHC is a common laboratory procedure that has largely replaced IF in the laboratory setting due to its higher sensitivity and signal amplification. It has several limitations in diagnostics, however; the most serious being the inability to simultaneously visualize multiple antigens. Although IF may have poorer sensitivity than IHC, there are several advantages for its use. It can simultaneously detect multiple antigens, provides higher resolution, and allows for quantitative signals for analysis. Thus, IF remains a valuable tool in diagnostics and should not be completely replaced by IHC.

**REFERENCES**

THE Aesthetic Show™ 2011

JUNE 2-5 • ARIA RESORT • LAS VEGAS

www.aestheticshow.com
SKINmed. 2011;9:56–58

CONGRESS REPORT
Marcia Ramos-e-Silva, MD, PhD, Section Editor

Scratching the Surface:
The History of Skin, Its Diseases and Their Treatment—
History of Medicine Unit, University of Birmingham,
October 29–30, 2010 [Parallel Publication]*

Rebecca Wynter, MPhil, PhD

Sponsored by the Wellcome Trust and the Society for Social History of Medicine, this international conference gathered postgraduates and scholars from medical, cultural studies, and histories of medicine and art backgrounds whose research incorporates skin, its diseases, and treatment since 1700. The organizers—Jonathan Reinarz (University of Birmingham, United Kingdom) and Kevin Siena (Trent University, Canada), with Rebecca Wynter (University of Birmingham)—constructed a program with 21 speakers from 7 nations, divided into 8 panels, garnering an audience with a strong clinical presence.

READING THE SKIN

After the opening remarks, Professor Philip K. Wilson (Penn State College of Medicine, Hershey, PA) gave the keynote address, situating the conference papers within the wider terrain of history in “Reading the Skin, Discerning the Landscape: Geo-historical Descriptions of the Human Surface.” Space and place featured heavily throughout the event (Figures 1 and 2). The first panel commenced with “‘Italic Scurvy,’ ‘Pellarina,’ ‘Pellagra’: Medical Reactions to a New Disease in Italy, 1770–1830” by Professor David Gentilcore (University of Leicester, United Kingdom), and was followed by Timothy J. Peters’ (University of Birmingham) “The Skin Disease of Admiral Frances Beaufort,” written with Nick Levell (Norfolk and Norwich University Hospital, United Kingdom). This panel on diagnostic confusion highlighted issues that resurfaced throughout the event: skin as a barrier between practitioners, patients, classes, and nationalities, and skin disease as symptomatic of a deeper malaise, either physical or of hereditary, social, or cultural taint.

These themes were fused by syphilis, which dominated the second panel of forgotten skin diseases. Kevin Siena’s “The Moral Biology of ‘the Itch’ in Eighteenth-Century London” indicated that the English blamed the immoral poor and located “the Itch” on the syphilitic spectrum and as Scottish (Figure 3). In “St Paul’s Bay Disease: Skin and Scourge in Eighteenth-Century Quebec,” James Moran (University of Prince Edward Island, Canada) found contemporary English etiology pinpointing the Francophone population. The illness precipitated prophecies of colonial degeneration and public health measures administered through local priests. “The Coming into Being and Passing Away of the Norwegian Radesyge” by Anne Kveim Lie (University of Oslo, Norway) echoed Quebecois symptomology: lesions, skeletal corrosion, and soft tissue deterioration. Radesyge was connected with the decent lifestyle of the poor and the development of independent nationhood.

VISUALIZING THE SKIN

The afternoon began with visualizing skin disease. Mechthild Fend (University College London, United Kingdom) spoke about “Portraying Skin Disease: Robert Carswell’s Dermatological Watercolors.” Scottish physician Carswell visited Parisian hospitals, 1827–1829. His paintings were placed within wider medical taxonomy, and depicted tensions between representing patients or their conditions. In “Visualizing Venereal Disease: The Functions of Visual Representations,” Harriet Palfreyman (PhD student, University of Warwick, United Kingdom) incorporated disembodied plastinates and emphasized pedagogy at 18th-century anatomical schools. Venereal disease also featured in the dubious practices panel. Fiona Clark (Queen’s University, Belfast, Northern Ireland) explored the role of medical practitioners in diagnosing and treating skin diseases.
Ireland) conveyed an Irish surgeon’s determination to counteract Catholic hospital administration and a high-profile quack by campaigning for mercury treatment in “Scratching Below the Surface: Politics, Intrigue and Anti-Venereal Clinical Trials, Mexico City (1790–91).” Adrien Minard (Sciences Po, Paris, France) presented the day’s final paper, “Syphilis and Indigenous Skin Lesions through French Physicians’ Eyes in Colonial Maghreb, 1830–1930.” The virulence of the “Arabian” strain was considered a way to witness Medieval French syphilis and was thought indicative of foreigners’ filth and degeneracy.

The early-evening facilitated a viewing of the original medical texts and dermatological atlases that had informed many of the papers. The visit to the recently refurbished premises of the University’s Special Collections enabled clinicians to locate teaching material and stimulated interdisciplinary exchange. The later meal at one of Birmingham’s famous curry houses was a chance to relax before a second full day of presentations.

WORKING WITH THE SKIN

The morning began with “working with skin.” Lynda Payne (Medical Humanities and Bioethics School of Medicine, Kansas City, MO) offered valuable insights into the practice and pedagogy of men like Percivall Pott in “Drain, Blister, Bleed: Surgeons Open and Close the Skin in Georgian London.” These discussions provided a milieu to “‘Skin Politics’: Scrotal Cancer and the Regulation of Child Labour in Chimney Sweeping in Britain, c.1775–1840” by Niels Van Manen (PhD candidate, University of York, United Kingdom). Pott identified the cancerous industrial disease, stimulating the study of labor-related sickness. This prompted medical and political debate surrounding hygiene and working conditions.

The next panel considered skin as text. Matthew Newsom Kerr (Santa Clara University, Santa Clara, CA) provoked complexity in “An Alteration in the Human Countenance: Inoculation, Vaccination and the Face of Smallpox Following Jenner.” The 18th-century tell-tale signs of acquired immunity helped secure employment and were even considered beautiful in women; notions that fed into later pox eradication controversies and the success expressed on smooth faces. Gemma Angel (PhD student, University College London) then considered 300 preserved skins of sailors, soldiers, and criminals. “Atavistic Marks and Risky Practices: The Tattoo in Medico-Legal Debate, 1850–1950” noted the connections made between tattoos and deviance in anatomizing the criminal and in syphilitic infection. In a challenging paper, Nikki Halpern (European Institute for Jewish Studies, Stockholm, Sweden) discussed “The Word Made Flesh: Charcot and Skin-Writing.” Here again, at the late 19th-century Salpêtrière asylum, Paris, complexion was gandered, the capacity to present dermatography a stigmata of hysteria.
LEPROSY

After lunch, Daniel Ham (University of Cambridge, United Kingdom) began the barriers and borders session with “An El Dorado for a Leprous Chinaman?: Leprosy in Hong Kong in the Late 19th and Early 20th Centuries.” Amidst British concerns that Hong Kong was a beacon for sick Chinese, there was local colonial reticence to formulate coherent strategies for the discovery, prevention, and care of leprosy and non-British subjects—a gap addressed by missionary activity. These patterns were echoed by Kathleen Vongasthorn (University of Oxford, United Kingdom) in “A Disease Apart: Fear and Acceptance of Leprosy in Mid-Twentieth-Century Uganda.” Missionaries exported leprosy myths (of virulence and stigma) to local ethnic groups with varied belief systems. The Bakiga, for example, had previously accepted the diseased in their community, rather than enforcing the isolation of sufferers.

ANTHRAX AND AIDS

The final panel, signs on the skin, opened with “Classic, Characteristic or Typical: Cutaneous Anthrax, Lesions and Industrial Posters in the Early Twentieth Century” by James Francis Stark (University of Leeds and Thackray Museum, United Kingdom). A color-illustrated 1927 poster generated an examination of Bradford’s woolen industry and Anthrax Investigation Board. The poster (designed in 1916 and still used in 1952) both informed workers of lesion appearance and warned against self-diagnosis. Tania Woloshyn (Richmond University and University of Nottingham, United Kingdom) also considered images in “Lupus and Light: The Visual Culture of Nature and Artificial Light Therapeutics, c.1890–1930.” Through light, doctors restored patients’ faces with systems of phototherapy, tanning, and skin health instituted by the Finsen Light Institute and Battle Creek Sanitarium. In the last paper, fresh from his successful viva, Richard McKay (University of Oxford, United Kingdom) conveyed a darker picture of “Sex and Skin Cancer: Kaposi’s Sarcoma becomes the ‘Stigmata of AIDS’, 1979–1983.” Just as had been the case in Italy, Britain, Quebec, Norway, France, Mexico, Maghreb, Hong Kong, Uganda, and America since c.1700, skin disease was subject to diagnostic confusion and conflicting nomenclature and was understood as an indicator of the “Other”—the minority or the outsider. The closing discussion by Lesley Hall (Wellcome Trust, London) identified themes that emerged from the event: skin surface as symptomatic of something deeper; skin as a microcosm of a socially constructed story, one manifested locally and through the visibility of shape, shade, pigment, and sickness; and skin as metaphor and stigma, concealing, expelling, and being invaded. There were aspects of skin that remained untouched, such as skin and feeling, allergies, and rarer conditions.

CONCLUSIONS

There is much more to discuss about the history of skin, its diseases, and their treatment—and much more that can be learned through dermatologists and historians coming together and sharing their ideas, expertise, and experience. The conference successfully achieved what it was designed to do: it scratched the surface and will provide a platform on which to build further interest and knowledge.

WAX MOULAGE


Courtesy of Michael Geiges, MD
8th World Congress of the International Academy of Cosmetic Dermatology

CANCUN 2012

www.wcocd2012.com
info@wcocd2012.com
011 52 55- 5531 0865
011 5255 - 5203 6454

CANCUN
QUINTANA ROO, MEXICO
Hilton Cancun Golf & Spa Resort
January 31st to February 4th, 2012
A 71-year-old man presented to the authors’ clinic for evaluation of a red line under his right thumb. He noticed a red streak develop during the past year. It slowly grew in width and become more prominent in color (Figure 1). It did not cause pain. He delayed presentation because he perceived it to be only a cosmetic issue. Medical history included a metastatic atypical carcinoid tumor to the liver, lung, and the bone diagnosed 9 years ago. He had undergone multiple debulking surgeries and was currently taking octreotide and zoledronic acid. He had not started any new medications in the past 2 years. Review of systems was unremarkable. On physical examination, the right thumb nail was noted to have a red streak that began at the distal matrix. The line ended at the distal nail plate with distal disintegration and subungual hyperkeratosis. A biopsy was performed through the nail plate. The site removed by biopsy included the area in which the erythronychia visibly started, as well as the preceding normal nail matrix. The ventral nail plate was noted to have a groove of thinning, with slight purple discoloration. The nail bed/matrix was red in a linear pattern and no clinically apparent hyperkeratosis was noted. Notable findings included an acanthotic epidermis with some enlarged nuclei (Figure 2). Mild capillary dilatation was present in papillary dermis. Focal solar elastosis in the distal portion of the nail bed was identified. In situ hybridization for low- and high-risk human papillomavirus was negative. An immunohistochemical study using a panmelanocytic cocktail (HMB45, anti-MART1, anti-tyrosinase) failed to reveal any melanocytic lesion. Perl’s iron stain was negative. Metastatic carcinoid or primary squamous cell carcinoma were not identified.

Most patients and physicians perceive the nail unit as a cosmetic appendage. The authors believe, however, that the cosmetic-medical value is dramatically understated. In fact, alterations in appearance of the nail unit can be signs of more serious pathology despite the lack of other symptoms. For example, longitudinal erythronychia is an easily overlooked clinical presentation. Many cases are asymptomatic, and thus managed with minimal intervention. In fact, this presentation is often only considered a cosmetic issue to patients and physicians. The underlying changes, however, can be of utmost clinical concern and biopsy is warranted. Here, the authors present a detailed characterization of a case with clinical changes that could not be explained despite extensive histologic analysis.

This case and review illustrates the value of careful examination of the nail unit and the traditionally perceived cosmetic aspect of nail function. Recently, longitudinal erythronychia has been reported as a presentation of Bowen disease and may continue to be an underreported and often undiagnosed pathology. Although clinically identical to previous reported cases of longitudinal erythronychia, this presentation illustrates several unusual deviations. Histopathologic examination of our case showed acanthosis and focal keratinocytic atypia. Only mild capillary vascular dilation was present. Increased iron deposition and extravasated red blood cells were not identified.

The term onychopapillomas of the nail bed has been proposed to describe localized, distal, subungual keratosis with multinucleated cells. This terminology is used to characterize a papilloma with histology that shows a keratogenous zone identical to the nail matrix (matrix metaplasia). Although a common histologic finding in the initial elegantly prepared reports on longitudinal erythronychia, this histologic change was not present in our case. Multinucleated giant cells were not present either. The presence of acanthosis and mild papillomatosis, however, suggests that this lesion belongs to the spectrum of the distal subungual keratosis. It is possible that the discoloration was primarily produced at the distal nail matrix and was transferred to the nail plate and distal nail bed. The color could also be a result of the altered physical features of the nail plate. Although human papillomavirus was a theorized etiology in previous reports, our case ruled out viral presence.

We believe this case illustrates a unique and unusual presentation of longitudinal erythronychia. It is possible that at least some of the cases clinically suggestive of subungual keratosis may lack matrix metaplasia on histologic examination. Despite the apparent idiopathic nature of this presentation, however, we still place high value on the previous reports of longitudinal erythronychia being an initial presentation of malignancy and thus requiring biopsy. Long-term follow-up for recurrence and/or resolution is also recommended.
Finally, differential diagnosis must also be considered, evaluated for, and ruled out as appropriate. In particular, physicians must consider amelanotic melanoma, Darier disease, lichen planus, and psoriasis.5

REFERENCES
Save the Date & Register Early!  $395 before June 30th!

Plan to attend the 7th Annual Maui Derm Conference! “Cutting edge, a great blend of science and clinical medicine and a world class faculty” describe Maui Derm 2011. Our faculty will share with you the most important developments in medical and cosmetic dermatology vital to your practice. Our live patient demonstration workshops in lasers, Botulinum Toxin A and fillers have set the standard for “hands on” workshops. Our format has been specifically designed to allow optimal time for discussion with our faculty. We are certain that you will find this to be an outstanding and memorable educational event that you will not want to miss. Put Maui Derm on your calendar for 2011!

FEATURED LECTURES
Medical Dermatology
- Skin Cancer/Chemoprevention
- Acne/Rosacea
- Pediatric Dermatology
- Infectious Diseases
- Psoriasis
- Pigmentary Disorders
- Contact Dermatitis
- Cosmeceuticals
- Collagen Vascular Diseases
- Office Surgery Tips
- Practice Management
- Skin of Color

Cosmetic Dermatology
- Botulinum Toxin A and Fillers
- Lasers
- Skin of Color

“Lunch with the Faculty” – Controversial Topics, Case-based Discussions

Interactive Workshops
Small Group, Live Patient, Hands-On Demonstrations:
- Botulinum Toxins/Fillers

Maui Derm 2011 has special/reduced rates at the Grand Wailea and the Wailea Marriott

For more details, visit our website at www.acmd-derm-hawaii.com

MAUI DERM 2011 FACULTY
Chairman: Dr. George Martin

Dr. Rox Anderson
Dr. Andrew Blauvelt
Dr. Joel Cohen
Dr. Ilona Frieden
Dr. Sheila Fallon-Friedlander
Dr. Michael Gold
Dr. Mitchel Goldman
Dr. Pearl Grimes
Dr. Arthur Kavanaugh
Dr. Suzanne Klimer
Dr. David Laub
Dr. Craig Leonardi

Dr. Stuart Maddin
Dr. Sam Moschella
Dr. Stuart Nelson
Dr. Kevin Pinski
Dr. Ted Rosen
Dr. Vic Ross
Dr. Alan Shalita
Dr. Bruce Strober
Dr. Hensin Tsao
Dr. Sandy Tsao
Dr. Guy Webster
Dr. Philip Werscheler

* Subject to Change

Official Meeting Publication Sponsor

Dermatology Times

Maui Derm 2011
ADVANCES IN COSMETIC + MEDICAL DERMATOLOGY
CASE STUDY

A Case of Cinderella:
Erythema Dyschromicum Perstans
(Ashy Dermatosis or Dermatosis Cinecienta)

Claudia Muñoz, MD, MPH; Anne Lynn S. Chang, MD

A 33-year-old healthy Latina (from either Mexico or Central America) woman with Fitzpatrick type V skin complained of a 2-year history of progressive hyperpigmentation on the axillary folds, dorsal hands, upper neck spilling onto the jawline area, and lower abdomen. There was no preceding dermatitis. The lesions were asymptomatic. She did not use any prescription or over-the-counter drugs or any herbal supplements. She denied contact with any new substances and did not start any new activities. A full review of systems was negative. Physical examination revealed diffuse symmetric gray patches on the proximal arms radiating from the axillary folds with extension onto the trunk (Figure 1). This discoloration was also present on the dorsal hands (Figure 2), upper neck and jawline, and lower abdomen. The lesions were nonpalpable and without erythema. Thyroid function test results and morning cortisol levels were normal. Two adjacent 4-mm punch biopsies were performed on the right axillary skin, one consisted of unaffected skin and one of hyperpigmented skin. Figure 3 shows affected axillary skin with an interface dermatitis and significant pigment dropout. There was no evidence of depositional process of substances such as heavy metals, drugs, or tattoo. There was no evidence of an actinic process. Differential diagnosis included erythema dyschromicum perstans (EDP), fixed-drug reaction, or interface drug reaction. As the patient was not taking any medications, the overall clinical and histologic impression was most consistent with EDP. The patient was started on a low-potency topical steroid twice a day to the affected areas. In addition, because the patient was concerned about the cosmetic appearance of the hyperpigmentation, a 4% hydroquinone cream was started twice daily to the neck area.

Erythema dyschromicum perstans (EDP) was first reported in El Salvador in 1957 by Ramirez, who described his patients as the “ashen.” This description was later connected with “cinecienta,” or Cinderella, a reference to the storybook character sitting by the ashes and acquiring a gray appearance on the skin. EDP has been described in a range of populations, but most cases have been found in Latin American populations. The age of onset of EDP is almost always before age 40, with a chronic course. Lesions are typically symmetric and generalized. In a 2007 report of 23 patients, the most common location of lesions was the trunk (in 74% of patients), followed by lesions on the upper limbs (65%). Lesions can also affect the face (35%), neck (30%), lower extremities (30%), and lower abdomen (13%). Lesions are ashy gray macules and patches, although a palpable, fine, erythematous border has been reported on the periphery of some lesions. This difficult-to-find, erythematous border is the source of the word “erythema” in the term EDP. Lesions are not pruritic. The cause of EDP is unknown, although the involvement of cell-mediated immunity or certain HLA antigen types have been postulated.

EDP is difficult to treat. In the acute inflammatory stages, topical steroids or other anti-inflammatory agents such as topical
tacrolimus have been reported, although no treatments have been subjected to controlled clinical trials. Older, pigmented lesions do not respond well to treatment. Clofazimine has been reported to induce a response in a small number of patients, although clofazimine itself may lead to pigmentation. Response to dapsone has been reported in a few cases as well.

In the United States, Latinos are the largest minority group, comprising 36% of the California population and 15% of the US population according to the US Census Bureau in 2006. The Latino population is growing at 3% per year and estimated to represent 25% of the US population by the year 2050. Dermatologists are likely to see more cases of this condition in the future.

REFERENCES

Darier-White disease is an autosomal dominant disorder of keratinization caused by mutations in the ATP2A2 gene, locus 12q23-q24.1, which encodes the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase.\(^1\) Many cases are considered new mutations. Darier disease in general starts in the first or second decade of life, but eruptive forms of late onset have been described, as well as less frequent forms, including hypertrophic, linear, vesiculobullous, and hemorrhagic types.

Discrete vesicular lesions, caused by enlargement of the intraepidermal lacunae, may occur in Darier disease, and blistering may be precipitated by factors such as high humidity, ultraviolet radiation, surgery, physical stress, and treatment with etretinate.\(^2,3\) Our patient had not received retinoids before presentation and had no evidence of bacterial infection, so the mechanism is uncertain. Blistering persisted throughout the summer, in exposed sites, suggesting sunlight and trauma as exacerbating factors.

Hemorrhagic Darier disease was first described in 1964 in 4 patients, 2 of whom were mother and daughter.\(^4\) Biopsy specimens from these patients showed intraepidermal lacunae filled with red blood cells; in older lesions (black lesions), the red blood cells were located higher in the epidermis and were amorphous. Otherwise, the histopathologic findings were typical of Darier disease. Investigators\(^5\) reported hemorrhagic lesions in 6% of patients with Darier disease but did not comment on familial incidence of this finding. Another investigator\(^6\) did not describe hemorrhagic lesions in the 79 patients examined. In addition, researchers\(^7\) examined 34 patients from three large pedigrees, and hemorrhagic lesions were limited to one of the pedigrees. This

CASE STUDY

**Bullous-Hemorrhagic Darier Disease**

María Pilar Sánchez-Salas, MD; Francisco Javier García Latasa de Aranibar, MD; Rosa Oncíns Torres, MD; Paula Gambó Grasa, MD

A 48-year-old man presented with a 4-month history of papular hyperkeratotic diffuse lesions on his trunk, arms, and neck that were highly pruritic (Figure 1). He also had “V”-shaped nicks in the nails, mucous white papules on his palate, and diffuse desquamation on the scalp. Abnormal laboratory values included elevated levels of uric acid and triglycerides. Serum electrolytes, blood sugar, and renal and liver function test results were within normal range. X-ray film and abdominal ultrasonography findings were also normal. Histopathologic study of the biopsy from the thorax revealed acantholysis with suprabasal clefting, intraepidermal lacunae, and dyskeratosis with corps ronds. The clinical features and results of the histopathologic studies suggested a diagnosis of Darier disease (Figure 2), but the course was not typical of this entity because the patient had no family or personal history of previous cutaneous lesions and the age of onset was older than usual. In the course of the disease, he developed blisters and small black hemorrhagic macules with jagged borders on the back of his hands (Figure 3). Nikolsky’s sign was negative. A biopsy of a blister was performed, which confirmed Darier disease, studied by means of immunofluorescence. Measurement of porphyrins in the urine was also ordered. Direct immunofluorescence did not show deposition of immunoglobulins or complement, and the study of porphyrins was normal. The patient was treated with an oral retinoid (acitretin 10 mg daily), but treatment was stopped because he developed an increase in triglycerides; therefore, control of the disease with oral antihistamines, 5-fluorouracil 1% cream, and topical tazarotene was used, with mild improvement.

![Figure 1. Hyperkeratotic papules on the trunk typical of Darier disease.](image-url)
fact suggests a possible genetic heterogeneity of Darier disease. Studies to map the genes for Darier disease are in progress and the molecular basis for this heterogeneity will be of great interest.

We would like to emphasize the atypical and late onset of the disease in our patient, and the association of two uncommon clinical features of Darier disease: blistering and hemorrhagic lesions. The mechanism remains unclear, but it may be the clinical expression of suprabasal clefting present histologically.

REFERENCES


**Figure 2.** Intraepidermal lacunae and dyskeratosis with corps ronds (hematoxylin and eosin, original magnification \(\times200\)).

**Figure 3.** Blisters on the back of the hand.

---

**ERRATUM: September/October 2010 • Volume 8 • Issue 5 • Page 306**

**CASE STUDY**

**Purpuric Nodules and Macules on the Scalp of an 18-Month-Old Boy**

Baris Malbora, MD; Engin Senel, MD; Zekai Avci, MD; Namik Ozbek, MD

**Published: Figure 2.** Diffuse dermal and subcutaneous infiltration by monomorphic cells (Hematoxylin-eosin stain, original magnification \(\times10\)).

**Correct: Figure 2.** Diffuse monomorphic cell infiltration, bone marrow biopsy (Hematoxylin-eosin stain, original magnification, \(\times10\)).
Membership in the International Academy of Cosmetic Dermatology is open to physicians with an interest in cosmetic dermatology and to members of the pharmaceutical and cosmetic industry who share similar goals.

Membership in the IACD is only $195.00 a year and includes:

- Clinics in Dermatology - six issues per year
- Journal of Cosmetic Dermatology - four issues per year
- SKINmed - six issues per year
- Special discounts on travel and surgical supplies
- Reduced registration fee at IACD events

Corporate memberships are available at the Benefactor, Diamond, Platinum, Gold and Silver levels.

Individual Membership Application

First Name ____________________________________ Last Name ____________________________

Title:  □ MD  □ PhD  □ MD,PhD  □ MS  □ Other ____________________________

Specialty: □ Dermatologist  □ Plastic Surgeon  □ Other ____________________________

Address ________________________________________________________________

City ____________________________ State ____________________________

Zip Code ____________________________ Country ____________________________

Tel ____________________________ Fax ____________________________

E-mail ____________________________

Annual dues are US$195, payable by: □ VISA □ MASTERCARD □ AMEX □ Check

Card #__________________________________________ Expiration date__________

Name on card ____________________________________________

Signature if by fax or mail__________________________ Date__________

Please forward your completed application for processing to:
Larry Millikan, MD, Secretary-Treasurer General
Ms Sandy Silverstein, Executive Secretary
602 Merion Avenue
Havertown, PA 19083 USA
Tel: +1.610.668.1170
Fax: +1.610.449.8637
E-mail: IACDworld@yahoo.com

For further information, please visit our website

www.IACDworld.org

or access our online form
Tattoos and body piercings are enjoying a good deal of popularity in contemporary Western culture, becoming even more trendy in recent years. Such adornment may look quite alluring in a young person, but as the recipient approaches middle age or has a change of mind about the decoration, problems ensue—tattoos blurring, pigment dropping down, or names of significant others no longer being significant. The initial process may lead to contact dermatitis, cutaneous infection, or even keloid formation, which may be immediately evident or delayed in affecting the recipient.

This short multi-authored volume begins with an excellent historical chapter, well illustrated in color. Neither tattoos nor piercings are new and can be traced back to antiquity. For the record, the first tattoo parlor opened in New York in 1846, while the introduction of an electric tattooing apparatus is credited to the innovations of “Professor” Samuel O’Reilly in 1891. By 1929, modifications were sufficiently advanced that current machines are little changed from then.

This is followed by “Materials used in body art,” which describes the components of ink for permanent tattoos and the use of henna for temporary tattoos. The metals used in piercings include stainless steel, titanium, silver, and gold. In the chapter on complications arising from tattooing, the list ranges from molluscum contagiosum to syphilis, and from contact dermatitis to keloids. Immediate problems can also be related to bleeding and pyogenic infections. Unwanted effects from piercings, as might be expected, concern similar problems, but the more unusual are the development of argyrosis and angiofibroma.

Tattoos can also be employed to return pigment to an area of vitiligo or to make an areola appear more natural following breast surgery. Cosmetically, tattoos can be used for eyeliners and lip liners, but such procedures are not without complications of pigment spreading or the reactivation of a herpes simplex infection.

Because contact dermatitis is one of the most common complications of both types of body adornment, a chapter is devoted to this problem. In addition to an eczematous dermatitis, granulomatous dermatitis is not unknown. Knowing the component of the ink can be helpful in determining the offending agent, ie, black: carbon, iron oxide, or dichromates; brown: ferric oxide; white: zinc or titanium oxide; or yellow: cadmium sulfide.

Removing a tattoo is fraught with problems, and the fact remains that the evidence for a tattoo, and for that matter a piercing, can never be eliminated. Whereas a piercing will leave a scar even without complications, the ink from a tattoo will still be visible, depending upon the color. Methods have involved salabrasion: rubbing salt, dermabrasion, electrodesiccation, excision, application of caustic chemicals such as trichloracetic acid, and more recently, laser surgery with the q-switched laser being the most effective.

This thin volume contains a great deal of information, but the publisher did not do the contributors justice. The use of core messages, when there are often summaries and conclusions, is annoying. Color pictures are fine, but they are wasted on showing bottles of ink or sterilization equipment; it would have been better to present more pictures of tattoos or piercings and their complications. The editing is erratic, with a mixture of British and American spellings and no uniformity of the references.

REFERENCES

and bilateral papilledema. Manifestations of intracranial hypertension include bulging fontanelles, headaches, include low plasma cortisol levels to an absence of response to ACTH stimulation. 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.

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

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

Pediatric Use
Safety and efficacy in pediatric patients below 3 months of age have not been established.

Because of higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (three times daily) 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 18 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 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.
Now younger eczema patients have something to smile about

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

Locoid Lipocream®
(hydrocortisone butyrate 0.1%) Cream

The power of an ointment with the elegance of a cream

Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Safety and effectiveness in pediatric patients below 3 months of age have not been established.

Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

Visit us at www.locoid.com

©2010 Triax Pharmaceuticals, LLC. All rights reserved. Locoid is a registered trademark of Astellas Pharma Europe B.V. Licensed to Triax Pharmaceuticals, LLC. LOC-0410-01