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Decubitus ulcers are not always due to prolonged recumbency, and pressure is not always the chief cause of pressure ulcers, but the 2 terms describe the same lesions. Essentially, any ulceration that “good nursing” might have prevented, can be hastily, but not necessarily correctly, classified as a decubitus ulcer.

CAUSATION
A little thought confirms that neither nursing nor medical care need be at fault by being implicated in the pathologic process. Think of an elderly person living alone who has a sudden stroke, causing severe hemiplegia, while his or her heels are resting on a hard floor. Similarly, any person who is alone when a disabling accident occurs may experience prolonged skin pressure (Figure 1).

Nurses strive to prevent any break in their patients’ skin, whether this is due to pressure, shear, abrasions, kinetic friction, tears from excessive skin tension, or diathermy burns (sometimes mistakenly categorized as decubitus ulcers). Yet, good intentions do not always bring good results.

Some argue that certain superficial decubitus ulcers that are associated with frictional forces on skin that has been long soaked in urine or feces should be called “moisture lesions.” The rationale concerning such superficial lesions points out that they are probably less serious than deeper ones. If this were to be accepted, it would create definition problems for nursing staff and, possibly, some kind of (unjustifiable) downgrading of superficial sores (Figure 2).

CLASSIFICATION
The grading and classification of decubitus ulcers is still controversial; however, practically all classifications and grading systems currently include both superficial ulcers and deep ones, in 4 or 5 grades. All such systems are less than perfect. What is needed is some agreement on a generally accepted definition.

The National Pressure Ulcer Advisory Panel (NPUAP), for example, has been searching for such an agreement, as has the European Pressure Ulcer Advisory Panel (EPUAP). Even so, as discussed in 2005, these classifications are often amended, and it can be confidently predicted that an agreed classification will remain elusive, while significant disagreements on etiology continue.

Obtaining a consensus on the etiology of superficial ulcers ought not to be too difficult, as they are usually caused by trauma to the skin surface (e.g., abrasions, friction burns, self abuse, sitting on small, hard objects, or sitting on skin folds). The main problem is still a lack of agreement about the pathogenesis of those deep penetrating ulcers which, from the nurse’s viewpoint, appear to have no overt event to account for them.

LITERATURE
A recently updated contribution suggests (under “pathophysiology”) that reperfusion injury can somehow combine with pressure ischemia to produce a severe decubitus ulcer, yet this report fails to mention the alternative idea of “distraction.” This latter term implies that sustained tissue distortion, induced by pressure and/or angled forces (shear), causes stretching of the subcutaneous tissues, including the local microcirculation. This leads to multiple microthrombi, which then cause sustained ischemia—deep over a bony prominence.

The omission in this report was most probably an oversight, but it is not unknown for other workers in this field to favor very similar ideas while omitting the distraction explanation. It seems unlikely that these specialists would just ignore contributions that discuss the distraction effect, but perhaps some follow the most popular view, while others are trying to avoid either giving offence or engaging in a dispute? Yet, all of these attitudes are regrettable. After all, science does not advance by avoiding ideas or arguments or both.

Any specialists, including the authors of this publication, run
the risk of becoming so focussed on their own subject that they become “compartmentalists,” who cannot accommodate new ideas or “lateral thinking.” Contrary to this, new ideas are emerging rapidly in many branches of medicine, as well as science in general. How much of this new knowledge impacts on one's own field? One has to look to find out and, indeed, a relevant example has emerged in recent advances in the biomechanics of articular cartilage.

**Articular Cartilage**

Articular cartilage, like subcutaneous tissue, is held together by a network of fibers (collagen fibers in cartilage) which is filled with a fluid (including fat cells in the panniculus adiposus). Obviously, cartilage is much firmer than the panniculus adiposus, but the way it responds to pressure from a bone is very similar. An obvious difference is that point (uniaxial) pressure on articular cartilage causes its interstitial fluid to squeeze through the collagen network and out onto the cartilage surface, whereas, the same pressure on the panniculus adiposus does not cause any cells or interstitial fluid to escape through the epidermis.

**Hoop Stresses**

In the case of the skin and subcutaneous tissues, under sufficient pressure, lymph and blood is squeezed away laterally. As compression proceeds, it produces tighter and tighter interstices in the network of superficial fascia. Through these interstices fat cells, interstitial fluid, and ground substance gel all strive to escape. This effect is now recognized as a factor that limits the expression of fluid from articular cartilage, when under point pressure. It is also understood that the pressure from this outwardly-moving fluid stretches the collagen network. Similarly, this should apply to the superficial facial network in the panniculus adiposus. Because this network is intertwined with a network of microscopic blood vessels, these are also stretched. In short, a distraction force is produced. Poitout describes this by saying that “tensile forces” (created by compression) occur within the “solid phase” (ie, collagen network) of articular cartilage; these tensile stresses are called “hoop stresses.” They behave like the hoops of a barrel that stop it from bursting.

It can be deduced that these hoop stresses also occur in the panniculus adiposus fascial network when the tissue distraction mentioned above is taking place. This network of fibers (collagen and elastin) is not as strong as the dense collagen network (or matrix) in articular cartilage. In consequence, when under sustained pressure, and not protected by cutaneous pain receptors, it gives way; causing many microvessels to tear and thrombose. At the same time, directly under the bony prominence involved, the tissues can become so compressed and dehydrated that they virtually cohere. This cohesive plaque of tissue starts to necrose and, we can deduce, its blood vessels are no longer capable of reperfusion.

**Conclusions**

Although this pathology often starts subcutaneously, necrotic autolysis weakens the overlying cutis, the pressure insult persists, a large bulla forms, and a deep ulcer soon appears. This sequence of events has been actually observed by one of us (PTL). This occurred on a hemiplegic patient in a Care of the Elderly ward. With hindsight, the main problem then was that the nurses involved had not been taught to palpate pressure areas for induration, which can often be the first sign of deep pressure damage. There are, of course, many other factors that may contribute to the formation of a decubitus ulcer, and these should not be overlooked. We agree that the treatment of these lesions should take into account the likelihood that deep tissue is involved, even if this is not apparent during visual assessment.
REFERENCES


WAX MOULAGE

Viral warts (especially common variant) are among the most prevalent skin lesions seen by dermatologists. In Iran, the incidence of these lesions represents nearly 5%–10% of patients referred to dermatologists. Curing warts is one of the most difficult and perturbing procedures offered by dermatologists. Although common, warts are inconsistently treated by any single method.

The current treatment of warts primarily involves physical destruction of the infected cells using different procedures, including chemical caustic agents, cryotherapy, electrosurgery, and lasers. Oral immunomodulator agents, such as cimetidine, zinc sulfate, and levamisole have also been used.

In this trial, we used 85% formic acid in distilled water solution, which is a carboxylic acid for the treatment of common warts. Formic acid was named for its relation to red ants (formica means “ant” in Latin). It is used in various industries. In medicine, formic acid 8% has been used to remove nits in pediculosis capitis.

**MATERIALS AND METHODS**

A placebo-controlled, clinical prospective study was designed for patients with common warts who attended the dermatology centers of Khorshid and Beheshti Hospitals in Isfahan, Iran in 2003 and 2004. Thirty-four patients (15 [44%] men and 19 [56%] women, aged 10–50 years) were included in the study. For ethical purposes pregnant and lactating women, infants, patients with facial and genital warts, and immunocompromised patients were excluded. Informed consent was obtained from patients. After cleaning the lesions with alcohol, either 85% formic acid in distilled water solution or distilled water (as placebo) was applied on the surface of the lesions with a cotton swab. On alternate days, the lesions were then punctured on contralateral parts using a 30-gauge disposable needle. Punctures were performed using a superficial tattooing procedure: about 6–10 times in each lesion, nearly 2 mm interval between punctures, with the needle at a 90° angle, without causing bleeding. The treatment was continued for a maximum of 12 sessions or complete recovery. Follow-up occurred every 2 weeks up to 3 months. At each visit, treatment response and occurrence of side effects, such as secondary infection and pigmented alterations, were considered. The data were analyzed with the chi-square test.

**RESULTS**

The average duration of the disease was 4 years (standard deviation [SD] = 4.3 years). The average number of lesions was 3.38
The mechanism of action of salicylic acid in warts involves keratolysis of virally infected tissue. Trichloroacetic acid and bichloroacetic acid are powerful irritants that work by hydrolyzing the cellular proteins, leading to inflammation and cell death. The exact mechanism of action of formic acid is not known. It probably acts in a manner similar to formalin which causes destruction of the wart-infected tissue by dehydration. After application of formic acid, the wart becomes slightly whitish in color and the superficial layer peels off indicating a keratolytic effect. Formic acid puncture may also help in inducing regression of warts. Regression of plane warts following spontaneous inflammation has been reported. In our study, however, the placebo group—who also underwent puncture with a needle—did not show the resolution of warts, indicating that puncture alone is not sufficient to produce the resolution of warts. Induction of immunity may also be considered as a possible mechanism of action, as in squaric acid dibutylester contact immunotherapy for the treatment of recalcitrant warts. Although 85% formic acid in distilled water solution is caustic, careful application over the wart area only prevents its harmful effects on the skin.

**CONCLUSIONS**

We believe that 85% formic acid in distilled water solution application can serve as a safe, inexpensive, and effective alternative in the treatment of common warts. A multicenter trial with this strength or more of formic acid puncture for common warts may help to standardize the treatment regimen and safety.

**Acknowledgements and Disclosure:** The authors thank the research chancellor of Isfahan University of Medical Sciences for providing a grant for this project, and the staff of Sajjad Pharmacy associated with the pharmacy faculty of Isfahan.

**REFERENCES**


A topic dermatitis (AD) is a pruritic disease characterized by chronic or relapsing eczema in a pattern of distribution that is linked to the age of the patient as essential features, with xerosis, atopy (immunoglobulin E reactivity), and early age of onset as important features, and an array of associated features.

AD is the most common chronic inflammatory skin condition of the pediatric population, affecting 2%–20% of infants and children in the United States, drastically impacting quality of life.

Hydrocortisone butyrate (HCB), the active molecule in the study drug is a synthetic, nonfluorinated glucocorticosteroid (GC) approved for topical use for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The formulation used in this study is the same approved and marketed for adult use since 1997. It is ranked, in a I to VII potency scale that utilizes a vasoconstriction assay, as lower mid-strength class V.

Corticosteroids for topical use are absorbed and act locally inducing phospholipase A2 inhibitory proteins that control the biosynthesis of inflammation mediators such as prostaglandins and leukotrienes. Absorption can be enhanced occlusion, application over extensive areas, or where the skin barrier function is compromised. With increased absorption the risk of systemic side effects rises.

**METHODS**

**Trial Design**

The efficacy and safety of HCB 0.1% lipocream (LCr) for the treatment of AD was investigated in a phase 3 multicenter, randomized, double blinded vehicle-control study. Patients were enrolled from July 6, 2005 to May 17, 2006. Prior signed consent was obtained from legal representation, according to national regulations. The trial was submitted to the Food and Drug Administration as a sponsor-initiated investigation on a new drug presentation for the pediatric population (Figure 1).

**Study Population**

Two hundred sixty-four pediatric patients aged 3 months to less than 18 years were enrolled into the study. Analyses were conducted on the intent-to-treat (ITT) population (all participants receiving study drug) for efficacy and safety, with supportive efficacy analyses on the per-protocol population.

**Demographic and Other Baseline Characteristics**

Age averaged 7.08 years across both treatment groups with age of the HCB 0.1% LCr group averaging 7.37 years and the age of vehicle-treated participants averaging 6.80 years.
Overall, 57% of participants included in the ITT population were boys (150/264) and 43% were girls (114/264). The distribution of race was predominantly white in both treatment groups (64%, 168/264) with the majority of non-Hispanic/non-Latino descent (80%, 212/264). Analyses were conducted to test for differences in population characteristics between the 2 treatment groups. There was not a significant difference between treatment groups for the comparison of age ($P=0.414$), gender ($P=0.690$), or ethnicity ($P=0.114$).

The treatment groups were comparable for the baseline characteristics of Physician’s Global Assessment (PGA) ($P=0.781$), pruritus ($P=0.421$), erythema ($P=0.619$), induration/papulation ($P=0.659$), excoriations ($P=0.936$), lichenification ($P=0.707$), oozing/crusting ($P=0.737$), scaling ($P=0.540$), total percent body surface area (BSA) affected ($P=0.920$), and Eczema Area and Severity Index (EASI) score ($P=0.821$). Overall, 39% of participants included in the ITT population (103/264) were assessed as mild on the PGA scale and 61% were moderate (161/264). Two percent of participants (2/264) had no pruritus, 30% had mild pruritus (79/264), 54% had moderate pruritus (142/264), and 15% had severe pruritus (39/264). The majority of participants had mild to moderate erythema (93%, 247/264), mild to moderate induration/papulation (92%, 243/264), mild to moderate excoriations (77%, 201/264), mild to moderate lichenification (78%, 207/264), none to mild oozing/crusting (81%, 214/264), and mild to moderate scaling (76%, 203/264). Overall, the mean total percent BSA was $22.58\pm13.69\%$ (range: 10%–94%).

**CLINICAL DIAGNOSTIC CRITERIA**

The 3 major diagnostic criteria for entry into the study included:

1. Participant had a clinical diagnosis of stable, mild to moderate AD defined by the criteria per Hanifin and Rajka.2,10–12

2. Participant’s severity of AD according to the PGA scale was 2 or 3 (Table I).

3. A minimum percent surface area involvement of at least 10% BSA.

**TREATMENT**

HCB LCr 0.1% or vehicle was to be applied to the affected areas twice daily for up to 1 month, without occlusive dressing.

A participant was considered compliant with the dosing regimen if the participant did not miss more than 4 consecutive doses and applied at least 75% of the expected number of applications of study medication. If the participant was confirmed clear at day 21, then the expected number of applications was 42. If a participant was not confirmed clear at day 21 and was to continue dosing to the end of the day 29 treatment period, the expected number of applications was 56.

**Figure 1.** Trial design. HCB indicates hydrocortisone butyrate. Adapted with permission from Abramovits W, Connelly EA, Breneman D, et al., unpublished data, 2007.

**Figure 2.** Primary efficacy endpoint: treatment success at day 29. ITT indicates intent to treat; HCB, hydrocortisone butyrate; PGA, Physician’s Global Assessment. Last observation carried forward was used to impute missing data prior to dichotomization. The PGA for each participant was dichotomized to “success” and “failure” at day 29. $P$ value from a Cochran-Mantel-Haenszel Test, stratified by analysis center. Reproduced with permission from Abramovits W, Connelly EA, Breneman D, et al., unpublished data, 2007.

Of the ITT participants, those who dosed with HCB LCr 0.1% applied, on average, 51.4±9.3 doses of study medication. Of these participants, 123/131 (94%) were compliant with the
Overall pruritus was assessed and documented at the baseline visit and each subsequent visit (excluding day 15) using a 4-point numerical scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Pruritus was assessed by the primary caregiver, in discussion with the participant or legal custodian, and concerned the intensity of overall pruritus/scratching/discomfort in the 24 hours prior to the visit.

**Efficacy Results**

The primary efficacy endpoint was the percentage of participants who achieved treatment success based upon the dichotomized PGA at the final day 29 visit using the 5-point ordinate PGA scale. Treatment success was defined as those participants with a final PGA score of 0 or 1 that had a 2-point or more reduction from baseline to day 29.

In the HCB 0.1% LCr group, 82/131 participants (63%) were considered a "success," compared to 37/133 participants (28%) in the vehicle group, which resulted in a significant treatment effect ($P<0.001$) in favor of HCB 0.1% LCr (Figure 2).

The secondary endpoint was the change from baseline in pruritus score at day 29. In the ITT analysis, the change in pruritus ranged from −1 to 3 within the HCB 0.1% LCr group and from −2 to 3 in the vehicle group. There was a significant treatment effect ($P<0.001$) in favor of HCB 0.1% LCr. In the HCB 0.1% LCr group, pruritus worsened by 1 grade in 2% of participants, showed no change in 18% of participants, showed a 1-grade improvement in 37% of participants, a 2-grade improvement in 36% of participants, and a 3-grade improvement in 7% of participants. In the vehicle group, pruritus worsened by 2 grades in 2% of participants, worsened by 1 grade in 5% of participants, showed no change in 39% of participants, showed a 1-grade improvement in 37% of participants, a 2-grade improvement in 36% of participants, and a 3-grade improvement in 7% of participants (Figure 3).

Assessments of signs/symptoms and area involvement by body region was measured at the baseline visit and each subsequent visit (excluding day 15), the investigator assessed the severity of the individual signs for the overall body and of each body region (head and neck, upper limbs, trunk, and lower limbs). The individual signs of erythema, induration/population, lichenification, and excoriation were rated using a 4-point scale, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Individual signs of oozing/crusting and scaling for the overall body were rated using the same scale.

In the HCB 0.1% LCr ITT group, percent change in EASI scores averaged 84.2% compared to the vehicle group, which averaged 45.3%. There was a significant treatment effect ($P<0.001$) in favor of HCB 0.1% LCr.

Figure 4 graphs the mean BSA affected at each evaluation for the ITT population. Summary statistics are also presented for
the percent change from baseline in BSA affected at each post-baseline evaluation. In the HCB 0.1% LCr group, BSA averaged 22.5% at baseline and decreased 82.1% at day 29 to 4.2%. In the vehicle group, BSA averaged 22.6% at baseline and decreased 43.6% at day 29 to 14.0%.

Table II presents summary statistics for the signs of AD at each evaluation for the ITT population. Figures 5 and 6 graph the average scores of signs and symptoms of AD including erythema, induration/papulation, excoriations, lichenification, oozing/crusting, and scaling for the ITT population at each evaluation.

### SAFETY RESULTS

In the HCB 0.1% LCr group, 29/131 participants (22%) reported a total of 46 adverse events, none of which (0%) was serious. Thirty-four of 46 events (74%) were of mild severity, 12/46 (26%) events were of moderate severity, and none (0%) was severe.

In the vehicle group, 28/131 participants (21%) reported a total of 42 adverse events, none of which (0%) was serious. Thirty-two of 42 events (76%) were of mild severity, 10/42 events (24%) were of moderate severity, and none (0%) was severe (Table III).
In the HCB 0.1% LCr group, 29/131 participants (22%) reported at least one adverse event compared to 28/133 participants (21%) in the vehicle group. The difference between treatment groups was not statistically significant (P=0.319). No serious adverse events related to study drug were reported. The majority of reports of the severity of adverse events were described as mild, and none of the adverse events related to study drug were reported as severe (Table IV).

**DISCUSSION**

This study provides an evidence based approach to assess the efficacy and safety of HCB 0.1% LCr in a pediatric population with mild to moderate AD.

Although hypothalamic-pituitary-adrenal suppression is common in those AD patients receiving some potent topical GC preparations, it is rarely found in children or adolescents with AD who used mild or moderately potent topical GC even over many years.13–19

The efficacy and safety of topical GC in a pediatric population as young as 3 months of age has been documented by studies that withstand the rigors of evidence based medicine, they exist only for a few preparations.20
On the other hand, the misuse of high potency topical GCs in AD to the point of inducing Cushing’s syndrome, has been repeatedly reported. The inappropriate use of high potency topical GC by pediatricians has been a matter of concern.

Besides the relatively uncommon systemic adverse events reported with their use, topical GCs cause a significant array of application site reactions, these include: skin atrophy, telangiectasias, striae distentiae, acneiform eruptions, folliculitis, erythema, irritation, contact dermatitis, and dyspigmentation.

The results of this study support the contention that HCB 0.1% LCr is not only effective in reducing the pruritus characteristic of AD, the cutaneous signs of disease activity which include erythema, scaling, induration, papulation, lichenification, oozing, crusting, and excoriation in a statistically significant way, but was able to do so without a significantly increased risk for adverse events in a pediatric population.

Disclosure: The authors certify that there are no real or apparent conflicts of interest.

REFERENCES

## Table III. Summary of Participants With Adverse Events (Intent-to-Treat Subjects) (1 of 3)

<table>
<thead>
<tr>
<th></th>
<th><strong>ACTIVE</strong>&lt;sup&gt;a&lt;/sup&gt; (N=131)</th>
<th><strong>VEHICLE</strong> (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events reported</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>Number of subjects reporting one or more events</td>
<td>29 (22%)</td>
<td>28 (21%)</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No</td>
<td>46 (100%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td><strong>Severity of event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>34 (74%)</td>
<td>32 (76%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (26%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Relationship to study drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unassessable</td>
<td>0 (0%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Not related</td>
<td>41 (89%)</td>
<td>34 (81%)</td>
</tr>
<tr>
<td>Possible</td>
<td>4 (9%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Probable</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>System organ class</strong></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>14 (11%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>7 (5%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vocal cord inflammation</td>
<td>1 (1%)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>6 (5%)</td>
<td>5 (4%)</td>
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<td>Abdominal pain upper</td>
<td>0 (0%)</td>
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<tr>
<td>Diarrhea</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
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<td>Gastroesophageal reflux disease</td>
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<tr>
<td>Vomiting</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
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<tr>
<td>Application site dermatitis</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

## Table III. Summary of Participants With Adverse Events (Intent-to-Treat Subjects) (2 of 3)

<table>
<thead>
<tr>
<th></th>
<th><strong>ACTIVE</strong>&lt;sup&gt;a&lt;/sup&gt; (N=131)</th>
<th><strong>VEHICLE</strong> (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site erythema</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Application site urticaria</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Upper respiratory tract fraction</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Viral rash</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>Application site folliculitis</td>
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<td>0 (0%)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
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<td>0 (0%)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
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<td>0 (0%)</td>
</tr>
<tr>
<td>Respiratory syncitial virus infection</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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</tr>
<tr>
<td>Telangiectasia</td>
<td>0 (0%)</td>
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<tr>
<td>Ingrowing nail</td>
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<td>1 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
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<td>1 (1%)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Acne</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dermatitis diaper</td>
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<td>0 (0%)</td>
</tr>
<tr>
<td>Skin atrophy</td>
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</tr>
<tr>
<td>Urticaria</td>
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<td><strong>Psychiatric disorders</strong></td>
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</tr>
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</tr>
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<td>Ear and labyrinth disorders</td>
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</tr>
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<td>Immune system disorders</td>
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</tr>
<tr>
<td>Hypersensitivity</td>
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<td>1 (1%)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
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<td>1 (1%)</td>
</tr>
<tr>
<td>Accident</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
Table III. Summary of Participants With Adverse Events (Intent-to-Treat Subjects) (3 of 3)

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE* (N=131)</th>
<th>VEHICLE (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nodule on extremity</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Congenital, familial, and genetic disorders</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Hydrocortisone butyrate 0.1% lipocream. Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ classes. At each level of summarization (system organ class or event), subjects are only counted once. Percentages of subjects in each treatment group are also given.

Table IV. Summary of the Number of Participants With Adverse Events by Relationship (Possible or Probable) to Study Medication

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE* (N=131)</th>
<th>VEHICLE (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site folliculitis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Application site dermatitis</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Acne</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Hydrocortisone butyrate 0.1% lipocream.
Stretch marks, also known as striae distensae, are a common concern for post-pubertal men and women patients seeking dermatologic care. They appear as linear thinned skin most often found on the breasts, abdomen, hips, and thighs. Stretch marks may appear due to the rapid hormonal changes and growth associated with puberty, during pregnancy, or with medical diseases, such as Cushing syndrome. Under the microscope, they appear as dermal atrophy accompanied by loss of the rete ridges, a finding similar to scar tissue. The development of striae distensae has been described as similar to that of wound healing or scar formation. Earlier stage or immature striae distensae, also known as striae rubra, appear pink or red in color and over time become white, flat, and depressed, known as striae alba. There is no clear consensus as to the cause of striae distensae.

The treatment for stretch marks is limited. The most invasive therapies for stretch marks involve physician administered laser surgery. Improvement in stretch marks (ie, diminution of the signs for striae) with laser therapy is accomplished by wounding the scarred skin and hoping that the newly healed skin will have a more normal, cosmetically acceptable appearance. Medical reports of Nd:YAG laser, radiofrequency devices, and fractional photothermolysis have shown some degree of stretch mark appearance improvement, but not resolution. Topical tretinoin is the best studied topical stretch mark pharmaceutical product, however, some trials have yielded variable results. Camouflage is often selected as the best option for treatment to hide the scars. In addition to physician administered stretch mark therapies, a variety of over-the-counter products can be purchased for improving stretch mark appearance. These products contain cocoa butter, emu oil, vitamin E, and other oils to apply while massaging the stretch marks. Many dermatologists recommend massaging the stretch mark in a circular motion with oil on the finger to reduce friction and make the skin more pliable, improving appearance—although no evidence exists for this recommendation. Researchers published on the lack of evidence for topical ointments and creams in stretch mark improvement.

This study evaluated the effect of an onion extract cream with Centella asiatica and hyaluronic acid in improving the appearance of striae rubra (SR). Women participants with bilateral, outer aspect of the thigh SR were randomized to apply a quarter-sized amount of the onion extract cream twice daily for 12 weeks to the randomized left or right, outer aspect of the thigh. No treatment was administered to the contralateral side. Participants were evaluated at weeks 2, 4, 8, and 12. Primary efficacy endpoints included color, texture, softness, and overall appearance of SR by the participant and investigator at week 12. The treated thigh demonstrated a statistically significant difference in the mean change in participant and investigator evaluations in overall appearance, texture, color, and softness compared with the untreated thigh at week 12. No adverse events occurred during the study. The onion extract cream was well tolerated and significantly improved the appearance of SR in women. (SKINmed. 2010;8:80–86)

ABSTRACT
This study evaluated the effect of an onion extract cream with Centella asiatica and hyaluronic acid in improving the appearance of striae rubra (SR). Women participants with bilateral, outer aspect of the thigh SR were randomized to apply a quarter-sized amount of the onion extract cream twice daily for 12 weeks to the randomized left or right, outer aspect of the thigh. No treatment was administered to the contralateral side. Participants were evaluated at weeks 2, 4, 8, and 12. Primary efficacy endpoints included color, texture, softness, and overall appearance of SR by the participant and investigator at week 12. The treated thigh demonstrated a statistically significant difference in the mean change in participant and investigator evaluations in overall appearance, texture, color, and softness compared with the untreated thigh at week 12. No adverse events occurred during the study. The onion extract cream was well tolerated and significantly improved the appearance of SR in women. (SKINmed. 2010;8:80–86)
improve the appearance of post-surgical shave excision scars. Another botanical with *in vitro* and *in vivo* efficacy in scars and stretch marks (data on file, Merz Pharmaceuticals, LLC) is Centella asiatica. Centella asiatica, also known as Indian pennywort, is a plant found in Asia, Africa, and North and South America used widely in Indian naturopathic medicine for ulcer healing. It contains asiaticoside, which is purported to increase the production of collagen I enhancing wound healing and scar maturation. The leaves are harvested, dried, and 95% ethanol extracted to obtain the medicinal botanical.

This research evaluated the effect of a formulation containing onion extract and Centella asiatica on newly formed striae rubra on the proximal aspect of the thighs of women. The botanical extracts are contained in a moisturizing emollient vehicle containing hyaluronic acid, a potent humectant aiding in the water holding capacity of the skin and previously studied in wound healing.

This research evaluated the effect of a formulation containing onion extract and Centella asiatica on newly formed striae rubra on the proximal aspect of the thighs of women. The botanical extracts are contained in a moisturizing emollient vehicle containing hyaluronic acid, a potent humectant aiding in the water holding capacity of the skin and previously studied in wound healing.

**METHODS**

**Materials**

All participants applied the study onion extract cream (Mederma for Stretch Marks, Merz Pharmaceuticals, LLC, Greensboro, NC) to one randomized thigh and no treatment to the other thigh. No placebo cream was utilized in this study. Adverse events were captured for the safety analysis.

**Participant Selection and Study Design**

This randomized, controlled, investigator-blinded, institutional review board approved study (Concordia Clinical Research, Institutional Review Board, Cedar Knolls, NJ) was conducted at one site in the United States from November 2008 to March 2009. The study was performed in accordance with globally accepted standards of Good Clinical Practice (as defined by the May 1, 1996, International Council on Harmonisation E6 Guidelines for Good Clinical Practice). Women participants between the ages of 18 and 45 years having symmetrical striae rubra on the proximal aspect of the thighs were enrolled since it was felt that mature striae alba would not be amenable to improvement. Participants with known allergies or sensitivities to the study ingredients, history of keloids or hypertrophic scars, excessive sun exposure, pregnancy, breast feeding, and treatment with an investigational drug or device within a period of 30 days prior to the study were excluded. In addition, participants with any systemic or dermatologic disorder that, in the opinion of the investigator, would interfere with the study, body mass index above 30, prior surgical or prescription topical striae distensae were excluded. Participants did not apply any products to the areas of observation for 2 weeks prior to the initiation of therapy.

After successful completion of Health Insurance Portability and Accountability Act authorization, informed consent, photography consent, and investigator screening, study participants were randomized to apply a quarter-sized amount of the onion extract cream twice daily for 12 weeks to either the assigned right or left thigh. The opposite thigh received no treatment. Participants returned to the study center for evaluation at weeks 2, 4, 8, and 12. Participant and investigator assessments were obtained regarding striae rubra softness, texture, color, and overall appearance. Standardized digital photography (Nikon E3, Canfield, NJ) by the investigator with a fixed focal length and exposure of the right and left striae rubra was obtained at each visit.

**Noninvasive Assessments**

Skin elasticity was selected as the most appropriate noninvasive assessment parameter for striae rubra. This evaluation was included to determine if the study product modified the recoil of the skin. Skin elasticity measurements were obtained via a negative pressure suction device (DermaLab, Hadsund, Denmark). The device functioned by applying negative pressure to the skin until distended into a suction cup with a light beam across the top of the cup. When the skin was adequately distended, the light beam was interrupted, the negative suction discontinued, and the skin relaxation evaluated. This cycle was repeated and recorded to obtain 5 distention and relaxation curves.

**Clinical Efficacy Parameters**

Clinical efficacy was based on the unblinded participant assessments and the blinded investigator assessments comparing the treated to the untreated striae rubra both visually and tactiley. The primary efficacy parameter was the participant assessment of striae rubra softness, texture, color, and overall appearance of the untreated vs treated striae rubra at 12 weeks using a 5-point ordinal scale: 0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement. The secondary efficacy outcomes included participant assessment of striae rubra softness, texture, color, and overall appearance at weeks 2, 4, and 8 using a 5-point ordinal scale; physician assessment of striae rubra using a 5-point ordinal scale at all visits; and noninvasive skin elasticity measurements.

**Statistical Methodology**

The safety evaluation set was the subset of randomized participants who received study treatment at least once. The full analysis set was the subset of randomized participants who received study treatment at least once and for whom at least one post-baseline value of efficacy was available. For all efficacy variables, descriptive summary statistics and paired two-sided *t* tests with confidence intervals were performed for each visit based on the full analysis set. The post-baseline last observation carried forward method was used to impute missing post-baseline efficacy variables. Baseline values were not imputed into follow-up visits.
RESULTS

Fifty-five women participants between the ages of 18 and 45 years were randomized. Fifty-two participants successfully completed the trial (1 discontinued due to lack of compliance, 2 were lost to follow-up). Fifty-five participants were in the safety evaluation set population and 54 participants were in the full analysis set population.

For all of the participant assessment endpoints (overall appearance, color, softness, and texture), the difference between the striae rubra treated with the onion extract cream and the untreated side at week 12 were statistically significant using last observation carried forward imputed values (Table I). There were statistically significant differences in the mean changes from baseline to weeks 2, 4, 8, and 12 in participant assessments of overall appearance, color, softness, and texture.

The mean change from baseline in the investigator assessments were statistically significant (P<0.01) at all time points in terms of overall appearance, softness, and texture on the side treated with the onion extract cream than on the untreated side (Table II). At weeks 2 and 4, no significant difference in mean change from baseline in investigator assessment of color between the treated and untreated sides was present. Representative photographs of the treated and untreated sides are presented in the Figure.

A responder analysis was completed in which responders were defined as having at least a one-grade improvement from baseline in the assessment (Table III). At each visit there were more responders on the side treated with onion extract cream vs the untreated side as assessed by both the investigator and participant.

The mean baseline skin elasticity was 17.86 pounds per square inch (psi) for the side treated with the onion extract cream and 16.82 psi for the untreated side. After 12 weeks of treatment, a trend favoring the use of the onion extract was observed with mean skin elasticity.

---

Table I. Summary of Changes From Baseline to Weeks 2, 4, 8, and 12 in Participant Assessment of Striae Rubra (FAS Population, Last Observation Carried Forward)

<table>
<thead>
<tr>
<th>Week</th>
<th>Treated (Onion Extract Cream)</th>
<th>Untreated</th>
<th>Difference (Treated–Untreated)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall appearance, mean (SD)</td>
<td>n=50</td>
<td>n=50</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>0.56 (0.644)</td>
<td>0.10 (0.364)</td>
<td>0.46 (0.613)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Color, mean (SD)</td>
<td>0.28 (0.701)</td>
<td>0.08 (0.566)</td>
<td>0.20 (0.452)</td>
</tr>
<tr>
<td></td>
<td>Softness, mean (SD)</td>
<td>0.74 (0.922)</td>
<td>0.20 (0.670)</td>
<td>0.54 (0.813)</td>
</tr>
<tr>
<td></td>
<td>Texture, mean (SD)</td>
<td>0.48 (0.814)</td>
<td>0.14 (0.606)</td>
<td>0.34 (0.626)</td>
</tr>
<tr>
<td>Week 4</td>
<td>Overall appearance, mean (SD)</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.15 (0.878)</td>
<td>0.15 (0.452)</td>
<td>1.00 (0.890)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Color, mean (SD)</td>
<td>0.70 (0.882)</td>
<td>0.06 (0.231)</td>
<td>0.65 (0.894)</td>
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<tr>
<td></td>
<td>Softness, mean (SD)</td>
<td>1.26 (0.894)</td>
<td>0.20 (0.528)</td>
<td>1.06 (1.054)</td>
</tr>
<tr>
<td></td>
<td>Texture, mean (SD)</td>
<td>0.89 (0.883)</td>
<td>0.11 (0.317)</td>
<td>0.78 (0.945)</td>
</tr>
<tr>
<td>Week 8</td>
<td>Overall appearance, mean (SD)</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.94 (0.712)</td>
<td>0.20 (0.562)</td>
<td>0.74 (0.935)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Color, mean (SD)</td>
<td>0.69 (0.773)</td>
<td>0.11 (0.462)</td>
<td>0.57 (0.924)</td>
</tr>
<tr>
<td></td>
<td>Softness, mean (SD)</td>
<td>1.17 (0.795)</td>
<td>0.22 (0.538)</td>
<td>0.94 (0.979)</td>
</tr>
<tr>
<td></td>
<td>Texture, mean (SD)</td>
<td>1.00 (0.777)</td>
<td>0.22 (0.604)</td>
<td>0.78 (0.984)</td>
</tr>
<tr>
<td>Week 12</td>
<td>Overall appearance, mean (SD)</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.13 (0.802)</td>
<td>0.20 (0.562)</td>
<td>0.93 (0.843)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Color, mean (SD)</td>
<td>0.70 (0.792)</td>
<td>0.07 (0.328)</td>
<td>0.63 (0.784)</td>
</tr>
<tr>
<td></td>
<td>Softness, mean (SD)</td>
<td>1.31 (0.865)</td>
<td>0.15 (0.408)</td>
<td>1.17 (0.986)</td>
</tr>
<tr>
<td></td>
<td>Texture, mean (SD)</td>
<td>1.06 (0.856)</td>
<td>0.19 (0.552)</td>
<td>0.87 (0.848)</td>
</tr>
</tbody>
</table>

Five-point ordinal scale (0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement). Abbreviations: FAS, full analysis population; SD, standard deviation.
decreasing by 1.40 psi for the treated side vs 0.10 psi for the untreated side, but statistical significance was not reached \((P=0.23)\).

There were no adverse events reported among the 55 participants who participated in this trial.

**DISCUSSION**

In this randomized, controlled, investigator-blinded 12-week study examining a cream containing onion extract, Centella asiatica, and hyaluronic acid, there was a statistically significant improvement in proximal aspect of the thigh striae rubra in terms of overall appearance, softness, color, and texture as evaluated by the participants and the investigator. Using participants with symmetrical striae rubra on the proximal aspect of the thighs allowed each participant to serve as their own control. Improvement in skin elasticity was not statistically significant between treated and untreated sides; however, it is envisaged that perhaps with longer use and/or an increase in the study sample size, the skin elasticity measurement might achieve statistical significance.

It is important to recognize that this study demonstrated only improvement (ie, diminution of the signs for striae) in the feel and appearance of striae rubra, not a reduction in their size or elimination of the scar tissue. Stretch marks are such a common occurrence that it is hard to classify them as a dermatologic disease, yet they are designated by an International Classification of Diseases, Ninth Revision code. They typically occur in women and men at or around puberty on the proximal, medial aspect of the arms, lateral aspect of the breasts, lumbar region of the torso, and proximal aspect of the thighs.\(^{24}\) A second common time for the formation of striae distensae is during pregnancy, again a time of hormonal change characterized by corticosteroid secretion. During pregnancy, striae distensae

<table>
<thead>
<tr>
<th>WEEK</th>
<th>TREATED (ONION EXTRACT CREAM)</th>
<th>UNTREATED</th>
<th>DIFFERENCE (TREATED–UNTREATED)</th>
<th>(P) VALUE</th>
<th>PAIRED (t) TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>n=50</td>
<td>n=50</td>
<td>n=50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall appearance, mean (SD)</td>
<td>0.68 (0.741)</td>
<td>0.10 (0.303)</td>
<td>0.58 (0.859)</td>
<td>&lt;0.01</td>
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<tr>
<td>Color, mean (SD)</td>
<td>0.02 (0.247)</td>
<td>0.02 (0.141)</td>
<td>0.00 (0.286)</td>
<td>1.000</td>
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<tr>
<td>Softness, mean (SD)</td>
<td>0.74 (0.723)</td>
<td>0.18 (0.388)</td>
<td>0.56 (0.884)</td>
<td>&lt;0.01</td>
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<tr>
<td>Texture, mean (SD)</td>
<td>0.42 (0.758)</td>
<td>0.04 (0.198)</td>
<td>0.38 (0.805)</td>
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<td></td>
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<tr>
<td>Week 4</td>
<td>n=54</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall appearance, mean (SD)</td>
<td>1.06 (0.738)</td>
<td>0.20 (0.451)</td>
<td>0.85 (0.998)</td>
<td>&lt;0.01</td>
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<tr>
<td>Color, mean (SD)</td>
<td>0.11 (0.420)</td>
<td>0.00 (0.000)</td>
<td>0.11 (0.420)</td>
<td>0.0570</td>
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</tr>
<tr>
<td>Softness, mean (SD)</td>
<td>1.09 (0.759)</td>
<td>0.22 (0.462)</td>
<td>0.87 (1.047)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Texture, mean (SD)</td>
<td>0.96 (0.800)</td>
<td>0.19 (0.438)</td>
<td>0.78 (1.022)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>n=54</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall appearance, mean (SD)</td>
<td>1.48 (0.746)</td>
<td>0.17 (0.423)</td>
<td>1.31 (1.006)</td>
<td>&lt;0.01</td>
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<tr>
<td>Color, mean (SD)</td>
<td>0.30 (0.633)</td>
<td>0.0 (0.0)</td>
<td>0.30 (0.633)</td>
<td>&lt;0.01</td>
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<tr>
<td>Softness, mean (SD)</td>
<td>1.61 (0.763)</td>
<td>0.19 (0.438)</td>
<td>1.43 (1.021)</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td>Texture, mean (SD)</td>
<td>1.46 (0.818)</td>
<td>0.15 (0.408)</td>
<td>1.31 (1.043)</td>
<td>&lt;0.01</td>
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<tr>
<td>Week 12</td>
<td>n=54</td>
<td>n=54</td>
<td>n=54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall appearance, mean (SD)</td>
<td>1.72 (0.712)</td>
<td>0.09 (0.351)</td>
<td>1.63 (0.853)</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>Color, mean (SD)</td>
<td>0.61 (0.627)</td>
<td>0.00 (0.00)</td>
<td>0.61 (0.627)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Softness, mean (SD)</td>
<td>1.87 (0.825)</td>
<td>0.11 (0.317)</td>
<td>1.76 (0.970)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Texture, mean (SD)</td>
<td>1.72 (0.738)</td>
<td>0.07 (0.328)</td>
<td>1.65 (0.872)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Five-point ordinal scale (0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement). Abbreviations: FAS, full analysis population; SD, standard deviation.
can occur in the previously mentioned locations, but also commonly on the abdomen. All of the women enrolled in this study had striae rubra on the proximal aspect of the thighs due to pregnancy.

There are some important limitations of this research. The first limitation is that the participants were not blinded to treatment, which could lead to a bias toward the treated side. Since a moisturizing vehicle by itself could induce enhanced moisturization of the skin and improve the appearance of the striae rubra, it was not possible to have a true placebo controlled study. The investigator was blinded, however the study compared some treatment to no treatment. Some of the improvement noted with the study product might be due to hydration and massage; however, it is not possible to determine if the improvement may have been solely due to these factors or due to the active ingredients in the study product. The results are probably due to a combination of all factors.

This product was designed for use in the over-the-counter market and thus was only evaluated for appearance changes and claims. It is for this reason that it could only be formulated with botanical ingredients, which contain active plant extracts. This research methodology and the study cream combining onion extract, Centella asiatica, and hyaluronic acid demonstrated improvement (ie, diminution of the signs for striae) in striae rubra appearance in women.

Disclosure: This study was sponsored by Merz Pharmaceuticals, LLC. Acknowledgements: The authors want to acknowledge Wendy Murray of Merz Pharmaceuticals, LLC, for her project management of this study and Wendy Jones of Merz Pharmaceuticals, LLC, for her feedback on study design and regulatory questions.

REFERENCES

Table III. Responder Analysis

<table>
<thead>
<tr>
<th>WEEK</th>
<th>INVESTIGATOR ASSESSMENT</th>
<th>PARTICIPANT ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TREATED SIDE (ONION EXTRACT CREAM)</td>
<td>UNTREATED SIDE</td>
</tr>
<tr>
<td></td>
<td>NUMBER OF RESPONDERS,* N</td>
<td>NUMBER OF RESPONDERS,* N</td>
</tr>
<tr>
<td>Week 2</td>
<td>n=50</td>
<td>n=50</td>
</tr>
<tr>
<td>Overall appearance</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Color</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Softness</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Texture</td>
<td>34</td>
<td>9</td>
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<tr>
<td>Week 4</td>
<td>n=54</td>
<td>n=54</td>
</tr>
<tr>
<td>Overall appearance</td>
<td>46</td>
<td>10</td>
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<td>Color</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Softness</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Texture</td>
<td>46</td>
<td>11</td>
</tr>
<tr>
<td>Week 8</td>
<td>n=54</td>
<td>n=54</td>
</tr>
<tr>
<td>Overall appearance</td>
<td>49</td>
<td>8</td>
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<tr>
<td>Color</td>
<td>46</td>
<td>7</td>
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<td>Softness</td>
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<td>0</td>
</tr>
<tr>
<td>Texture</td>
<td>49</td>
<td>9</td>
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<tr>
<td>Week 12</td>
<td>n=54</td>
<td>n=54</td>
</tr>
<tr>
<td>Overall appearance</td>
<td>50</td>
<td>4</td>
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<tr>
<td>Color</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Softness</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Texture</td>
<td>50</td>
<td>6</td>
</tr>
</tbody>
</table>

* A participant that has at least a one-grade improvement from baseline in the assessment.

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

Synonyms: Rubeola; Measles

DIAGNOSIS: The length of the prodromal period, the catarrhal symptoms, the presence of Koplik’s spots, the swollen, blotchy appearance of the face, the macular character and crescentic arrangement of the lesions, the prevalence of an epidemic and the nature of the disease from which the contagion arose, are the points to be considered in a differential diagnosis from other exanthemata, drug rashes or syphilis.

TREATMENT: The patient should be put on a light diet, confined to bed, and isolated in a darkened but well ventilated room. The severe symptoms are to be mitigated by appropriate symptomatic treatment and the patient is to be guarded against exposure, especially during convalescence.
Gynecomastia is a benign condition that involves enlargement of the male breast secondary to the proliferation of mammary ductules. It is seen in one-third to two-thirds of men. A prevalence rate of 15.2% was reported in a recent study involving children 6 to 8 years of age who were clinically followed for a period of 7 years.

PATHOGENESIS OF GYNECOMASTIA

Ductal breast tissue in men is under the influence of circulating sex hormones especially estrogen and testosterone. These hormones have opposite effects on ductal breast tissue. Thus, while testosterone tends to decrease ductal breast tissue proliferation, estrogen tends to stimulate ductal breast tissue proliferation. Any alteration in the serum free levels of these hormones disturbs the “hormonal milieu intérieur” thus resulting in gynecomastia. For instance, individuals with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome usually have hyperestrogenemia resulting in gynecomastia. Gynecomastia has been reported following the use of medications such as fenofibrate and even natural plant oils such as lavender tree oil.

CLINICAL DIAGNOSIS OF GYNECOMASTIA

A clinical diagnosis of gynecomastia is made by palpation of the involved breast. On physical examination the patient has a sub-areolar disc of firm tissue that should be more than half a centimeter in diameter for making a clinical diagnosis of gynecomastia. Gynecomastia may occur as a result of a number of systemic conditions such as cirrhosis and Klinefelter syndrome. Many of these systemic conditions also have cutaneous manifestations (Table). The correct identification of these skin lesions can usually point to the correct etiology of the gynecomastia. The cutaneous manifestations of some of these common systemic conditions that cause secondary gynecomastia are discussed below.

SYSTEMIC CONDITIONS ASSOCIATED WITH GYNECOMASTIA AND CUTANEOUS MANIFESTATIONS

CHRONIC METABOLIC DISORDERS

Cirrhosis and chronic renal failure are the two most significant causes of gynecomastia.

Cirrhosis

Gynecomastia is a common finding in patients with hepatic diseases, especially cirrhosis. There is a decrease in the hepatic clearance of androstenedione in patients with cirrhosis. The excess androstenedione is converted to estrogen in the peripheral fatty tissue resulting in the characteristic gynecomastia noted in patients with extensive cirrhosis.

Examination of the skin in patients with cirrhosis may reveal blanching and spider angiomas (telangiectasia) especially on the upper chest. In a recent study, 33% of the patients with cirrhosis had telangiectasia. Another characteristic feature is “paper money skin” characterized by the appearance of scattered, single, cutaneous blood vessels. In another study involving 235 patients with cirrhosis and 20 controls, the estradiol:free testosterone ratio was the highest in cirrhotic men with spider angiomas. This hormonal imbalance is the most likely cause of these nevi. Other researchers have suggested that other pathophysiological mechanisms may be responsible for the appearance of these lesions. For instance, some researchers believe that substance P may have a role in the pathogenesis of these cutaneous lesions. Interestingly, the examination of the anterior abdominal wall may reveal “caput medusae.” These are dilated cutaneous blood vessels that result from the increased pressure in the capillaries and veins of the abdominal wall due to the increased pressure in the portal vein.
secondary to the opening of collaterals following the development of portal hypertension in patients with severe cirrhosis. Examination of the hands in patients with cirrhosis may reveal palmar erythema, Dupuytren's contractures, as well as prominent nail abnormalities. The clinical spectrum of these nail changes ranges from pale, brittle nails to severe clubbing.

### Chronic Renal Failure

Chronic renal failure is another common chronic condition associated with the hyperproliferation of ductal breast tissue. Decreased production of testosterone by the testicular interstitial cells of Leydig in patients with chronic renal failure alters the estrogen:testosterone ratio in the blood, thus resulting in clinical gynecomastia.

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**Table. Cutaneous Manifestations of Systemic Conditions Associated With Gynecomastia**

<table>
<thead>
<tr>
<th>SYSTEMIC CONDITIONS ASSOCIATED WITH GYNECOMASTIA</th>
<th>PATHOGENESIS OF GYNECOMASTIA</th>
<th>CUTANEOUS MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Chronic metabolic disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis&lt;sup&gt;6–8&lt;/sup&gt;</td>
<td>Decrease in the hepatic clearance of androstenedione. The excess androstenedione is converted to estrogens in the peripheral fatty tissue.</td>
<td>Spider angiomas,&lt;sup&gt;6,7&lt;/sup&gt; paper money skin,&lt;sup&gt;8&lt;/sup&gt; caput medusae,&lt;sup&gt;13&lt;/sup&gt; palmar erythema, Dupuytren's contractures,&lt;sup&gt;7&lt;/sup&gt; pale, brittle nails, clubbing</td>
</tr>
<tr>
<td>Chronic renal failure&lt;sup&gt;1,15&lt;/sup&gt;</td>
<td>Decreased production of testosterone by testes</td>
<td>Pruritis,&lt;sup&gt;12,13&lt;/sup&gt; hyperpigmentation,&lt;sup&gt;13&lt;/sup&gt; xerosis,&lt;sup&gt;14&lt;/sup&gt; dermatitis, keratotic pits, uremic frost, half-and-half nails,&lt;sup&gt;15&lt;/sup&gt; Beau's lines,&lt;sup&gt;15&lt;/sup&gt; Mee's lines,&lt;sup&gt;15&lt;/sup&gt; scleromyxedema-like skin lesions,&lt;sup&gt;16&lt;/sup&gt; Kyrle's disease&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>B. Endocrine disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Graves' disease&lt;sup&gt;19,20&lt;/sup&gt;</td>
<td>Decrease in serum free testosterone levels Increase in extra gonadal aromatase activity that results in the increased peripheral conversion of testosterone to estradiol</td>
<td>Warm, moist skin; pretibial myxedema&lt;sup&gt;18&lt;/sup&gt;; Plummer's nails&lt;sup&gt;19&lt;/sup&gt;; thyroid acropathy&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Decreased production of testosterone by testes</td>
<td>Epidermal thinning; decreased pubic, axillary and facial hair; “parchment like,” cold, hypohidrotic, and hyperkeratotic skin; β-carotenemia&lt;sup&gt;11&lt;/sup&gt;; loss of the lateral third of the eyebrows; erythema ab igne</td>
</tr>
<tr>
<td><strong>C. Systemic infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leprosy&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Testicular atrophy</td>
<td>Hypoesthetic, hypopigmented macules&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Human immunodeficiency virus&lt;sup&gt;1,25,26&lt;/sup&gt;</td>
<td>Decreased testosterone</td>
<td>Seborrheic dermatitis, Kaposi’s sarcoma,&lt;sup&gt;25,26&lt;/sup&gt; Merkel cell carcinomas, basal cell carcinomas</td>
</tr>
<tr>
<td><strong>D. Malignancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal malignancies&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Increased secretion of human chorionic gonadotropin by tumors such as gastric choriocarcinomas</td>
<td>Cutaneous metastasis,&lt;sup&gt;27,28&lt;/sup&gt; acanthosis nigricans</td>
</tr>
<tr>
<td><strong>E. Genetic causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentiginosis syndromes&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Due to feminizing Sertoli cell tumors</td>
<td>Peutz-Jeghers syndrome: mucocutaneous lentigines (“peri-orificale”)&lt;sup&gt;36&lt;/sup&gt;; Cowden disease: multiple hamartomas, hyperkeratotic papules&lt;sup&gt;31&lt;/sup&gt;; Carney complex: mucocutaneous lentigines, cutaneous blue nevi, skin myxomas&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>Decreased testosterone production Increased extra gonadal aromatase activity resulting in the increased peripheral conversion of testosterone to estradiol</td>
<td>Skin ulcers&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>F. Substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Testicular atrophy Cirrhosis</td>
<td>Seborrheic dermatitis,&lt;sup&gt;35&lt;/sup&gt; acne rosacea,&lt;sup&gt;36&lt;/sup&gt; pellagra,&lt;sup&gt;37,38&lt;/sup&gt; neurodermatitis,&lt;sup&gt;39&lt;/sup&gt; cutaneous flushing</td>
</tr>
</tbody>
</table>
One of the most common dermatologic complaints of patients with chronic renal failure is pruritis. The pruritis is usually secondary to uremia. In a recent study, 55% of the patients with chronic renal failure complained of pruritis. In another study involving 102 participants with chronic renal failure, 100% of the patients had some sort of a cutaneous lesion. Hyperpigmentation was the most common abnormality noticed in this study. Similar results were reported in another recent study involving children with chronic renal failure. Xerosis was the most common abnormality noticed in this study. In a more recent study involving 100 patients with chronic renal failure, 100% of the patients had some sort of cutaneous abnormality on clinical examination. The most common of these was xerosis, which was seen in 79% of the patients. Other common cutaneous manifestations in this study included hyperpigmentation and dermatitis. Examination of the palms and soles in patients with renal failure may reveal keratotic pits. Deposition of urea crystals in the skin may result in uremic frost. Lindsay's nails or half-and-half nails was the most common nail abnormality noticed by researchers in a study of patients with chronic renal failure. In a recent study this lesion was reported in 19% of the patients with chronic renal failure. In a recent study this lesion was reported in 19% of renal failure patients who were on dialysis and 40% of those who had renal transplantation. Other common nail abnormalities that may be seen include Beau's lines and Mee's lines. An increased incidence of scleromyxedema-like skin lesions has also been reported in patients on renal dialysis. Kyrle's disease is another characteristic feature of chronic renal disease. The lesions appear as follicular or extrafollicular, dome-shaped, umbilicated papules with a central keratotic plug and surrounding acanthosis. Ultraviolet B phototherapy is highly effective in controlling the symptoms of uremic pruritis, though renal transplantation remains the treatment of choice.

ENDOCRINE DISORDERS

The two main endocrine disorders that result in gynecomastia are thyrotoxicosis and hypopituitarism.

Thyrotoxicosis

Thyrotoxicosis or Basedow's disease is characterized by a decrease in serum free testosterone levels. There is a simultaneous increase in extraglandular aromatase activity that results in the increased peripheral conversion of testosterone to estradiol. The resulting decrease in serum free testosterone accounts for the increased incidence of gynecomastia seen in patients with Graves' disease. Thyrotoxicosis is associated with a number of characteristic cutaneous manifestations. For instance, patients with thyrotoxicosis often have warm, moist skin. Dermal proliferation of fibroblasts and mucin accumulation in the dermis result in the highly characteristic "pretibial myxedema" which is seen in 4% of all patients with thyrotoxicosis. In fact, the lesions of pretibial myxedema may be massive. For instance, investigators recently described the case of a 41 year old with elephantiasic pretibial myxedema and underlying Grave's disease. The neck and the abdomen are other sites where pretibial myxedema may appear. The typical lesions are violaceous and firm and may have a "peau d’orange" appearance. Patients with pretibial myxedema almost always also have ophthalmopathy. Nail involvement in thyrotoxicosis can result in "Plummer's nails" characterized by the separation of the nail plates from the nail beds. Another rare but unique feature of thyrotoxicosis is "thyroid acropathy" characterized by pathological osteogenesis, clubbing, and characteristic swelling of the extremities. In a recent retrospective study involving 178 patients with thyroid dermopathy, 23% of the patients also had thyroid acropathy.

Hypopituitarism

Patients with hypopituitarism often develop gynecomastia. The gynecomastia results because of the decreased secretion of testicular testosterone secondary to the decreased secretion of gonadotrophic hormones by the pituitary.

The universal prevalence of hypopituitarism is 45.5 per 100,000 population. Causes of hypopituitarism range from trauma to xanthoma disseminatum. Hypopituitarism may result in a wide variety of cutaneous lesions. The loss of growth hormone may result in epidermal thinning. The loss of follicle stimulating hormone and lutinizing hormone may result in decreased pubic, axillary, and facial hair. Hypothyroidism secondary to hypopituitarism is often associated with "parchment-like," cold, hypohidrotic, and hyperkeratotic skin. Hypothyroidism may also result in β-carotenemia which may manifest as a yellowish hue of the hands. For instance, researchers have described the case of a woman who initially presented with xanthoderma and was ultimately found to have hypothyroidism. Hair loss is another common feature of hypothyroidism as is loss of the lateral third of the eyebrows. "Erythema ab igne" is another characteristic feature associated with hypothyroidism. Nail changes such as dry, cracked nails are also common.

SYSTEMIC INFECTIONS

The two main systemic infections that result in gynecomastia are leprosy and human immunodeficiency virus (HIV).

Leprosy

In a recent study involving 41 patients with lepromatous leprosy, 27% of the patients had gynecomastia. Gynecomastia is relatively less common in patients with tuberculoid leprosy. Cutaneous involvement in leprosy is characterized by the appearance of hyposthetic, hypopigmented macules. While lepromatous leprosy is usually generalized at the time of presentation, tuberculoid leprosy is usually localized. Nerves such as the posterior tibial in the lower extremity and the ulnar in the upper extremity are often affected. In a recent study of leprosy in children, direct contact was reported in 8.7% of the cases. The World Health Organization (WHO) regimen for the treatment of multibacillary leprosy involves the daily
intake of 100 mg of dapsone and 50 mg of clofazimine along with the monthly administration of 600 mg of rifampicin and 300 mg of clofazimine for a minimum period of 12 months. The WHO regimen of treatment of paucibacillary leprosy involves the daily intake of 100 mg of dapsone along with the monthly administration of 600 mg of rifampicin for a period of 6 months.

**HIV Infection**

Gynecomastia is often seen in patients with HIV. Studies indicate that the free testosterone index in patients with HIV is markedly decreased resulting in the hyperproliferation of breast ductal tissue.

HIV is associated with a number of cutaneous conditions. One of the most characteristic cutaneous features of HIV is Kaposi’s sarcoma. This sarcomatous lesion is caused by infection with the human herpes virus 8. The sarcoma may metastasize to the gastrointestinal tract or the oral cavity. Rarely, Kaposi’s sarcoma may affect the breast itself. Liposomal doxorubicin and daunorubicin are the first-step treatments of choice. HIV patients also have an increased incidence of Merkel cell carcinomas and basal cell carcinomas.

**Malignancies**

Gynecomastia may be associated with a number of internal malignancies including those of the testes and the gastrointestinal system. Cutaneous manifestations, however, are relatively more common with gastrointestinal malignancies, especially those of the stomach. For instance, gastric choriocarcinomas secrete human chorionic gonadotropin. Human chorionic gonadotropin results in the increased endogenous production of estrogens thus resulting in gynecomastia.

Gastrointestinal malignancies may result in a myriad of cutaneous manifestations. For instance, gastrointestinal malignancies may metastasize to the skin resulting in the formation of nodular cutaneous lesions. Rarely, these metastatic lesions may appear atypically. For instance, investigators recently described the case of a 64-year-old man presenting with keratotic lesions and gynecomastia who was ultimately diagnosed with Cowden disease. This is another autosomal dominant lentiginosis disorder characterized by the appearance of multiple hamartomas along with gynecomastia and dermatological changes. Examination of the skin in these patients usually reveals hyperkeratotic papules.

The genetic locus for Carney complex is located on 2p16. It is another autosomal dominant lentiginosis disorder characterized by the appearance of testicular Sertoli cell tumors and cardiac myxomas besides gynecomastia and mucocutaneous lentigines.

Cushing syndrome is often seen in these patients. Cutaneous blue nevi are another common finding. Skin myxomas are also common and are most often seen on the eyelids and the external auditory canals.

**Klinefelter Syndrome**

Patients with Klinefelter syndrome have the XXY karyotype. Gynecomastia is a frequent finding in these patients. The gynecomastia in patients with Klinefelter syndrome usually results because of decreased testosterone production by the Leydig cells of the testes combined with increased extragonadal aromatase activity resulting in the increased peripheral conversion of testosterone to estradiol.

Klinefelter syndrome is associated with a number of cutaneous conditions. Skin ulcers are the most common of these cutaneous manifestations. For instance, the case of a 54-year-old man who initially presented with skin ulcers and was ultimately found to have Klinefelter syndrome was recently reported. Increased activity of the plasminogen activator inhibitor-1 has been reported in a patient with Klinefelter syndrome. This might explain the increased predisposition to venous thrombosis and subsequent leg ulcers in patients with Klinefelter syndrome.
Substance Abuse
A number of illicit drugs such as marijuana and alcohol may cause gynecomastia. However, cutaneous manifestations associated with gynecomastia are more common in alcohol abusers.

Alcohol Abuse
Gynecomastia is a common finding in chronic alcoholics. Chronic alcohol use may directly affect the testes resulting in atrophy and thus an imbalance in the estrogen:testosterone ratio.1 In addition, chronic alcohol use may result in cirrhosis which in turn may further aggravate the gynecomastia.2 Both of these factors have a significant role to play in the pathogenesis of gynecomastia in chronic alcoholics.

Skin conditions such as seborrhic dermatitis are exacerbated by chronic ethanol consumption.35 An increased prevalence of acne rosacea has been reported (5.6%).36 The appearance of diarrhea and neurodermatitis are relatively more common in alcoholics. About 2.5% of alcoholics also have neurodermatitis.39 A vast myriad of other nonspecific skin alterations in patients with chronic renal failure.38 Studies suggest that cutaneous fungal infections such as sporotrichosis and paracoccidioidomycosis are also relatively more common in alcoholics. About 2.5% of alcoholics also have neurodermatitis.39 A vast myriad of other nonspecific skin changes, such as cutaneous flushing, may be seen in alcoholics. In one study, nearly 43% of all alcohol abusers had some sort of cutaneous abnormalities.40 Tinea versicolor (14%) was the most common dermatologic abnormality identified in this study.

CONCLUSIONS
As is evident from the above examples, most of the systemic conditions associated with gynecomastia affect the skin also. Correct recognition of these lesions can go a long way in identifying the underlying etiology of the gynecomastia.

Disclosure: The author has no conflicting interests or any financial interests in this manuscript.

REFERENCES


**SELF TEST REVIEW QUESTIONS**

W. Clark Lambert, MD, PhD, Editor

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

1) The two main endocrine disorders that result in gynecomastia are hypopituitarism and:
   a. Addison’s disease.
   b. Cushing syndrome.
   c. hyperaldosteronism.
   d. hyperparathyroidism.
   e. hypothyroidism.
   f. thyrotoxicosis.

2) The two main systemic infections that result in gynecomastia are human immunodeficiency virus (HIV) infection and:
   a. dengue.
   b. leprosy.
   c. paracoccidioidomycosis.
   d. tuberculosis.
   e. tularemia.

3) The most common cutaneous manifestation of Klinefelter syndrome is:
   a. cutaneous ulcers.
   b. dry, cracked nails.
   c. keratotic pits of the palms and soles.
   d. palmar erythema.
   e. yellow palms.

4) “Paper money skin,” characterized by the clinical appearance of scattered, single cutaneous blood vessels, is a sign of:
   a. chronic renal failure.
   b. cirrhosis.
   c. hypopituitarism.
   d. stomach cancer.
   e. thyrotoxicosis.

5) Which of the following nail changes is (are) associated with renal failure?
   a. Beau’s lines
   b. Half-and-half nails
   c. Lindsay’s nails
   d. Mee’s lines
   e. All of the above are correct.
   f. None of the above is correct.

**ANSWERS TO SELF TEST REVIEW QUESTIONS:**

© 92
DESCRIPTION
LidoWorx is a new topical anesthetic designed for local or dermal analgesia which incorporates a novel drug delivery system trademarked as Small Molecule Solubilization System (SMSS). This system is designed to increase the solubility of the active ingredient, thus allowing the lidocaine to exhibit a rapid onset of action. LidoWorx is a non–oil-based, alcoholic gel containing 4% lidocaine with skin permeation enhancers (cis-unsaturated fatty acids which fluidize stratum corneum) indicated as a topical analgesic to be used on normal, intact skin (Baumann LS, et al., unpublished data, 2010).

CLINICAL PHARMACOLOGY
MECHANISM OF ACTION
LidoWorx achieves dermal analgesia by the release of lidocaine from the gel vehicle into the epidermis and dermis. The amide anesthetic, lidocaine, then reversibly blocks initiation and propagation of nerve impulses by arresting sodium ion flux through neuronal membranes.

PHARMACOKINETICS
LidoWorx is designed to deliver lidocaine into the skin, but depending on factors such as duration of use and surface area of application, systemic absorption may occur. In reference to intravenous infusion of lidocaine, systemic toxic effects have been observed at plasma lidocaine concentrations of 6–10 µg/mL. In one study of 14 subjects in which it was applied without occlusion for up to 60 minutes on the lateral, periorbital regions of the face, lidocaine plasma levels were between 0 and 16 ng/mL with a maximum average of 4 ng/mL.

CLINICAL STUDIES
The safety and efficacy of LidoWorx Gel as a rapid acting topical analgesic for use on normal, intact skin were assessed in 2 prospective studies on patients 18 years of age and older.

EFFICACY
In both an efficacy study (clinical study 1) and a safety and efficacy study (clinical study 2), (N=12 and N=14, respectively) the anesthetic profile over time of LidoWorx Gel was assessed (Baumann LS, et al., unpublished data, 2010). In both studies, subjects received a total of 6 botulinum toxin type A injections in 6 demarcated areas of the lateral periorbital regions for “crow’s feet” type wrinkles on the face. The initial injection being at time zero, in the absence of anesthetic, the following injections were placed in randomized periorbital zones at regular intervals with the final injection at 45 minutes. Perceived pain was recorded immediately after each injection on a visual analog scale (VAS) from 0 to 10. Results indicated that optimum analgesic effects of LidoWorx were observed 35–40 minutes after application.

SAFETY/ADVERSE EVENTS
In both of the studies described above, LidoWorx Gel demonstrated itself to be safe and well tolerated. In the safety and efficacy study (clinical study 2), 14 patients had plasma lidocaine levels drawn at times 0, 20, 30, 35, 40, and 45 minutes with one last sample taken at 60 minutes (15 minutes after all LidoWorx Gel had been removed from the face). Lidocaine plasma levels ranged between 0 and 16 ng/mL, with the average level being 4 ng/mL—safety beneath the reported toxicity level of 6.0 µg/mL.

INDICATION, DOSAGE, AND ADMINISTRATION
LidoWorx Gel is indicated for rapid, temporary analgesia for penetrating local pain on normal, intact, noninflamed skin in adults and children 2 years of age and older. It is recommended that a moderately thick layer (approximately 1/8 inch thick) be applied to the area to be treated. Numbness should develop approximately 15 minutes after application, with optimum analgesia occurring at 35–40 minutes. LidoWorx Gel should not be applied to large body surface areas, used under occlusion, or placed on mucous membranes or on inflamed skin. It is contraindicated in any patient allergic to amide-type local anesthetics or any component of the product.

SAFETY AND PRECAUTIONS
Though generally considered safe medications, topical anesthetics have been reported to cause rare, but sometimes serious, complications.
These have included case reports of methemoglobinemia, and even one report of arrhythmia and cardiovascular collapse (also Baumann LS, et al., unpublished data, 2010). It is for this reason that authorities such as the US Food and Drug Administration (FDA) advise caution, and strongly recommend against using these products over large surface areas, under occlusion, or on skin whose barrier has been disrupted. Systemic (dose related) reactions usually observed at plasma lidocaine levels greater than 10,000 ng/mL include: central nervous system (CNS) excitation and/or depression (light-headedness, nervousness, confusion, dizziness, drowsiness, tinnitus, blurred vision, vomiting, numbness, convulsions, respiratory depression or arrest). Similarly, possible cardiovascular complications seen at these plasma concentrations include bradycardia, hypotension, and cardiovascular collapse and arrest.

LidoWorx Gel falls into pregnancy category B. Lidocaine has shown no harm to fetal rats (30 mg/kg subcutaneously, 22 times single dermal administration [SDA]), but no adequate, well controlled studies on pregnant women exist. Lidocaine hydrochloride has been tested and found to have no mutagenic effects, but the mutagenicity and genotoxicity of 2,6-xylidine, a metabolite of lidocaine, is unclear. 2,6-xylidine has, however, been shown to be carcinogenic in laboratory animals at doses of 900 mg/m² (60 times SDA). This effect was not observed at daily doses of 300 mg/m² (20 times SDA).

DISCUSSION
Numerous topical anesthetics containing lidocaine as an active ingredient are commercially available. All make varying claims of efficacy and cost-effectiveness. A lack of standardized head-to-head trials makes comparison problematic. Nevertheless, we have adapted and updated a summary of some representative competitors in the lidocaine based topical anesthetic market (Table). LidoWorx Gel has been shown in these studies to be both efficacious and safe when used appropriately. The rapid (25 minute) onset of action, which is achieved without the need for occlusion, places it competitively among other topical lidocaine anesthetics. Due to the fact that it is strictly an amide-class anesthetic, there is no need to worry about the para-aminobenzoic acid metabolite sensitivity associated with anesthetics belonging to other chemical classes. Head-to-head studies are needed to fully evaluate relative efficacy among these anesthetics, but it is clear that LidoWorx Gel represents a comparatively cost-effective and safe product.

REFERENCES
1 LidoWorx (4% lidocaine) Gel [package insert]. Hallandale, FL: DermWorx Incorporated; 2009.

Table. Topical Anesthetics Containing Lidocaine

<table>
<thead>
<tr>
<th>PRODUCT AND MANUFACTURER</th>
<th>ACTIVE INGREDIENTS</th>
<th>DELIVERY VEHICLE</th>
<th>ONSET OF ACTION</th>
<th>AVERAGE WHOLESALE PRICE PER APPLICATIONa</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMLA (Astra-Zeneca Pharmaceuticals LP)</td>
<td>2.5% Prilocaine, 2.5% lidocaine</td>
<td>Oil in water emulsion</td>
<td>60 Minb</td>
<td>$1.80 per 1 gram</td>
</tr>
<tr>
<td>Topicaine (ESBA Laboratories)</td>
<td>4%–5% Lidocaine</td>
<td>Microemulsion gel</td>
<td>30–60 Min</td>
<td>$0.80 per 1 gram</td>
</tr>
<tr>
<td>LMX4 (Ferndale Laboratories, Inc)</td>
<td>4% Liposomal lidocaine</td>
<td>Liposomes</td>
<td>30 Min</td>
<td>$1.58 per 1 gram</td>
</tr>
<tr>
<td>LidoWorx (DermWorx)</td>
<td>4% Lidocaine</td>
<td>SMSS gel</td>
<td>25 Min</td>
<td>$1.30 per 1 gram</td>
</tr>
<tr>
<td>Synera (S-Caine)c (Endo Pharmaceuticals)</td>
<td>70 mg Lidocaine, 70 mg tetracaine</td>
<td>Controlled heat-activated patch</td>
<td>20–30 Min</td>
<td>$15.36 per patch</td>
</tr>
</tbody>
</table>

aAWP 2009 Red Book Price. bUnder occlusion, per package insert. cDesigned for use prior to venous canalization. SMSS indicates Small Molecule Solubilization System.
A Natural Approach to Soothing Atopic Skin
Howard A. Epstein, PhD

Nature’s solutions have been used to combat health problems since antiquity. A 60,000-year-old burial site excavated in Iraq was found to contain a variety of medicinal plants.1 Use of botanicals to treat diseases of the skin was documented 3000 years ago in the Egyptian papyrus of Ebers.2 The traditional description for use of medicinal plants, however, is usually not linked to topical application. It is not unusual to read about the claimed medicinal benefits of a botanical which is lacking appropriate in vitro and in vivo data to support the claims. The ability to identify new cosmetic uses for botanicals is enhanced when science is able to advance beyond anecdotal information to elucidation of the mechanism of activity.

Botanicals are the primary source of medicinal products in many parts of the globe, particularly less developed countries. As other industrialized countries achieved a higher standard of living, synthetic medicinal compounds replaced plant-derived pharmaceutical products. The popularity of synthetic medicines resulted in a decline of the knowledge base and use of plant-derived medicinal compounds. Renewed interest in green chemistry and natural products for skin has reinvigorated research in understanding how nature provides solutions for skin care.

MEDICINAL BOTANICALS
Tiliroside
Tiliroside is an example of a single compound found in numerous plants responsible for protecting the plant and also beneficial for human skin. Tiliroside is a flavonoid found in a variety of medicinal plants including several species of tilia and malva that grow in Europe and tropical regions of the world. It protects plants from ultraviolet (UV)-induced and other forms of environmental stress. Tiliroside is found in the hairy protrusions

Figure 1. Effect of tiliroside on the redness of skin. (A) The redness is evaluated by measuring the a-value (Minolta Chromameter [Konica Minolta, Tokyo, Japan]) after 6, 24, and 48 hours post-induction of erythema (*statistically significant vs placebo: P value <0.05). (B) The results of all time points are shown as area under the curve (P value = 0.048). UV indicates ultraviolet.
and young leaves of plants where environmental protection is particularly important for plant health.2

What Data Are Available?

Tiliroside was tested on 20 healthy, women volunteers with dry, atopic skin for its influence on erythema (redness and capillary flow). Following UV irradiation with 1 minimal erythemal dose on the volar forearm, the test substances were applied after 6, 24, and 48 hours. Erythema formation and capillary flow were evaluated using a Minolta Chromameter CR 300 (Konica Minolta, Tokyo, Japan) and a laser-Doppler flow meter, respectively. A Solar Simulator (SOL3 Honle, Munich, Germany) emitting 1 minimal erythemal dose was used as the UV source. The erythema threshold was determined for each volunteer by using different light intensity. The development of erythema was examined after the application of the respective test substances at measuring time 6, 24, and 48 hours in comparison with an untreated reference (negative control and a 1% hydrocortisone cream (positive control). One test area remained untreated (empty field). Reapplication of the test substances followed the readings after 6 and 24 hours. The study duration was conducted for a period of 3 days. A statistical analysis was conducted on the data obtained from the study2 (Figure 1, Figure 2, Table).

FURTHER COMMENTS AND CONCLUSIONS

Oxidative stress is thought to play an important role in initiating the cellular response following UV irradiation. Increasing levels of hydrogen peroxides and reactive oxygen species and decreases in antioxidative enzymes result as skin is exposed to UV irradiation. Plant-derived flavonoids are known to inhibit processes initiated by oxidative stress. Antioxidant mechanisms include inhibition of enzymes involved in the formation of reactive oxygen species. Flavonoids also act as chelators of free iron or copper, which are potential enhancers of free radical formation.3 Skin

<table>
<thead>
<tr>
<th>Table. Statistical Analysis of In Vivo Results</th>
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<tbody>
<tr>
<td>REDNESS&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verum vs UV-control</td>
</tr>
<tr>
<td>Verum vs placebo</td>
</tr>
<tr>
<td>CAPILLARY FLOW&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verum vs UV-control</td>
</tr>
<tr>
<td>Verum vs placebo</td>
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</table>

The pre-post difference to baseline at 6, 24, and 48 hours was calculated for redness and capillary flow. The ultraviolet (UV)-control was only irradiated and not treated with any test product. The analysis of the whole test period was done according to the area under curve (AUC) procedure. *Not significant (NS), P value >0.05.
reddening and increased capillary blood flow may be considered as indicators of UV stress to skin and suitable measurable parameters for inflammation of skin. The findings of this in vivo study support the conclusion regarding the ability of tiliroside (Figure 3) to function as a potential anti-aging agent for skin exposed to UV irradiation. The study supports in vitro findings conducted by other investigators that have shown the ability of tiliroside to down-regulate overproduction of nitric oxide and tumor necrosis factor-α in mononuclear cell culture. Nitric oxide and tumor necrosis factor-α are markers of inflammation. The study confirms the ability of the flavonoids, a natural compound known to protect the plant from environmental stress to also benefit human skin from similar environmental stress.

Editors Note: Further information regarding the reported study may be found in the original publication, SOFW J. 2009;135(4): 3–7.

REFERENCES

Figure 3. Chemical structure of tiliroside.

OZOAMBLYROSIS
Medications known to cause sufficient body odor to lead to diminished to absent sexual interest in a partner

<table>
<thead>
<tr>
<th>Felbatol</th>
<th>Omega-3-acids</th>
<th>Selenium</th>
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<tbody>
<tr>
<td>Leocarnitine</td>
<td>Provera</td>
<td>Synarel</td>
</tr>
<tr>
<td>Lupron</td>
<td>Salagen</td>
<td>Topamax</td>
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Adapted from Litt JZ. Curious, Odd, Rare, and Abnormal Reactions to Medications. Fort Lee, NJ: Barricade Books; 2009:155–156.
Biopsies are properly accepted as definitive tests providing diagnoses and, from them, management and prognostic guides, but have the critical limitation that not all of the lesional tissue is actually examined. The physician may choose to biopsy only part of the lesion, using a destructive mode for the remainder or even leaving it alone, and the pathologist can never section everything submitted, since each section is typically only 4 or 5 microns in thickness. Usually this arrangement provides adequate—even excellent—care, but there is always a risk that the most important tissue is not examined. This risk may be markedly exacerbated when there is a tissue reaction to the primary lesion that is more apparent clinically or grossly than the lesion itself. Of the several tissue reactions that may occur, including fibrosis, calcification, and granulation tissue, the latter is the more likely to cause a problem. In its full-blown presentation, granulation tissue is known as a pyogenic granuloma (ie, granuloma pyogenicum [GP]), a lesion that has plagued medicine in different ways for centuries.

NOMENCLATURE

Like the Holy Roman Empire, which was not holy, not Roman, and not an empire,1 GP is not a granuloma and is not pyogenic.2,3 It does not contain epithelioid cells (which, despite their name, are differentiated macrophages that secrete cytokines) which are required for a lesion to qualify as a granuloma.4 It is also not generated from pus (ie, pyogenic). For this reason we prefer the Latin name, GP, to the English term, pyogenic granuloma, since the latter implies that the terms may be separated and that this is, in fact, a form of granuloma.

DISCUSSION

When a wound heals by primary intention, capillaries, epithelial cells, fibroblasts, and acute inflammatory cells migrate into it from adjacent tissue as part of the healing process. When, coming from different directions, they meet within the wound, the process begins to progress to its later stages, but if they do not meet they continue growing, projecting upward to form a GP. The GP undergoes rapid growth, sometimes outstripping the epithelium's ability to cover it, until it abruptly stops after attaining a thickness that may exceed 1 centimeter. This process may lead to spontaneous ulceration or the lesion may ulcerate as a result of mild trauma. Either process may result in a massive infiltrate of neutrophils, generating pus on the surface of the lesion. The pus was once erroneously thought to be responsible for the generation of the GP, supporting the notion—widely held in nineteenth century medicine—that pus promoted tissue growth and healing and was, indeed, a highly desirable, if not a necessary, part of the healing process. When Joseph Lister promoted antiseptic surgery at the Glasgow Royal Infirmary in the latter part of that century, he was widely attacked because his approach was not associated with pus in the patients' surgical wounds. This delayed acceptance of Lister's new surgical methods, and may have discouraged earlier surgeons from introducing such methods at all.5

The stresses created by the presence of a lesion, particularly a neoplasm, may generate granulation tissue. This granulation tissue, whether or not forming a full blown GP, may be more apparent than the primary lesional tissue, causing it to be biopsied or selected for sectioning instead of the underlying lesion.3 It is certainly not bad medicine to biopsy the most prominent part of a lesion, nor is it necessarily bad medicine to biopsy only part of the lesion and proceed with management based on the biopsy results, not necessarily submitting further tissue for pathological analysis. However, this “anatomically correct” approach, followed by a “histopathologically correct” diagnosis on the submitted tissue, may nevertheless produce potentially disastrous consequences if the primary lesion is not sectioned or is not recognized in the sections examined.
Two examples illustrate this point: In the first case, a subungual lesion of a finger produced a GP of the adjacent skin that was far more apparent than the primary lesion. A biopsy showed only the GP (Figure 1). Subsequent follow-up resulted in an additional biopsy, revealing that the primary lesion was a squamous cell carcinoma—which was excised, but only after a delay in diagnosis. In the second case, a postauricular basal cell carcinoma was excised, followed by a second lesion which on biopsy showed only acute inflammation and granulation tissue. Deeper levels on the pathological block showed nests of recurrent basal cell carcinoma within the lesion (Figure 2).

CONCLUSIONS
The risk that a biopsy may show only secondary changes that are more clinically/grossly prominent than the more serious primary lesion should be considered in evaluating cutaneous and mucous membrane conditions, especially if only part of the lesional tissue is biopsied. This is in addition to the risk that a long-standing inflammatory condition may give rise to a secondary malignancy—as is seen in some chronic ulcers or burns—with a biopsy showing only the primary, nonmalignant lesion.

REFERENCES
Born in 1854 on a plantation near Selma, North Carolina, Richardson was to have lived a genteel life. But his father drowned when he was 2 years old, and his family’s fortune was destroyed by the invading Union Army during the Civil War.\(^1\) Despite impoverishment, Richardson was determined to receive a college education. He majored in chemistry and obtained honors in Latin, Greek, and debate. Although he had intended to become a lawyer, he ran short of funds and reluctantly accepted a teaching position in a local school. Although he rose to become principal, his interests still lay in a different career, one that could combine his mastery of Latin and knowledge of chemistry.\(^1,2\)

In 1880 he bought a drug store with his meager savings.\(^2\) As a pharmacist he labored to study his customers’ ailments and find the drugs that would best alleviate them. He focused on less serious conditions, which though discomfiting, were not serious enough for the patient to consult a doctor and pay large fees.

His success allowed him to marry Mary Lynn Smith\(^2\) of Greensboro, North Carolina, and open a pharmacy in that city. Richardson continued to devise products that soothed common ailments, some 21 medicines listed in what was then called Vicks Family Remedies. Most importantly, the products could be bought directly from the store without a doctor’s prescription.\(^1\) Their popularity resulted in the launch of a wholesale company, which dominated the state’s pharmaceutical distribution.

Later, his son, Henry Smith Richardson, took the reins of the company.\(^3,4\) Industrious, and with experience in sales, Henry rightly perceived that the market outside North Carolina had yet to be tapped. Henry made the crucial decision to concentrate on marketing a single product out of the 21, what was then called Vicks’s Salve. To emphasize that it was for external use only, it was renamed VapoRub.\(^1,2\) This balm had menthol as a distinctive ingredient, which was not at that time a new and little known drug imported from Japan.\(^7\) Vicks VapoRub became a household staple throughout the United States.

Although Vicks VapoRub ointment and cream are used externally on the skin, they are not marketed as a remedy for dermatoses. However, there are claims that it might be effective as a foot care product\(^5\) and in fungal infections of the nails, since some of the essential oils, like turpentine, possess antimycotic action.\(^6,7\)

Richardson was as clever at marketing as he was in compounding remedies. In 1906 he became the first to mail advertisements to “box holders,” current residents at an address, rather than to specific names. He is thus, arguably, the father of junk mail.

The company expanded and diversified, and was finally purchased by Procter & Gamble in 1985.\(^1,2\)

Beyond his success in pharmaceuticals, Lunsford Richardson was also a man of noble character. He was a staunch supporter of African-American rights, in a time and place where such sympathies were shocking and even dangerous. A devoted Christian, he taught Sunday school to African-American children for many years.

Richardson noted that Greensboro’s blacks were woefully underserved medically. There were only 6 hospital beds open to African Americans in the entire city. He joined in an effort to build a medical center to serve the black community, a facility where the best care would be available, and where black doctors could practice alongside white professionals. The hospital would also open a nursing school for African Americans. The medical center was later renamed the L. Richardson Memorial Hospital.

**HISTORICAL VIGNETTE**

_Charles Steffen, MD, Section Editor_

**The Founder of Vicks:**

Lunsford Richardson (1854–1919)

Khalid Al Aboud, MD

Vicks VapoRub (Procter & Gamble, Cincinnati, OH) is one of the most popular over-the-counter therapies in the world, used to provide relief from the symptoms of the common cold and non–life-threatening respiratory infections. Even as more advanced products have come and gone, VapoRub continues to dominate the market almost 9 decades after the death of its formulator, Lunsford Richardson (Figure).
It would have pleased him to see that it, and eventually all of Greensboro’s medical services, would become fully integrated.

During World War II a Liberty ship was christened as the S.S. Lunsford Richardson at the “special request of the leading Negro citizens of North Carolina, to honor the memory of a white friend.”

Richardson’s life came to an abrupt end during the height of his success, when he succumbed to pneumonia during an epidemic. An obituary in the *Greensboro Daily News* of August 22, 1919 had this to say about Lunsford Richardson’s fine nature: “He never passed anyone on the street, young or old, black or white, without a nod and a smile.”


REFERENCES

Urea is one of the natural moisturizing factors (NMFs) of the stratum corneum (SC). Urea plays an important role in maintaining the epidermal water level. It possesses concentration-dependent proteolytic properties and can modify the structure of amino chains and polypeptides. Urea helps to dissolve amino acids contained in filaggrin (the cornerstone protein of the epidermis) and to break down protein connections between corneocytes, which can then hold more moisture, maintaining the barrier function of the skin. Urea is a humectant, an agent that attracts water to the skin, in particular from the dermis. Urea preparations in strengths ranging from 3% to 50% include cream, lotion, shampoo, gel, gel stick, wipe, emulsion, solution, suspension, spray, ointment, paste, foam, and shower/bath wash. The 10% concentration appears to provide the best balance of effectiveness and side effects for use on the body skin, although individual patients may benefit from stronger concentrations.

Urea is useful in treating many skin diseases including xerosis; ungual and cutaneous hyperkeratosis; ichthyosis; keratosis pilaris; keratoderma; clavi; calluses, cracked heels; psoriasis; hand dermatitis; black hairy tongue; and acne conglobata. The side effects of urea are mild and include cutaneous eruptions, allergic contact dermatitis, stinging, and irritation. While urea clearly helps to moisturize dry skin, its ability to restore skin that is inherently lacking in barrier function, as occurs in the elderly, has yet to be defined. Urea, a substance that has been in use for over a century in topical preparation, still has a place in the dermatologic armamentarium.

This review focuses on the role of urea in skin health and disease. Urea, lactic acid (LA) (as sodium lactate), salts (as ions), sugars, pyrrolidone carboxylic acid (PCA) (as sodium pyrrolidone carboxylate), and amino acids (ie, filaggrin breakdown products) are the NMFs in the SC. Keratinocytes (corneocytes) make urea from proteins. The NMFs may be up to 10% of the SC weight. The SC forms a very active part of epidermis, possesses secretory functions, and furnishes urea with a setting in which to work its hydrating functions.

The water content by weight of the SC is normally about 30%. Urea plays an important, albeit nonprimary, role in maintaining this epidermal water level. As stated, NMF are up to 10% of the weight of the SC, of which urea represents 7%, amino acids 50%, PCA 12%, lactic acid 12%, and other factors 19%. In healthy epidermis, there are ≈28 µg of urea per square inch (2.5 cm²). Urea attracts water from the dermis, and binding water gives the epidermis the capacity to hold moisture and maintain the barrier integrity of the skin. In xerotic skin, the urea concentration is cut in half, in psoriatic skin it is decreased by 40%, and in actively atopic skin urea concentration is decreased by 85%. Topical treatment by urea reduces epidermal hyperproliferation and induces differentiation in psoriasis.

Urea possesses concentration-dependent proteolytic properties and can modify the structure of amino chains and polypeptides; it also helps to dissolve amino acids contained in filaggrin (the cornerstone protein of the epidermis) and to break protein connections between corneocytes, which can hold moisture, maintaining the barrier function of the skin. Urea is a humectant, an agent that attracts water to the skin, in particular from the dermis. Other humectants include amino acids, LAs, a hydroxy acids, propylene glycol, and glycerine.

**CHEMISTRY**

Urea is an organic compound of carbon, nitrogen, oxygen, and hydrogen, with the formula CON₂H₄ or (NH₂)₂CO. Urea is also known as carbamide, especially in the recommended International Nonproprietary Names in use in Europe (ie, the medicinal compound hydroxyurea [old British approved name] is now hydroxy carbamide).

**CLINICAL USE**

Urea has been a part of natural medicine since biblical times. In modern times, urea has been used as a therapeutic topical preparation since 1906. The scientific basis for using urea has been underlined in recent years as its role as an NMF has been defined. The mechanisms of urea's actions involve its numerous effects on keratin. Urea preparations include cream, lotion, shampoo, gel, gel stick, emulsion, solution, suspension, spray, ointment, paste, wipe, foam, and shower/bath wash and are available from many companies (Table). Strengths of urea preparations range from 3% to 50%.

The most commonly used urea preparation is the over-the-counter
10% cream. The 10% concentration appears to be the concentration of urea that parallels that of normal skin and is the highest concentration that is commonly tolerated on the skin.

Urea's advantages as a moisturizer include the following:

1. Hydrating effects: Urea is strongly hygroscopic and draws from the dermis and retains water within the epidermis. Urea causes the dry skin cells to “unpack” and expose their water-binding sites, thus enabling the cell to absorb and retain additional moisture.

2. Keratolytic effects: Urea softens the SC, facilitating desquamation, a particular advantage on callused or pedal skin. Urea dissolves the intercellular matrix, facilitating its keratolytic effects.

3. Regenerative skin protection: Urea has a direct protective effect against drying influences and, if used regularly, improves the capacity of the epidermal barriers for regeneration.

4. Barrier function enhancement: Urea prevents water loss by slowing down evaporation.

5. Anti-irritation/soothing effects: Urea has antipruritic activity based on local anesthetic effects.

6. Moisturizers influence and urea increases the skin barrier function of normal skin and atopic skin, as measured by transepidermal water loss and susceptibility to irritants (eg, sodium lauryl sulfate).

7. Penetration-assisting effects: Urea can potentiate the effectiveness of antifungal and corticosteroid preparations by increasing preparation penetration.

8. Moist skin care with 3% urea lotion delays the occurrence and reduces the grade of acute skin reactions in percutaneously irradiated patients with head and neck tumors.

9. Urea can exert its effect in concentrations as low as 10%.

10. Urea also hydrates and dissolves the intercellular matrix of the nail plate, which can result in the softening and eventual debridement of the nail plate.

Forty percent to 50% urea products are useful agents in the treatment of nail diseases; preparations with this concentration of urea improve the clinical appearance of toenails by softening nails, decreasing nail thickness, and serving as a debriding agent in such diseases as onychomycotic nails, psoriatic nails, and ingrown nails. Products with urea concentrations of 40% to 50% are useful for treating nail hyperkeratosis induced by repetitive trauma and friction. When urea is applied to the nails, the surrounding skin should be covered because urea is a very strong keratinolytic.

**Penetration and Chemical Effects**

Penetration of urea is dependent on the vehicle in which it is contained. Studies indicate that urea alters the physical and chemical properties of keratin so that permeation of monosubstances in urea-altered keratin is increased. The moisturizing effect of urea may be enhanced if the urea is applied while the skin is still damp after washing or bathing. Results have shown that barrier-improving and hydrating abilities of urea are bidirectional and dependent on both the type of vehicle used for its delivery and the state of skin. It has been shown that the penetration is much deeper in the layers of the SC (which contains 30 layers of flattened cells) when the urea is applied in appropriate vehicles.

The chemical effects of urea on the skin are complex. The closer the urea cream is to a pH of 7, the less burning there is with application. Addition of sodium chloride preparations does not increase the effectiveness of creams with urea. Clinical improvement of xerosis following treatment with a urea-containing cream was not accompanied by any significant change in the amino acid content of the SC. The damaging effect of oil-in-water emulsions, which dry the skin, can be reduced by the addition of glycerol and urea. Urea is not a panacea for enhancing penetration. Evaluation of the efficacy of short-incubation, broad-area aminolevulinic acid/photodynamic therapy for actinic keratoses and diffuse photodamage found no benefits of pretreatment with 40% urea cream for penetration enhancement.

**Side Effects.** The side effects of urea are mild and include cutaneous eruptions, stinging, and irritation. It should not be applied to broken skin or the eyes. Urea's low pH and sensory reactions may reduce patient acceptance, in particular in the elderly with broken skin. Strong odor is also present with urea and can reduce acceptance. Urea can cause allergic contact dermatitis. Patch tests with a cream containing 10% urea were performed on 79 patients with eczematous skin disease; 7 (8.9%) had positive results to urea alone.

**Urea Study Data.** A variety of studies have assessed the utility of urea as a moisturizer. In a study of 1905 patients, the combination of urea and hydrocortisone was used for acute attacks of neurodermatitis, and urea ointment for chronic therapy. Eight-four percent of the
patients showed good to very good results. Local therapy with other corticosteroids was only reported as necessary in 16% of cases.

A randomized, double-blind, bilateral paired-comparison study involving 25 patients with moderate to severe xerosis showed that improvement is achieved quicker with 40% urea cream than with 12% ammonium lactate lotion, with superior day 14 skin roughness, fissure reduction, thickness, and dryness measurements.26 Ten percent urea lotion has a strong positive effect on generalized ichthyotic keratinization disorders.20 In patients with

### Table. Productsa With Ureab

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<thead>
<tr>
<th>Product</th>
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<tbody>
<tr>
<td>Aqua Care, 10%</td>
<td>Keralac 50% cream</td>
<td>Rea-Lo Lotion, 30%</td>
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<tr>
<td>Aquaphilic, 10%</td>
<td>Keralac Nailstik, 50%</td>
<td>Rinnovi nail system 50% solution, cuticle protectant spray, cuticle cleanser spray</td>
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<tr>
<td>Atrac-Tain Cream (10% urea and 4% alpha hydroxy acid [lactic acid])</td>
<td>Keralac 50% Ointment</td>
<td>Rosula Sodium Sulacetamide 10% and Sulfur 4% in 10% Urea Base Clarifying Wash, Aqueous Cleanser and Gel, NS Medicated Pads</td>
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<tr>
<td>Bianca Rosa 10% Gel</td>
<td>Keralac 50% Gel</td>
<td>U-Kera E Emollient Cream, 40%</td>
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<tr>
<td>BP-K50 (50% suspension)</td>
<td>Keralac 35% Lotion</td>
<td>Ultra Mide 25, 25%</td>
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<tr>
<td>Carmol 10% cream</td>
<td>Keratol Zx 50% solution</td>
<td>Ultralytic 20% foam</td>
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<tr>
<td>Carmol 20% cream</td>
<td>Keratol Plus lotion, 35%</td>
<td>Ultralytic 2 (ammonium lactate and urea foam 20%)</td>
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<tr>
<td>Carmol HC Cream (1% hydrocortisone acetate and 10% urea)</td>
<td>Keratol plus gel, 50%</td>
<td>Umecta PD Bioadhesive Emulsion (urea 40% - sodium hyaluronate 0.3%)</td>
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<tr>
<td>Carmol 40% Cream, Lotion, Gel</td>
<td>Keratol 40% lotion, cream</td>
<td>Umecta 40% Mousse (foam)</td>
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<tr>
<td>Carmol 10% Deep Cleansing Antibacterial Shampoo</td>
<td>Keratol cream (10% urea and 1% hydrocortisone)</td>
<td>Umecta 40% Nail Film Pen</td>
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<tr>
<td>Carmol Scalp Treatment Lotion (10% sulacetamide sodium in a 10% urea vehicle)</td>
<td>Kerol 42% cloths</td>
<td>Umecta PD Topical Suspension (urea 40% - sodium hyaluronate 0.3%)</td>
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<tr>
<td>Cerovel 40% cream</td>
<td>Kerol AD 45% emulsion</td>
<td>Urea-generic/compounded 10%, 20% (solution, suspension, cream, lotion, ointment) over the counter</td>
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<tr>
<td>Dermatol 10% cream</td>
<td>Lanaphilic Ointment, 10%</td>
<td>Urea-generic/compounded 40%, 50% (solution, suspension, cream, lotion, ointment) prescription</td>
<td></td>
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<tr>
<td>Epimide 25% lotion</td>
<td>Mectalyte 40% emulsion</td>
<td>Ureacin-10 lotion, 10%</td>
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<tr>
<td>Epimide 50% Topical Paste</td>
<td>Mectalyte 40% suspension</td>
<td>Ureacin-20 Crème, 20% cream</td>
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<tr>
<td>Gord Urea 40% cream</td>
<td>Nutraplus cream/lotion, 10%</td>
<td>Ureacin-40 Crème, 40% cream</td>
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<tr>
<td>Gordons 22% cream</td>
<td>Lanaphilic 10% Ointment with lanolin</td>
<td>Urealac 35% lotion</td>
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<tr>
<td>Gordons 40% cream</td>
<td>Kerol AD 45% emulsion</td>
<td>Urealac 50% gel, cream, ointment, and nail stick</td>
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<tr>
<td>Gormel 10% lotion</td>
<td>RE Urea, 40%</td>
<td>Urix 40% Urea cream</td>
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<tr>
<td>Gormel 20% cream</td>
<td>RE Urea, 50%</td>
<td>Vanamid 40% cream</td>
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<tr>
<td>Hydro 35 foam, 35%</td>
<td>RE Urea 50% Nail Applicator</td>
<td>X Viate 40% cream, gel</td>
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<tr>
<td>Hydro 40 foam, 40%</td>
<td>RE40Gel, 40%</td>
<td>ZoDerm (benzoyl peroxide 6.5%, 8.5%) in 10% urea base Cream, Gel &amp; Cleanser</td>
<td></td>
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<tr>
<td>Kerafoam 30% emollient foam</td>
<td>RE-U40 foam, 40%</td>
<td>ZoDerm (benzoyl peroxide 6.5%, 8.5%) in 10% urea base Redi-Pads</td>
<td></td>
</tr>
<tr>
<td>Kerafoam, 42%</td>
<td>Rea-Lo cream, 30%</td>
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Products are presented as trade names. aNot all products are still available or are available in the United States. bUrea concentration provided as %.
diabetes, 10% urea and 4% lactic acid vs its emulsion base provided faster and better improvement with significantly less xerosis regression.\textsuperscript{9} Debridement of necrotic eschar with 40% urea paste speeds healing of residual limbs and avoids further surgery.

In a study of cases with evidence of dry skin according to measurements by noninvasive techniques, 47 patients were enrolled for a 3-week study with double-blind and randomized treatment of one forearm; both 3% urea cream and 10% urea cream improved hydration and reduced scaling. Of interest, the 3% urea cream turned the skin color golden, while the 10% urea cream improved the skin’s barrier function.\textsuperscript{21}

A 40% urea product in an emulsion vehicle system (Butyrospermum parkii fruit oil, Helianthus annuus oil, glyicine soja sterol, and stearic acid) significantly accelerated barrier recovery after tape stripping.\textsuperscript{22} When used in women aged 56 to 80 years old who had chronically dry, rough, thick, scaly skin of the legs, this preparation decreased roughness, pigmentation, and microtopography with no reports of stinging, burning, or itching.\textsuperscript{23}

A foam formulation of 40% urea\textsuperscript{24} effectively reduced, at 7 and 14 days, the signs and symptoms associated with dry skin. It also improved the visual appearance of the dry skin by physician and patient assessment based on a sign and symptom rating scale and photodocumentation. Participants preferred the urea foam formulation for the following attributes: creaminess, lack of oiliness, lack of stickiness, ease of rub in, and overall feel; this perhaps increased urea acceptance and patient compliance.\textsuperscript{25} No differences were noted for odor or odor type.

**CONCLUSIONS**

Urea is a useful moisturizer that is available in a variety of new formulations. It clearly helps to moisturize dry skin; however, its ability to restore skin that is inherently lacking in barrier function, as occurs in the elderly, has yet to be defined. Studies have not compared old formulations with new formulations in terms of efficacy. New formulations have been compared, rather, to their bases and have been shown to be more effective. Patients often cannot tolerate 40% to 50% urea on their bodies, but they find such concentrations useful and tolerable on the nails. As is true elsewhere, the literature would benefit from direct comparisons of urea products in clinical trials performed in specific patient groups and subgroups. Urea is particularly promising as a treatment for dystrophic toenails whether infected with fungus or not. It is hoped that clinical study will continue in the area. New vehicles have been developed by urea to make it more cosmetically acceptable. These include foams and an essential fatty acid.

**REFERENCES**


Clinicians and health workers in Europe and North America must be able to identify unique symptoms and signs of sexually transmitted diseases (STDs) in patients who are not of northern European descent. They must also be aware of cultural factors, which are crucial to correct investigation, diagnosis, treatment, and follow-up. This sensitivity is also important for appropriate counselling and contact tracing.

HISTORICAL AND SOCIAL BACKGROUND

Classical descriptions of STDs, especially of syphilis, evolved in Europe and North America from the studies of 19th-century teachers in metropolitan centers such as Vienna and Paris. Their conclusions were based on the observation of the poor of those cities, whose skin coloring prior to the late 20th century was predominately pale. Until World War II, illustrations in standard textbooks were almost all of light-skinned patients. When the United States entered World War II, its armed forces published manuals for health workers about venereal diseases which, for the first time, included photographs of black skin.

Other ethnicities were scarcely represented in the literature. One exception was “Voordrachten Over Tropische Huidzieten” by J.D. Kayser of the Tropical Diseases Institute of Rotterdam-Leiden, published in 1929, which included photographs of various stages of syphilis in Malays, in what was then the Dutch East Indies.

YAWS/SYPHILIS

Early 20th century treatises were greatly concerned about the differences between venereal syphilis and yaws, but with the World Health Organization’s mass eradication campaigns of the 1950s those differences were found to have little practical application. Hackett and Loewenthal state “The skin has a limited number of reaction patterns so that similar lesions may result from different causes. This concept, so clearly explained by Brocq, may even apply to all the characters of an eruption, its method of development, its distribution, and subjective symptoms, in addition to the morphology of its individual components. Only a few lesions are truly diagnostic of yaws and often the repetition of the same pattern in an endemic area tends to be taken as evidence of yaws.” They also pointed out that in yaws-endemic areas serologic tests to differentiate the treponematoses are of little value.

SOCIAL BACKGROUND—RACIAL AND GENETIC THEORIES

We should speak of groups of populations or ethnic groups, and eliminate the term race, not only because it does not exist on a biological plane, but because it lacks all scientific foundation.

Although the term “race” is useless on a clinical level, it took some 70 years to change ingrained prejudices in the literature. In 1943 Rudolph Kampmeir, practicing in Nashville, Tennessee, wrote that “Race is a factor which cannot be disregarded with respect to the reaction between host and invader. Surely the clinician treating syphilis in both the white and Negro races is struck by the difference in the morphology of the skin reactions in the secondary stage of syphilis. Furthermore, cardiovascular syphilis is much more common in the colored than in the white patient, and by contrast it is generally accepted that the reverse is true with respect to the incidence of central-nervous-system syphilis.”

In 1977 Robert Morton, writing about population movement and rising gonorrhoea rates in Sheffield, England, explained that immigration “has been a feature of the European scene for more than 20 years. Multiracialism is becoming an established fact, particularly in France, Holland, and the United Kingdom.” He went on to describe the conditions of immigrants to England from the West Indies, Pakistan, and Aden. Morton noted objective findings where race played no role in disease, but other factors did. He cited a 1970 study by Oller and Wood of the incidence of gonorrhoea from 1959 to 1968 in Bradford, an industrial city in England. It was found that of 5000 infected men, 80% were immigrants.

In 1976 Verkeij, studying gonorrhoea in Rotterdam, found the disease 6.7 times more common in immigrants than in Dutch men (and that the great majority of the immigrants had been infected by indigenous Dutch women). The reason for the high incidence...
had nothing to do with “race.” Rather, the young males who were most likely to immigrate to Europe did so without their families.

**TIPS FOR CLINICIANS AND HEALTH WORKERS**

The care of STDs is always delicate. However much braggadocio young adults, especially men, may show when seeking help for STDs, they are likely to be fearful and seeking compassion. This is even more so for those of cultural backgrounds where the concept of confidentiality in the medical care of STDs may be little understood.

A calm and welcome atmosphere should be provided by the treatment clinic as well as the clinician. Staff may need to be multilingual. They must become familiar with specific community customs and sexual mores.

Among the situations that need to be considered: refugees from chaotic parts of the world may have endured torture, rape, or other extremely traumatic events; young people from intolerant religious backgrounds may be terrified of encountering acquaintances at the clinic; patients from conservative societies may hesitate to admit sexual activity, even to themselves.

The young men from ethnic minorities who come for help for STDs after having sex with men (MSM), may need especially sympathetic care. In some societies, such as Latin America, the Caribbean, and much of the Islamic world, special opprobrium is heaped on the passive male. Participants in MSM may be reluctant to identify as homosexual, and may also have female contacts who will need to be examined and treated.

Women from some ethnic groups have little understanding of their own sexual rights in a liberal Western society. Havens of safety and confidentiality need to be made for them. It is difficult for any woman to give a true sexual history if a male or even a female relative or friend is accompanying her. Privacy must be assured.

With the growth of the international sex trade, the clinician should be on guard for women who have been forced into prostitution. Health professionals must be able to refer persecuted women to social agencies that can aid them immediately.

**CLINICAL DIFFERENCES IN “ETHNIC” SKINS**

There are several easily obtainable atlases of STDs in black skin. However, many of these are based on studies in Africa. Medical practice differs in Europe and North America, where physicians are more accessible, and conditions are generally less advanced before medical care is sought.

Generally, if an STD is primarily an infection of mucous surfaces, such as gonorrhea, chlamydial infection, trichomoniasis, or bacterial vaginosis, there is no difference in presentation, whatever the patient’s skin color. However, STDs that affect the skin: syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, herpes genitalis, condylomata acuminata, molluscum contagiosum, scabies, pediculosis pubis, and human immuno-deficiency virus (HIV) skin disease, may present some unique features. These may be overlooked if the examining physician is not well trained, makes a cursory examination, or is prejudiced.

A careful, full-skin examination is essential; it may alert the clinician to the secondary rash of syphilis, other dermatoses, or scabies. There may be useful clues in tattoos, tribal scars, piercings, and needle marks.

A Darkfield examination for Treponema Pallidum from the penis or vulva may make the diagnosis. However, if the patient has already taken antibiotics or used an antiseptic the test will be useless.

A Darkfield examination from the buccal cavity is not productive, as it may show commensal spirochetes. It should be remembered that serologic tests for syphilis, fluorescent treponemal antibody-absorption or rapid plasma reagin, may not be positive before 2 weeks.

**SECONDARY SYPHILIS**

As a general rule, the more pigmented the patient’s skin, the deeper the color of the lesions. But secondary syphilis may not always be classical and may only be present for a short time. Again, examining the patient fully, in good light is paramount.

Whatever its texture, the hair of the scalp and eyebrows must be examined for alopecia.

It has been said that condyloma lata may be more gross in humid climates or where hygiene/washing facilities are poor. The rash may not always look like a textbook example. Palmar and plantar syphilides may not be obvious in a dark skinned patient.

Skin biopsy should only be done as a last resort in dark-skinned patients because of the danger of subsequent keloid formation.

Nowadays in the West, tertiary or late congenital syphilis is very rarely seen, but it may be present in immigrants from third-world countries.

**CHANCROID**

Haemophilus Ducreyi cases are still seen in those who have recently travelled from Africa or the Indian subcontinent.

**DONOVANOSIS OR GRANULOMA INGUINALE (KLEBSIELLA GRANULOMATIS)**

Donovanosis or Granuloma Inguinale (Klebsiella Granulomatis) is another condition that is rare in Western practice, but occasionally seen in patients from the tropics, particularly the Indian subcontinent. The lesion begins as a small erosion or ulcer that expands on the surface of the penis to become larger with local spread. It often becomes secondarily infected and malodorous.
There is no inguinal gland enlargement. Diagnosis is made by biopsy from the edge of the lesion using Giemsa stain and finding Donovan bodies.

**Lymphogranuloma Venereum—L1, L2, L3 Serovars of Chlamydia Trachomatis**

Until recently this had been a rare disease in the West, mostly diagnosed in travellers returning from Asia, Africa, South America, or the Caribbean. Immigrants from these parts of the world have increased its incidence in the West. Initially there is a small transient ulcer at the point of inoculation, followed by firm, swollen, and painful regional lymph nodes, with fever and malaise. Late stage disease shows results of lymphatic damage, and includes scarring and fistulae.

**Herpes Genitalis**

Because herpes simplex infection is often dismissed as nothing more than an inconvenient minor sore or irritation on the lips, penis, vulva/vagina, or anal canal, both male and female patients from less-educated, impoverished groups may hesitate to bring it to a physician’s attention.

**Genital Warts—Condylomata Acuminata—Human Papilloma Virus**

Low risk, rarely associated with invasive cervical cancers—6, 11 and some later HPV genotypes.

High risk types, oncogenic—16, 18 and some later genotypes. These are caused through direct sexual contact and are occasionally transmitted from mother to child during childbirth. They warrant close attention in patients from countries where HIV is widespread among women. Lesions may become quite large and often pigmented in black patients.

Molluscum contagiosum, a pox virus, is not uncommon in ethnic minority patients. There are two main groups. The first appears in the pubic region of men who, for religious reasons, shave their pubic hair. The virus settles in small cuts, resulting in small dome-shaped papules with umbilicated centers, often in groups of lesions. They are frequently mixed with genital warts, both becoming pigmented. Lesions occur on the shaft of the penis and on the scrotum. The second manifestation is a sign of HIV disease, often in nongenital areas such as the eyelids, face, chest, loins, or arms. These may be very widespread. It is a frequent sign of HIV disease in sub-Saharan Africans.

**Scabies—Mite Sarcoptes Scabiei**

In young, adult men it often presents not only as itching, causing burrows in classical distribution, but also on the penis, scrotum, and buttocks. In impoverished groups living in cramped and poor housing it may spread to other inhabitants. Public health services may need to be enlisted in its eradication.

**Pediculosis Pubis—Crab Lice**

Crab lice may be difficult to see in black patients. On the other hand, in hirsute ethnic groups, such as Arabs, Turks, Persians, Afghans, and northern Indians, they may be widespread, occurring on the body, axilla, back, moustache, and eyelash hair. They are not to be confused with body lice.

**HIV Infection**

There are numerous skin and genital situations that should make the observer consider HIV infection, including herpes zoster, severe and chronic seborrhoic eczema, molluscum contagiosum, papular pruritic eruption, severe herpes simplex, severe human papilloma infection, scabies, and severe drug eruptions. In evaluating risk factors for HIV, one should be especially sensitive to cultural sensitivities.

**REFERENCES**

A 25-year-old African woman presented with a 7-month history of extensive ulceration of the skin and destruction of the nose.

Examination revealed generalized necrotic ulcers involving the scalp and body, destruction and collapse of the nasal bridge, associated with auto amputation of the finger. Investigations revealed the patient to be positive for human immunodeficiency virus with a CD4 count of 50/mm³.

Skin biopsy and culture confirmed disseminated cutaneous histoplasmosis caused by histoplasma capsulatum. Bone marrow aspirate confirmed bone involvement. Chest x-ray was normal.

The patient was officially diagnosed with disseminated cutaneous histoplasmosis with systemic involvement of the bones.
CASE STUDY

Pruritic, Papular Eruption, and Concomitant Neurologic Symptoms: Churg-Strauss Syndrome Presenting With Mononeuritis Multiplex

Jyoti Pathria, BA; James Collyer, MD; Stephanie Mehlis, MD; Joaquin Brieva, MD

A 38-year-old man with a medical history of sinusitis, nasal polyps, and asthma presented with a 2-week history of progressive sensory and motor loss in his right hand and foot. Dermatology was consulted to evaluate mildly pruritic lesions on the elbows and dorsal right hand that had been recurring for the past year. Since the initial outbreak, the patient had 6 flares of this eruption. Self-medication with oral prednisone for a few weeks resulted in near-complete resolution of the eruption. The lesions are rarely painful and only mildly tender.

On examination of the elbows and right hand, the patient had scattered, 1- to 2-mm erythematous, firm, nontender papules, some with overlying crust (Figure 1). No purpura or exudates were noted. Laboratory results revealed a perinuclear antineutrophilic cytoplasmic autoantibody (p-ANCA) of 1:320, peripheral eosinophils of 32%, and elevated serum IgE, D-dimer, erythrocyte sedimentation rate, and rheumatoid factor. Antinuclear antibody, classic ANCA (c-ANCA), hepatitis serologies, echocardiography, and cryoglobulin results were unremarkable. An electromyogram showed a demyelinating process. A biopsy of a papule on the right elbow (Figure 2 and Figure 3) revealed a serohemorrhagic crust and a dense dermal infiltrate on low power. Higher-power examination revealed inflammation of the blood vessels with hyalinization of the walls and histiocytes around degenerated collagen. The perivascular spaces showed an infiltrate composed of histiocytes including occasional multinucleated giant cells, numerous neutrophils with karyorrhexis, and many eosinophils. Gram stain results were negative. A diagnosis of Churg-Strauss syndrome presenting with mononeuritis multiplex was made.

The patient received intravenous pulse methylprednisolone 1 g for 3 days and was then discharged on oral prednisone 100 mg daily. The prednisone was tapered within 4 months, and he was switched to azathioprine 100 mg daily. He was also given 12 weekly doses of intravenous immunoglobulin (IVIG). He continues to feel better, with increased strength to his right foot and decreased paresthesias of the right lower extremity and bilateral upper extremities; however, he is not yet able to walk without residual foot drop.

DISCUSSION

In 1951, Churg and Strauss established the precise pathological entity of this disease. It is a rare multisystem vasculitis that is characterized by asthma, eosinophilia, and necrotizing vasculitis with extravascular granulomas. It typically occurs in the third and fourth decades of life.

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Characteristic cutaneous lesions occur in 50% to 60% of patients. These lesions consist of petechiae, purpura, and painful dermal and subcutaneous nodules.

Tissue biopsy specimens reveal an eosinophil-rich inflammatory infiltrate with granuloma formation in connective tissue and blood vessel walls. Necrotizing vasculitis with fibrinoid changes arises in small to medium vessels.¹

p-ANCA is present in the serum of approximately 70% of patients, whereas c-ANCA is found in only 7% of patients who are ANCA-positive. ANCA positivity may be positively associated with other organ system manifestations including purpura and mononeuritis multiplex.²

Criteria for the classification of Churg-Strauss syndrome were developed by comparing 20 patients who had the diagnosis with 787 control patients with other forms of vasculitis. For the traditional format classification, 6 criteria were selected: asthma, eosinophilia >10%, paranasal sinusitis, nonfixed pulmonary infiltrates, histological proof of vasculitis, and mononeuropathy (including multiplex) or polyneuropathy. If a patient met 4 of these 6 criteria, this traditional format classification had a sensitivity of 85% and a specificity of 99.7% for the diagnosis of Churg-Strauss syndrome.³ Our patient fulfilled 5 of the 6 criteria.

Peripheral neuropathy is common in patients with Churg-Strauss syndrome, with mononeuritis multiplex being the most frequent finding. Peripheral neuropathy is a well-recognized consequence of systemic vasculitis due to peripheral nerve infarction with Wallerian degeneration.⁴ If mononeuritis multiplex is seen in a patient with asthma and eosinophilia, the diagnosis of Churg-Strauss syndrome is almost certain.⁵

For vasculitic neuropathy, a long-term regimen of high-dose prednisone combined with intravenous pulse or oral cyclophosphamide is the standard initial therapy. Other immunosuppressants, such as azathioprine, methotrexate, or IVIG may be helpful if the patient has a contraindication to cyclophosphamide or is intolerant to it.⁴

REFERENCES

CASE STUDY

Pleomorphic Fibroma of the Skin

Philip R. Cohen, MD;1–3 Keith E. Schulze, MD;2,4 Scott A. Cohen, MD;5 Paul T. Martinelli, MD;2,6 Bruce R. Nelson, MD2

A 71-year-old white woman presented with a painless mass at the base of her right great toe of 8 months’ duration. She has chronic myelogenous leukemia, medication-controlled hypertension and hypothyroidism, and mitral valve prolapse. Her leukemia is in partial remission; it was diagnosed 8 years ago, and she underwent a stem cell transplant 3 years ago. Clinical evaluation revealed a firm, nontender, flesh-colored 1.5×1.0-cm well-circumscribed dermal nodule with a peripheral collarette of scale on the plantar base of her right great toe (Figure 1). A tangential excision was performed. Microscopic examination demonstrates compact orthokeratosis and a collarette of epithelium overlying a dermal tumor (Figure 2). The lateral portion of the neoplasm, beneath the collarette, shows an increased number of small telangiectatic vessels in the upper dermis. Within the fibrous dermis there is a hypocellular tumor predominantly consisting of cells with spindle-shaped nuclei. Some of the tumor cells are either large and multinucleated with nuclear atypia or mononuclear with pleomorphic nuclei (Figure 3). The pleomorphic tumor cells did not stain with antibody to CD34. The diagnosis of pleomorphic fibroma of the skin was established based on the correlation of the clinical findings and the pathologic changes. The postoperative defect was allowed to heal by granulation.

Pleomorphic fibroma of the skin is a benign fibrous tumor initially described by researchers in 1989.1 The dermal tumor is usually solitary, dome-shaped or polypoid, and is typically located either on the extremities or trunk.1–3 Less common, it may occur on the head.1,4 The peripheral collarette of scale and the plantar site of our patient’s tumor raised the clinical possibility of an eccrine poroma.

Microscopic examination of pleomorphic fibroma of the skin reveals a dermal tumor with sparse cellularity but striking nuclear atypia. The neoplastic cells typically have large pleomorphic and hyperchromatic nuclei with small nucleoli. In addition to these mononuclear cells, the atypical nuclear features can often also be observed in many of the multinucleated giant cells that are present.1,2,5

Immunoperoxidase staining of the atypical cells in pleomorphic fibroma of the skin is always positive for vimentin and negative for S-100 and cytokeratin. Inconsistent expression of muscle-specific actin (or smooth muscle actin), factor XIIIa, and CD34 by the pleomorphic tumor cells has also been observed.1–9

Some pleomorphic fibromas of the skin also have features of sclerotic fibromas.10 Indeed, some investigators have postulated that the pleomorphic fibroma of the skin is actually a variant of the sclerotic fibroma.1,6 Alternatively, other researchers have classified some of these tumors as pleomorphic sclerotic fibromas.6 Neither pleomorphic fibromas nor sclerotic fibromas have been associated with hematopoietic dysplasias.11 Other benign fibrous connective tissue tumors, however, such as multiple dermatofibromas, have been reported in patients with either chronic myelogenous leukemia12 or acute myelogenous leukemia.13 The hypothesized pathogenesis for the eruptive onset and proliferation of dermatofibromas in these oncology patients (malignancy-induced and/or antineoplastic therapy–associated alteration of their immune status) may be similar to the postulated etiology of multiple dermatofibromas that have previously been described in individuals receiving immunosuppressive therapy and/or with an acquired immunodeficiency or an autoimmune disorder or both.14,15

The prominent pleomorphic cells and nuclear atypia observed in pleomorphic fibromas may initially suggest a malignant dermal neoplasm, such as atypical fibroxanthoma, fibrosarcoma, and malignant fibrohistiocytoma or benign dermal tumors such as angiofibroma, desmoplastic or hyalinizing Spitz nevus, fibrous papule of the face, giant cell fibroblastoma, neurofibromas with atypia, and schwannomas with ancient changes.1,2,5,16 The pathologic differential diagnosis of pleomorphic fibromas of the skin also includes dermatofibromas with atypical or monster cells.17,18 In contrast to pleomorphic fibromas of the skin, however, dermatofibromas with atypical or monster cells: (1) are frequently more cellular, (2) often have areas indistinguishable from typical dermatofibromas, and (3) may have an overlying epidermis that is acanthotic and hyperpigmented.1,2,6

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Pleomorphic fibroma of the skin does not have a distinctive and pathognomonic clinical presentation; therefore, a biopsy of the new or persistent dermal nodule is required to establish the diagnosis of this tumor. The clinical behavior of this skin neoplasm is benign; recurrence is uncommon, even in tumors that have been incompletely removed. Partial or complete excision of a biopsy-confirmed pleomorphic fibroma of the skin, therefore, is an appropriate and conservative surgical approach to the management of the tumor.1,4

CONCLUSIONS

Pleomorphic fibroma of the skin is a benign nodular neoplasm with a fibrous stroma consisting of mononuclear and multinuclear cells with atypical nuclear features. The occurrence of a plantar pleomorphic fibroma of the skin with a surrounding epidermal collarette prompts us to recommend that pleomorphic fibroma of the skin be added to the clinical differential diagnosis of nodules, such as eccrine poromas, pyogenic granulomas, and keratoacanthomas, that can present morphologically with a peripheral collarette of scale. Conservative treatment of a pleomorphic fibroma of the skin is appropriate once a biopsy-confirmed diagnosis of the tumor has been established.

REFERENCES

Figure 3. The atypical tumor cells (A and B) of a pleomorphic fibroma of the skin: mononuclear cells with large pleomorphic nuclei and large multinucleated cells with nuclear atypia (hematoxylin-eosin: A, original magnification ×40; B, original magnification ×40).

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

Annular Elastolytic Giant Cell Granuloma

Dipankar De, MD;¹ Tarun Narang, MD;¹ Sunil Dogra, MD;¹ Uma Nahar Saikia, MD;² Amrinder J. Kanwar, MD¹

A 55-year-old woman presented with a minimally itchy, gradually progressive erythematous plaque of 2 months’ duration over the extensor aspect of her left forearm. There was no history of trauma or any scar at the local site before its onset. She did not have photosensitivity and denied similar eruptions in the past. She was known to have rheumatoid arthritis and type 2 diabetes mellitus. She has been taking metformin for diabetes mellitus; however, she was not taking any disease-modifying antirheumatic drugs. She complained of exertional dyspnea, which was later correlated with interstitial lung disease due to rheumatoid arthritis.

On cutaneous examination, there was a single, well-defined erythematous to violaceous infiltrated plaque with an elevated border measuring about 10 × 10 cm localized over the extensor aspect of the left forearm (Figure 1). Atrophic scarring was appreciated at places in the center of the lesion. Diascopy was noncontributory. There was no regional nerve trunk thickening or sensory impairment in the lesion. No other abnormality was detected on mucocutaneous examination.

In the workup to diagnosis, erythrocyte sedimentation rate was 42 mm after the first hour. Otherwise, the complete blood cell counts and liver and renal function tests were within normal limits. Rheumatoid factor was strongly positive, C-reactive protein was positive, and antinuclear antibody was mildly positive with a speckled pattern. Mantoux test result was equivocal. Skiagram of the chest revealed evidence of fibrosis.

A punch biopsy was taken for histopathology study from the margin of the lesion, which showed a thinned epidermis with loss of rete ridges (Figure 2 and Figure 3). The dermis showed palisading histiocytes surrounding mucinous material and degenerated collagen and elastin. Many multinucleated giant cells were also seen. Elastic van Gieson stain revealed giant cells engulfing degenerated elastin (Figure 4). Thereby, the diagnosis of annular elastolytic giant cell granuloma (AEGCG) was reached.

DISCUSSION

AEGCG is a rare granulomatous skin disease characterized by loss of elastic fibers due to elastophagocytosis of degenerated elastic fibers by multinucleated giant cells. In 1979, Hanke and associates¹ first recognized AEGCG as a distinct granulomatous skin disease. Prior to this, diseases of similar character were termed O’Brien’s actinic granuloma, atypical annular necrobiosis lipoidica, Miescher’s granuloma of the face, and granuloma multiforme, thus raising the speculation that they represent the same entity or different clinical expressions in the spectrum of elastolytic disorders.¹ O’Brien² initially described the condition in 1975 as:

Ring-shaped inflammatory lesions [that] sometimes develop in the abnormal ‘elastotic’ connective tissues of skin damaged by sun and heat. The lesions, which commence as papules and nodules, enlarge very slowly and may persist for years. Microscopical sections show that there is an infiltrate composed mainly of foreign-body giant cells, the cells being engaged in digesting and absorbing the abnormal elastotic fibers. The disorder, which occurs on several continents, should probably be regarded as a phenomenon of repair within damaged connective tissue.

Some believe that AEGCG and granuloma annulare may be related. Ragaz and Ackerman³ questioned the specificity of actinic granuloma as a specific connective tissue disorder, as was suggested by Ackerman. They presented the evidence that granulomatous inflammation does not result as a response to degenerated elastic fibers, but is a consequence of primary pathologic processes that are unrelated to damaged elastic material. They speculated that actinic granuloma and granuloma annulare are clinically and histologically similar.

The clinical picture is variable, with lesions varying in size, number, and shape. Lesions of AEGCG are localized primarily on sun-exposed areas, including the forearms, neck, upper back, and face, and are less common in covered areas.³ AEGCG is characterized by annular patches with erythematous borders...
and hypopigmented centers showing atrophy. It is common in middle-aged white women. AEGCG usually affects older adults, although it has been described in an infant aged 8 months. The systemic involvement is rare, although ocular, intestinal, and lymph node involvement has been reported in a single patient.

Why elastolysis and elastophagocytosis occur in AEGCG is a matter of conjecture. In granuloma annulare, the closest clinical mimicker of AEGCG, Th1 lymphocytes activate macrophages expressing tumor necrosis factor α and matrix metalloproteinases 2 and 9, which are capable of degradation of both collagen and elastic fibers. It can be speculated that in AEGCG the macrophages differentially degrade only elastic fibers. The capacity for elastolysis and elastophagocytosis may depend on differentiation status of macrophages. A patient with AEGCG has been reported in whom the lesions did not involve burn scars, thus suggesting that immune reaction might be specifically directed against or induced by intact elastic tissue. Other factors that have been hypothesized to cause AEGCG include UV radiation, heat, or other unknown factors that can change the antigenicity of elastic fibers and thus trigger a cellular immune response directed toward them. Moreover, diabetes mellitus–producing structural damage of the elastic tissue may incite the immune reaction.

AEGCG has been reported in association with systemic sarcoidosis, cutaneous amyloidosis, molluscum contagiosum, chronic hepatitis C, squamous cell carcinoma of the lung, and cutaneous T-cell lymphoma.

The dermatoses that can clinically as well as histopathologically mimic AEGCG include actinic granuloma, granuloma annulare, necrobiosis lipoidica, sarcoidosis, annular lichen planus, subacute lupus erythematosus, and type-2 inflammatory middermal elastolysis; the first two entities being the closest mimicker. The distinctive zone of elastophagocytosis, abundance and distribution of the giant cells, absence of collagen necrobiosis, and mucin deposition help to differentiate this entity from granuloma annulare.

The course of the disease is chronic. Rare spontaneous remission has also been reported. Different options have been tried in the treatment of AEGCG, although none are uniformly effective. These include excision of the solitary lesion, cryotherapy, cautery, intralesional or systemic corticosteroids, psoralen–UV-A (PUVA), RePUVA (oral retinoids + PUVA), cyclosporine, tranilast, dapsone, clofazimine, chloroquine, methotrexate, topical pimecrolimus, or a combination of these. In a review by Breuer and colleagues, remission was achieved in 1 of 3 patients.
treated with fumaric acid esters. Our patient was initially given colchicine for 1 month and subsequently hydroxychloroquine sulfate for 2 months without success.

REFERENCES


CASE STUDY

Chancriform Pyoderma: A Forgotten Disease

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CASE 1:
A 34-year-old male office worker first observed the appearance of a papular lesion on the right upper eyelid, which subsequently ulcerated (Figure 1). The ulcer, 5 × 10 mm in size, was well defined with an indurated base and a central eschar that was easily removed to reveal serous discharge. The edge of the ulcer was smooth and raised with minimal erythema and edema. No regional lymphadenopathy was detected. The patient had no previous history of any skin condition or serious illness. His physical status was normal, and so was standard blood and urine biochemistry. Bacteriologic examination was positive for *Staphylococcus aureus*. The mycologic examination was negative, as well as treponemal and human immunodeficiency virus (HIV) serology. Leishman-Donovan bodies were not demonstrated in smears taken from the ulcer and stained with Giemsa. The patient declined biopsy. He was treated with oral cloxacillin for 14 days, oral cephalexin, and mupirocine ointment for 10 days, with no therapeutic results. Treatment with 0.9% sodium chloride dressings and gentamycin-betamethasone ointment led to rapid improvement. The lesion healed with minimal scar.

CASE 2:
A 66-year-old male retiree presented with a 5-month history of an ulcer, 15 × 20 mm in size, on his left hand. The ulcer was indurated and covered with tawny eschar (Figure 2). No regional lymphadenopathy was detected. The patient was generally healthy, reporting only a gastric ulcer operation at age 53, and a colon polyp at age 65. Routine blood and urine biochemistry were normal. Lesion cultures were negative for fungi and positive for *S. aureus*. Syphilis and HIV serology were negative, as well as direct examination for Leishman-Donovan bodies. Histopathology showed acanthosis and numerous polymorphonuclear infiltrations around the blood vessels in the upper dermis. The patient was treated with oral clindamycin for 14 days and local antiseptic dressings, with no therapeutic results. Treatment with hydrocolloid dressings triggered ulcer epithelialization.

CONCLUSIONS

The diagnosis of chancriform pyoderma is based on detailed disease history, clinical picture, and negative laboratory findings for

Figure 1. The ulcer on the right upper eyelid.
all microbial agents except \textit{S. aureus}. Exclusion of other dermatoses that present with an ulcer, using direct examination, cultures, serology, and histopathology is of greatest importance.

\textbf{REFERENCES}


\begin{table}
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\hline
\textbf{DISEASE} & \textbf{CLINICAL PRESENTATION} \\
\hline
Primary lues & Macule/papule/ulcer \\
Chancroid & Papule/pustule/erosion/ulcer \\
Donovanosis & Papule/nodule/ulcer \\
Lymphogranuloma venereum & Papule/erosion/ulcer \\
Human orf & Papule/vesicle/nodule/ulcer \\
Milker’s nodule & Papule/vesicle/nodule/ulcer \\
Primary inoculation tuberculosis & Papule/nodule/ulcer \\
Swimming pool granuloma & Papule/nodule/plaque/ulcer \\
Ecthyma & Pustule/ulcer \\
Cat scratch disease & Papule/pustule/ulcer \\
Tularemia & Papule/pustule/ulcer \\
Rickettsialpox & Papule/ulcer \\
Sporotrichosis & Papule/pustule/nodule/ulcer \\
Blastomycosis & Plaque/ulcer \\
Cutaneous leishmaniasis & Papule/nodule/ulcer \\
Delusion of parasitoses & Erosion/ulcer \\
Dermatitis artefacta & Erosion/ulcer \\
Pyoderma gangrenosum & Pustule/nodule/ulcer \\
Basal cell carcinoma—ulcer type & Ulcer \\
Squamous cell carcinoma—ulcer type & Ulcer \\
Lymphomatoid papulosis & Papule/nodule/ulcer \\
Behçet disease & Ulcer \\
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\caption{Differential Diagnosis of Chancriform Pyoderma}
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CASE STUDY

Pemphigoid Gestationis: Cutaneous Manifestation of Impaired Fetal Allograft Tolerance

Anthony A. Nuara, MD, PhD; Joseph M. Obadiah, MD; Maria Yadira Hurley, MD

A 31-year-old prima gravida woman (32 weeks estimated gestational age) was referred by her obstetrician to rule out infection with varicella zoster virus. She presented with a several week history of multiple pruritic papules that began on her left thigh and were now present across her body. She had a positive childhood history of primary varicella zoster virus infection. On examination, there were multiple papules and plaques on the abdomen in a periumbilical distribution (Figure 1A), as well as on the lower extremities and mid-back. There were also small bullae on the medial and dorsal feet (Figure 1B). No mucosal lesions were observed. Punch biopsy of lesional skin demonstrated areas of focal parakeratosis, focal spongiosis, and a superficial lymphohistiocytic infiltrate with scattered eosinophils (Figure 2A). Direct immunofluorescence examination of nonlesional skin demonstrated linear deposition of C3 along the basement membrane (Figure 2B). Immunoglobulin stains were negative. These findings were consistent with the urticarial phase of pemphigoid gestationis. The patient was treated with oral prednisone (40 mg/d), diphenhydramine (50 mg every 6 hours as needed), and triamcinolone 0.1% cream topical to the body. There was improvement of her pruritus, but she experienced multiple flares when the prednisone was tapered. The fetus was delivered without complication and the patient's disease resolved approximately 4 weeks after delivery, followed by a successful prednisone taper over 5 weeks.

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Pemphigoid gestationis (PG) is a rare autoimmune bullous dermatosis. It is exclusively a disorder of pregnancy and the puerperium. The reported incidence of this condition is variable, but studies with immunofluorescence place the estimates at around 1:50,000 pregnancies. PG is predominantly a disease of white women and tends to present in the later stages of pregnancy, but may occur during the first trimester or postpartum. PG can initially manifest in prima- or multiparous women, although the disease almost invariably recurs in subsequent pregnancies and is usually earlier and more severe. The lesions are typically polymorphous consisting of pruritic papules and plaques, which may evolve into vesicles and bullae. PG was previously known as herpes gestationis because of the tendency of the lesions to start periumbilically and "creep" centripetally. Lesions tend to be confined to the body and rarely occur on the face or mucous membranes. The condition is also characterized by intense pruritus which may precede cutaneous eruption by days to weeks. Rarely, PG can develop into a protracted illness or evolve into bullous pemphigoid (BP). The sera of patients with PG contains complement fixing immunoglobulin G (IgG) antibody directed against a placental antigen, which cross reacts with an antigen in the skin basement membrane. The target antigen is the same as in BP, although the severity of their clinical presentation varies considerably. Anti-bodies in both diseases recognize determinants on the BP 180-kd antigen (BP180), a transmembrane glycoprotein integral in adhesion of basal cells to the basement membrane. The antigenic NC16A region of BP180 is in the extracellular domain which passes through the hemidesmosome and aids in attachment of the basal cell layer to the basement membrane. Deposition of anti-BP180 antibody along the hemidesmosomes in the basement membrane results in C3 fixation, activation of the classical complement cascade, and recruitment of leukocytes to the area. Destruction of the basal keratinocyte hemidesmosomes results in the formation of a subepidermal blister (Figure 2C). Animal models wherein antibodies to the BP180 antigen of mice and hamsters were passively transferred resulted in bullous disease further supporting the role of anti-BP180 in the pathogenesis of these dermatoses. The detection of anti-BP180 IgG along the amniotic and chorionic basement membrane support the notion that PG represents a cross reactivity between epidermal and placental antigens.

The histological findings of PG are dependent upon the stage of the lesion biopsied. Early papular lesions demonstrate a perivascular infiltrate comprised of lymphocytes, histiocytes, and eosinophils. This infiltrate is often accompanied by edema of the papillary dermis and spongiosis within the epidermis. Bullous lesions show a subepidermal blister with eosinophils. Direct immunofluorescence
studies of lesional and nonlesional skin shows a linear deposition of C3 and, less consistently, IgG along the epidermal basement membrane. Indirect immunofluorescence using monoclonal antibodies to IgG1 show anti-BP180 antibodies present in all cases of PG.2,4

Although topical steroids and antihistamines offer relief in mild cases, the mainstay of PG treatment is systemic corticosteroids (prednisone 0.5–1mg/kg/d).2 Refractory cases, or those progressing to BP, require more aggressive management including chemotherapeutic compounds like cyclophosphamide, methotrexate, and cyclosporine.8,9 Plasmapheresis or high dose intravenous immunoglobulin have been reported successful in some patients recalcitrant to systemic corticosteroids.10–12

Early case reports indicated an increase in morbidity and mortality in fetuses of affected mothers, although there are conflicting reports on the actual risk to the developing fetus.1,3 It is generally accepted, however, that risk to the fetus is low and may be comprised of signs of placental insufficiency such as low birth weight and infants who are small for gestational age. Placental insufficiency requiring delivery of the fetus has been reported and the authors recommended monitoring of end-diastolic umbilical artery velocity to assess placental function in patients with PG.13 PG associated autoantibodies have been detected in the cord blood of infants born to affected mothers and may result in transient erythema and blistering in up to 10% of infants born to affected mothers, resolving within a few weeks.12,4 Additionally, infants born to mothers treated with systemic glucocorticoids should be appropriately monitored and managed by a neonatologist.14

The differential diagnosis of PG includes many other dermatoses of pregnancy; however, PG is most often confused clinically with pruritic urticarial papules and plaques of pregnancy (PUPPP). Early lesions of PG closely resemble and must be distinguished from PUPPP. Both tend to occur in the second and third trimesters of the pregnancy; however, PUPPP shows a stronger predilection for prima gravida patients whereas PG may first appear in later pregnancies. Additionally, PG tends to develop periumbilically whereas PUPPP tends to develop within the abdominal striae. Both lesions are intensely pruritic and may progress from papules to vesicles or bullae, making clinical distinction difficult. Biopsy for fixed tissue and for direct immunofluorescence is key for diagnosis.1,3,4 Additionally, enzyme linked immunosorbent assays and protein immunoelectrophoresis using BP180 as a capture reagent, originally developed for evaluation of BP, have been used to diagnose and follow patients with PG.5

An intricate immune regulation system exists to prevent maternal rejection of the invading fetal allograft. Several studies have suggested a role for controlling this response by regulatory T cells (CD4+CD25+), Th3 cells (transforming growth factor-β), regulatory natural killer cells, as well as the expression of soluble local mediators such as macrophage migration inhibitory factor and local degradation of tryptophan by indolamine 2,3-deoxygenase.15,16 While the exact nature of fetal allograft tolerance is not completely understood, it is likely that PG represents a loss of tolerance to both fetal and self antigens during pregnancy. The autoantibodies in PG appear to be related to, or driven by, an antigenic stimulus that is unique to pregnancy. Although PG is a rare complication of trophoblastic tumors, it has not been reported in nongestational hormone producing malignancies, pointing to an essential gestational component.1,9 A major event in the development of PG is thought to be expression of major histocompatibility complex (MHC) class II molecules, particularly paternal alleles, by the placenta and recognition by the maternal immune system. The connection between these anti-HLA antibodies and the development of antiplacental basement membrane antibodies is poorly understood. Antibodies that are actually directed against the paternal MHC molecules are thought to be a parallel phenomenon, as they are present in many multiparous women without PG.1 Interestingly, PG may skip a pregnancy if there is a change in paternity or maternal fetal match at the HLA-D locus, supporting a role for paternal antigens in the pathophysiology of the disease.9 Like many other humoral autoimmune conditions, there is an increased incidence of the class II MHC alleles HLA-DR3 and HLA-DR4 in PG affected individuals (54%) as compared to the general population (3%).1 It seems then, that patients who develop PG may be genetically predisposed to such autoimmune conditions.

Although a rare complication of gestation, PG represents an interesting manifestation of maternal fetal allograft intolerance. The mechanisms responsible for maternal tolerance of invading alloimmune cells are complex and remain poorly understood. Even more remarkable is that these boundaries of immune tolerance do not fail more often. Indeed, PG represents a case wherein the maternal immune system fails to ignore antigens within the placenta. Of interest is that the predicted offending antigens, paternal MHC
class II, are not the target antigen in this disease process and antibodies to these molecules can be detected in multiparous women without PG. The coexistence of an anti-HLA reaction may only be an indicator of further derangement in the delicate immune environment of the placenta and not necessarily directly associated with PG or its clinical manifestations.

REFERENCES


Figure 2. (A) Patient histology showing areas of focal parakeratosis, spongiosis, and a superficial lymphohistiocytic infiltrate with scattered eosinophils. (B) Direct immunofluorescence examination of nonlesional skin demonstrated linear deposition of C3 along the basement membrane. (C) Late stage lesion demonstrating subepidermal blistering with eosinophilic infiltrate.
CASE STUDY

Eruptive Syringoma Associated With Hyperthyroidism

Muhterem Polat, MD;1 Aylin Pelitli, MD;3 Pınar Öztas, MD;1 Tuba Unal, MD;2 Nuran Alli, MD1

A 45-year-old woman presented with a 9-year history of eruptions that began as a few papules on the trunk and gradually spread to the whole trunk and face. The lesions were asymptomatic, and since they first appeared, the patient's skin had never been completely clear. The patient's notable past medical history was hyperthyroidism. She had been on oral antithyroid drug therapy (50 mg/d propylthiouracil) for 10 years. In her previous history, the patient was euthyroid at the onset of the syringoma lesions. No family member had ever had a similar skin condition, and a review of other systems was noncontributory. Physical examination revealed multiple skin-colored or reddish brown flat-topped papules 1–3 mm in diameter on the trunk, periorbital region, malar areas and forehead (Figure 1A, Figure 1B). The remainder of the physical examination was unremarkable.

A punch biopsy specimen from the trunk revealed cystic ducts lined with a double row of epithelium in the dermis (Figure 1C). A complete blood count and serum biochemistry were within normal ranges.

DISCUSSION

Syringoma is a benign tumor derived from the intraepidermal portion of the eccrine duct.

Clinical presentation of syringoma is variable. The lesion may be solitary or multiple. The distribution may be localized, multifocal, or generalized. They may also appear in eruptive manners. Classically, syringomas occur in women at puberty or later in life.1–3 The most frequent clinical variant is location on the infraocular areas in healthy people, but other clinical variants have been reported, as well as familial cases or an association with Down syndrome.4–7

Generalized eruptive syringoma is a rare variety, characterized by multiple lesions that arise in successive crops on the anterior body surfaces, generally in prepubertal or adolescent individuals.8

Our patient's lesions began when she was 36 years old. The higher incidence of syringomas in women and the frequent development of the lesions before or around puberty, as well as occasional exacerbation of the lesions during pregnancy, may imply a hormonal role in some cases.9 A strong expression of progesterone receptors by immunohistochemistry was noted in 2 studies.10,11 Syringoma is also seen with diabetes.12 Aliagaoglu and colleagues13 reported the first case of unilateral syringoma of the face associated with hyperthyroidism. Our patient’s lesions were of an eruptive manner that began 1 year after the diagnosis of hyperthyroidism. More cases on this association should be reported—despite the suggested hormonal interactions in the development of syringomas—before speculating whether hyperthyroidism and syringoma coincidentally occur or hyperthyroidism may have a role in the pathogenesis of syringoma. Although 2 cases of syringoma associated with hyperthyroidism is very limited to propose a hypothesis that hyperthyroidism may have a role in the pathogenesis of syringoma, future reported cases may help to show the relationship of syringoma with decreased thyroid stimulating hormone level, and increased triiodothyronine and thyroxine levels.

Clinically, syringomas may be mistaken for acne vulgaris, sebaceous hyperplasia, milia, lichen planus, and eruptive xanthoma.14 The definitive diagnosis of syringoma can be made on histological examination.

Syringomas are benign and usually asymptomatic, so treatment is offered primarily for cosmetic reasons.8,14,15 Unfortunately, there is no satisfactory treatment for eruptive syringomas, as in our patient, because any method of surgical or chemical destruction carries the risk of scarring. Furthermore, there is a high rate of recurrence. Our patient did not want any treatment.

CONCLUSIONS

In conclusion, eruptive syringoma associated with hyperthyroidism is unusual. Report of more cases on this association is needed to strengthen the hypothesis about the role of hyperthyroidism in the pathogenesis of syringoma and to show that this coexistence is not a coincidence.

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Figure 1. (A) Syringomas on the periorbital region, malar area, and forehead. (B) Multiple syringomas on the anterior surface of the trunk. (C) Cystic ducts lined with a double row of epithelium in the dermis (hematoxylin-eosin stain, original magnification, ×40).
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INDICATIONS AND USAGE
Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS
Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid. Systemic effects of topical corticosteroids may also include manifestations of Cushing's syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

ADVERSE REACTIONS
The most common adverse reactions (>1%) are HPA axis suppression and application site reactions. The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

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

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 than adults of HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for 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 3 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.

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.

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

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

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