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LETTER FROM THE EDITOR

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LETTER FROM THE EDITOR

SKINmed Resumes Publication

Lawrence Charles Parish, MD, MD (Hon), Editor in Chief

With this issue, Volume 8, Number 1, SKINmed resumes publication after nearly a 2-year hiatus. I assure you, dear reader, this was not to the liking of your editorial board or myself, but we are delighted to be back among the “alive and well” of dermatology publications.

THE NEW SKINMED

Transitioning from one publisher to another is not as simple as it might seem. Pulse Marketing & Communications, LLC, our new publisher, encountered obstacles never considered. As an example, CDs that contained manuscripts already edited were corrupted, resulting in unanticipated and additional work and causing a delay of several months.

While the format of SKINmed has not changed, some details have been selected for what we consider to be improvements. The cover has been simplified so that the entire table of contents now appears in a more legible font, making it easier for the reader to preview the contents. “Call-outs” throughout the issue have been eliminated, as suggested by many readers who found them distracting. “Fillers,” such as pictures of wax moulages from the University of Zurich Collection and labels from the New Orleans Pharmacy Museum, will complement the Photo Capsules from Durban, South Africa, and the stereopticon pictures of the past century, which we previously had published. When a contribution does not complete a page, filler provides more material for the reader to enjoy. The color of the cover remains with our traditional orange for better recognition, reminiscent of changes made by a then editor of JAMA, John H. Talbott, a half-century ago.

DEDICATION

This premier issue for our new publisher is dedicated to Art P. Kalaka and his late wife, Sophia, who devoted many years to the medical publications field. Their commitment to improving the practice of medicine, especially that of dermatology, is unprecedented and reflects well upon the mission of SKINmed as “Dermatology for the Clinician.” Art was also influential in publishing Drug-Therapy, a wonderful journal on whose editorial board I had the privilege to serve, in addition to Modern Medicine, The Journal of Clinical Hypertension, and The American Heart Hospital Journal. He was part of the team that launched SKINmed in the fall of 2002.

THE FUTURE

The editors and publishers of SKINmed will continue to provide a clinical journal, concerning dermatology and dermatologists, and one that, we hope, will continue to earn your attention and support.
EDITORIAL

The Most Important Medical Source:
Aunt Mabel Knows Best

Lawrence Charles Parish, MD, MD (Hon);1 Joseph A. Witkowski, MD2

From the Departments of Dermatology and Cutaneous Biology, Jefferson Center for International Dermatology, Jefferson Medical College of Thomas Jefferson University;1 and University of Pennsylvania School of Medicine;2 Philadelphia, PA

Address for Correspondence: Lawrence Charles Parish, MD, MD (Hon), 1760 Market Street, Suite 301, Philadelphia, PA 19103 • E-mail: larryderm@yahoo.com

Not so long ago, one of us was consulted by a middle-aged woman with rosacea. For many years, she had periodic flares of red papules and pustules on her nose and the adjoining areas. The confluent telangiectasia on her cheeks gave a permanent appearance of well-applied rouge. She had seen several dermatologists and had received a wide variety of medications, all of which seemed appropriate except to her, as would be subsequently revealed. She wanted a new approach, but there were limitations placed on her request: no pills or capsules; nothing odiferous; no agent that might bleach clothing; and nothing that would interfere with her night creams, eye restorer, or wrinkle control. All of these had been recommended by the cosmetic consultant—that is, the person behind the cosmetic counter who wears a white coat (Figure 1 and Figure 2).

The remainder of the history was unremarkable, and the physical examination confirmed the diagnosis of rosacea, possibly with the addition of mild rhinophyma. A therapeutic approach was outlined, which included the omission of occlusive agents and the use of an astringent and keratolytic gel. Oral antimicrobials were suggested but rapidly rejected.

WHY CONSULT A DERMATOLOGIST?

It was obvious that the patient's rosacea required treatment; at least, it was to the professionals. She wanted only natural products that were not adulterated by evil chemicals, the worst culprits being preservatives. After all, she had sensitive skin. She elected to use a concoction of aloe vera, mixed with vitamin E, and to take an herbal supplement.

We live in a free country, and there are no mandates about filling prescriptions, let alone using them. She informed us that Aunt Mabel always has the right idea about skin problems and how to treat them. If this would be correct, why did she ever consult a dermatologist?

One explanation might be that she was hoping for a miracle. Many a patient labors under the belief that the proverbial penicillin injection would remedy most situations. Opposed to this is the patient who claims allergy to all “-cillins” and “-cyclines.” Verifying the allergies becomes a tedious nightmare that leads to hostilities on the part of the patient. For example, penicillin once caused a sore on the lip, and this lesion reappears every few months. The fact that this represents herpes simplex labialis might interfere with Aunt Mabel’s dogma.

Along these lines are the concept that any condition might lend itself to plastic surgery, the idea being that the skin, like Silly Putty, can be put back together without any scarring or marring of the surface. The fact is that rosacea cannot be eliminated by one pill or one injection, let alone removed by excisions.

Still another consideration might be that she wanted to confirm that the medical profession knew less about therapeutics than did her coterie of friends and relatives. There may be some merit to this, when one considers the names of several patent medicines and the pictures of the matrons either making the product or endorsing it.

ANOTHER CONFLICT?

Sometimes our own colleagues fuel the compliance problem. Not every physician is keyed into the use of dermatologics, but that...
does not prevent his or her interceding with the treatment. Because dermatologic diagnosis and therapy may be more extensive than, let’s say, that of cardiology, the caregiver may interdict the use of appropriate topicals or systemic agents. Aunt Mabel was once warned about taking antibiotics. She has fostered this admonition for 4 decades. In fact, she may politely accept the written prescription, but then it is filed along with unused recipes.

Another patient, a 7-year-old girl, had atopic dermatitis since infancy. There were periodic flares, sometimes accompanied by secondary bacterial infection. Her mother never objected to her pediatrician’s prescribing of oral antimicrobials; when it came to the use of topical corticosteroids, anything more potent than hydrocortisone 1% cream was unacceptable. Again, Aunt Mabel’s counterpart had warned against the use of topical corticosteroids for a variety of misunderstood reasons, ranging from confusion with anabolic steroids to hysteria over the supposed side effects that area actually associated with significant doses of systemic corticosteroids, given for lengthy periods. Counseling on the dermatologic formulary proved useless. Aunt Mabel knew best, despite the fact that the emollient she recommended contained lanolin, to which the girl would later be proven to be allergic.

**CONCLUSIONS**

There will always be the Aunt Mabels of the world. Our problem is not necessarily their recommendations, but, rather, our concern is why it is brought to our attention. We did not solicit the patient, nor did we force our ideas on the patient. The unanswered question is why seek the professional consultation in the first place? If Aunt Mabel’s therapeutics had such high levels of efficacy, why was the medical opinion sought? This is much like the remedies huckstered on radio infomercials. If they really did what they claimed to do, then the medical community would no longer have patients.

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**ACNE**

**Medications known to cause acne**

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Adapted from Litt JZ. *Curious, Odd, Rare, and Abnormal Reactions to Medications*. Fort Lee, NJ: Barricade Books; 2009:120–122.
ORIGINAL CONTRIBUTION

Evaluation of Topical Steroids in the Treatment of Superficial Hemangioma

Anand Pandey, MS; Ajay N. Gangopadhyay, MCh; Shiv P. Sharma, MCh; Vijayendra Kumar, MCh; Dinesh K. Gupta, MCh; S. Chooramani Gopal, MCh

ABSTRACT

Infantile hemangioma is a common disease. Steroids have been used for its treatment; however, intralesional steroids cause pain and other problems. A treatment modality that can avoid these problems is desirable. The authors evaluated the role of topical steroids as an alternative to intralesional steroids in the treatment of superficial hemangioma. Inclusion criteria were <2 superficial type of hemangiomas <5 cm. The topical steroid mometasone furoate was applied twice daily. Intralesional triamcinolone acetonide was injected at monthly intervals using a 24-gauge needle at doses of 1 to 2 mg/kg. Forty-five (86.5%) patients responded to treatment with the topical steroids, of which 50% had excellent and 36.5% had good response. In the intralesional group, the response rate was 95.7%, of which 63.8% had excellent and 31.9% had good response. Complications in the topical steroid group were mild itching and irritation (19.2%) and hypopigmentation (7.6%). Complications in the intralesional group were pain (100%), bleeding (17%), infection (17%), cutaneous atrophy (8.5%), cushingoid facies (2.1%), and growth retardation (2.1%). Topical steroids are a reasonably good alternative to intralesional steroids as an initial choice for treating superficial hemangioma. (SKINmed. 2010;8:9–11)

Infantile hemangiomas, the most common tumor of infancy, are vascular tumors characterized by rapid proliferation of endothelial cells during the first few months of postnatal life followed by slow spontaneous involution.1 Steroids for treating hemangiomas have been in use for more than 30 years.2 Intralesional steroids have frequently been used for treating these lesions. Use of topical steroids for treating hemangioma is not common practice. We present our experience with topical steroids as an alternative to intralesional steroids for treating superficial-type infantile hemangiomas.

MATERIAL AND METHODS

This prospective study was carried out in the Department of Pediatric Surgery, Institute of Medical Sciences, at Banaras Hindu University Varanasi in India from June 2004 to June 2006. It was approved by the hospital ethical and post-graduate committees. Inclusion criteria included <2 superficial type of infantile hemangiomas of <5 cm. Exclusion criteria were >2 deep or mixed type of infantile hemangiomas of >5 cm. The patients were randomly divided into 2 groups. One was given a topical steroid of intermediate potency (mometasone furoate) and the other was given an intralesional steroid (triamcinolone acetonide). The topical steroid was applied twice daily as a thin film. The total number of patients receiving mometasone furoate was 52 and triamcinolone acetonide was 47. Intralesional triamcinolone was injected at monthly intervals using a 24-gauge needle (to minimize pain) at doses of 1 to 2 mg/kg. All patients were age, sex, and socioeconomically matched with controls. The follow-up period was 6 to 8 months. Results were evaluated on the basis of 3 factors: (1) cessation of growth, (2) lightening of color, and (3) flattening of surface. Lesions that showed positive response to all 3 parameters were graded as excellent or good if they responded to 2 parameters and poor if response was to a single parameter. Excellent and good were considered as responding to treatment. Congenital hemangiomas were not included in the study.

RESULTS

During the study period, the total number of patients attending the outpatient department was 231, of which 136 (58.8%) had superficial-type hemangioma. A total of 99 fulfilled the inclusion criteria. The topical steroid was used in 52 and the intralesional steroid in 47 patients. Forty-five (86.5%) patients in the topical steroid group responded to treatment, of which 50% had excellent and 36.5% had good response. In the intralesional group,
the response rate was 95.7%, of which 63.8% had excellent and 31.9% had good response (Table I). There was no difference in response in relation to age and sex.

Complications in the topical steroid group were mild itching and irritation (19.2%) and hypopigmentation (7.6%). No other significant complication was noticed. In the intralesional group, pain due to injection was present in all patients (100%) and transient bleeding was seen in 17% of patients. Other complications included infection after injection (17%), cutaneous atrophy (8.5%), transient cushingoid facies (2.1%), and growth retardation (2.1%), which normalized after 3 to 5 months of cessation of therapy (Table II).

DISCUSSION

Regression of hemangioma was reported while using steroids for the treatment of thrombocytopenia. Others also had good response to steroids. Although the usual tendency of hemangioma is to involute, growth in the proliferation phase is rapid and unpredictable. Furthermore, involution often takes many years, with attendant psychological sequelae to the child. This is aggravated by the fact that most hemangiomas affect the head and neck and are therefore visible and difficult to conceal. Thus, treatment may be needed for patient satisfaction even if the hemangioma is small; hence, we treated all patients with hemangiomas who presented to our department. Currently, if intervention is needed for hemangioma, steroids are the drug of choice. There are studies showing good response to intralesional steroids; however, reports of treating hemangioma with topical steroids are sporadic.

The mechanism of action of steroids on hemangiomas is unclear. Intralesional triamcinolone used for treating proliferating hemangioma has been shown to increase the mast cell number, reduce the transcription of the platelet-derived growth factors A and B, interleukin 6, and transforming growth factors β1 and β3, but does not affect basic fibroblast growth factor and vascular endothelial growth factor. In addition, there is upregulation of mitochondrial cyt b gene expression, which may have a role in the regression of hemangioma. It is probable that topical steroids act in the same way as intralesional steroids in that they reach the site by directly entering the thin skin of pediatric patients, which is more permeable to topical drugs.

The reported complications of topical steroids are irritation, itching, hypopigmentation, striae, telangiectasia, hypertrichosis, growth retardation, and even Cushing syndrome, Addisonian crisis, and death. The severe complications, however, occur after application over large areas, leading to increased systemic absorption. We had few reported complications probably due to the small amount applied over small lesions and because the steroid was of intermediate potency.

Complications related to use of intralesional steroids can be minor (eg, hypopigmentation, cutaneous atrophy, and infection) and major (eg, growth retardation, Cushing syndrome, and anaphylactic shock). Occlusion of the retinal artery has been reported. Moreover, high injection pressure can be a problem. Growth retardation and Cushing facies were not significant in our study (2.1% each), but pain, bleeding, and infection were measurable, adding much to the distress of the patients. We tried to minimize pain by using narrow-caliber needles (ie, 24-gauge), but pain was still sufficient to cause disturbance. We do not use 30-gauge needles in our department. Moreover, smaller needles have a shorter length, thereby necessitating more pricks to inject the drug evenly into the lesion. Smaller-gauge needles require more pressure for injection and the possibility of embolization of corticosteroid particles into the circulation, especially ocular circulation.

We had an 86.5% response rate with topical steroids. In one study, there was a 74% response rate in 34 infants, but the steroid was...
used in all types of hemangioma without any selection. Although other studies have found unclear results with the use of topical steroids, sample sizes have been small and inference difficult. Other studies have shown satisfactory response to topical steroids. Thus, topical steroids are associated with increased patient compliance and slightly fewer complications and can be comparable to topical steroids if the above benefits are taken into account.

Congenital hemangiomas were excluded from the study because of distinctive clinical and pathologic features, separating them from infantile hemangioma.

CONCLUSIONS

Topical use of moderately potent steroids can be a reasonably good alternative to intralesional steroids as an initial choice for treating superficial hemangioma, as in our study; however, one can switch to intralesional steroids if there is no or poor response on follow-up. We would recommend more studies in this field so that topical steroids find a better place for treating superficial hemangioma, a common ailment associated with much distress.

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Immunopathologic Features of Pemphigus in the East Mediterranean Region of Turkey: A Prospective Study

Ayse Akman, MD;1 Soner Uzun, MD;2 Erkan Alpsoy, MD1

ABSTRACT

Pemphigus, a life-threatening autoimmune disorder, is the most common autoimmune bullous disease in the Mediterranean region of Turkey. No studies have investigated the immunopathologic features of this geographic setting. To determine the immunopathologic features of pemphigus in the Eastern Mediterranean region of Turkey, the authors evaluated the histopathological, immunofluorescence (IF), and enzyme-linked immunosorbent assay (ELISA) results in a 4-year study. In this prospective study, tissue from 174 patients was analyzed by direct IF (DIF); 384 by indirect IF (IIF) from 61 patients with pemphigus; and 88 by ELISA for antibodies against desmoglein (Dsg) 1 and Dsg 3 from 50 of those 61 patients. Pemphigus vulgaris (PV) was the most commonly observed subtype (46 of 61 patients, 75.41%), followed by pemphigus foliaceus (9 of 61 patients, 14.75%), pemphigus erythematosus (5 of 61 patients, 8.2%), and pemphigus herpetiformis (1 of 61 patients, 1.64%). There was a significant correlation between clinical activity score (CAS) and IgG antibody titer in IF (P<.001) and ELISA tests (P=.024 for Dsg 1; P=.028 for Dsg 3). Antibody titers and C3 scale did not predict exacerbations and relapse. The commonest clinical subtype of pemphigus was PV in this region. Results indicate that IgG antibody titer in IF and ELISA tests of patients with pemphigus are correlated with CAS; however, they are not useful in predicting exacerbations and relapse of disease. (SKINmed. 2010;8:12–16)
MATERIALS AND METHODS

PATIENTS
The prospective study included 61 consecutive patients (36 women, 25 men; aged 13–85 years), 46 with PV and 15 with PF treated in the Department of Dermatology at the University of Çukurova, Adana, Turkey, during 4 years. The study was approved by the local ethics committee. The follow-up period varied from 2 months to 4 years (mean, 26 months). A total of 174 tissue samples were analyzed by DIF; 384 by IIF from 15 patients with superficial pemphigus and 46 patients with deep pemphigus; and 88 by ELISA for antibodies against Dsg 1 and Dsg 3 from 35 patients with PV and 15 with PF during follow-up. The clinical diagnosis of pemphigus was confirmed by histologic and immunopathologic findings. The clinical activity score (CAS) was graded as follows: 0=no lesion; 1=mild: disease localized to a few (1–3) regions of the body (scalp, face/neck, upper torso, lower torso, arms, legs); 2=moderate: disease localized to mucosa or disease localized to mucosa and to a few regions of the body; and 3=severe: extensive skin involvement (>3 regions of the body) plus ≥1 case of mucosal involvement. Clinical remission was described as a period of being lesion-free for more than 1 month without any systemic therapy. The patients were treated with a modified protocol of Vien according to past research. Patients were clinically (by CAS) and immunologically (by DIF, IIF, and ELISA for antibodies against Dsg 1 [anti–Dsg 1] and Dsg 3 [anti–Dsg 3]) re-examined once a month.

HISTOLOGY
Histologic examination was performed on hematoxylin and eosin–stained sections of paraffin-embedded lesional biopsy specimens.

DIRECT IMMUNOFluorescence
Biopsy specimens were obtained from perilesional areas in patients with active disease before therapy. For control biopsies, the specimens were taken from an area close to the previous biopsy site or perilesional areas if the active lesions were still remaining. The immunofluorescence procedures were performed by a modification of the method described by past researchers. The skin biopsies were sectioned at 4 μm in a cryostat and incubated with fluorescein-conjugated polyclonal sheep anti–human-IgG, -IgA, -IgM, -C3, and fibrinogen antibodies. The stained sections were examined in a fluorescent microscope at 525 nm. The level of the staining was graded according to the intensity of fluorescence with semiquantitative imaging between negative and 3+ for intercellular staining.

INDIRECT IMMUNOFluorescence
A 10-mL blood sample was drawn from each patient and centrifuged to separate the serum. The serum samples were prepared in serial dilutions of 1:0 to 1:5120. Cryosectioned substrates of rat esophagus were incubated with the diluted serum samples. After these slides were washed with phosphate-buffered saline Tween, a second incubation with 1:150 dilution of fluorescein-conjugated polyclonal sheep anti–human-IgG antibodies was performed for the presence of antibodies against keratinocyte cell surface proteins. The highest positive serum dilution was recorded as the antibody titer.

DSG 1 AND DSG 3 ELISA
ELISA using recombinant Dsg 1 and Dsg 3 as the antigen source was performed as previously described. The serum samples were diluted 100-fold. Antibodies against Dsg 1 and Dsg 3 were measured by a commercial ELISA kit. The index value was defined the following formula:

 Optical density [OD] of tested serum – OD of negative control
Index = X100
OD of positive control – OD of negative control

STATISTICS
To determine the correlation between CAS and antibody scores (DIF scale, IIF titer, and ELISA index value) we applied the Spearman correlation for nonparametric variables.

RESULTS

CLINICAL AND IMMUNOPATHOLOGIC FINDINGS
The clinical subtypes and demographic findings of study patients are presented in Table I. Five patients with PF had linear IgG

Table I. Clinical Subtypes and Demographic Findings of Pemphigus Patients

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Patients, No. (%)</th>
<th>Men/Women</th>
<th>Mean Age, Year ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep pemphigus</td>
<td>46 (75.41)</td>
<td>20/26</td>
<td>44.70 ± 12.40</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>5 (8.2)</td>
<td>3/2</td>
<td>43 ± 26.01</td>
</tr>
<tr>
<td>Superficial pemphigus</td>
<td>9 (14.75)</td>
<td>3/7</td>
<td>51.44 ± 16.90</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>1 (1.64)</td>
<td>0/1</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>25/36</td>
<td>46.21 ± 15.18</td>
</tr>
</tbody>
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and C3 deposition on the basement membrane zone. There was no deposition on the epithelium of rat bladder. Lesions of these patients were predominantly found on the face. Antinuclear antibody test results were negative in these patients. In addition, of these subtypes, PH was defined in one patient.

In 4 patients who presented with mucosal and skin lesions, new mild attacks were observed during the first 2 years of the follow-up period. Interestingly, they developed exacerbations restricted only to their scalp region during the last 2 years. Histopathologic examination of these skin lesions showed suprabasal separation. In addition to these patients, one patient with PV had only a skin lesion on the nose. He had both Dsg 3 and Dsg 1 antibodies in his serum. On the other hand, 15 patients with PV showed only oral mucosal involvement. A total of 4 of 15 of those patients presented with gingival lesions and persisted with the same localization in the subsequent attacks. One patient with PV had only one lesion on the larynx after clinical examination and suprabasal separation after histological examination. The patient had DIF +3 but no Dsg 3 antibody in her serum (Table II).

**Correlation of Immunopathologic Findings With Baseline CAS**

A significant relationship was found to exist between the IIF antibody titer and CAS, DIF IgG and CAS, and DIF C3 scale and CAS ($P<.001$). The data from PV and PF cases were separately analyzed to test whether their was a relationship between Dsg antibody titer and CAS. There was a significant relationship between the Dsg 3 antibody titer and CAS in PV patients ($P=.028$). In spite of a positive correlation between the Dsg 1 antibody titer and CAS in PV patients, there was almost a significant relationship ($P=.059$). This correlation, however, was statistically significant in patients with PV who had both skin and mucosal lesions ($P=.024$). Although there was a statistically significant relationship between the Dsg 1 antibody titer and CAS in PF patients ($P=.024$), there was no significant relationship between Dsg 3 and PF ($P=.278$). Correlation of the immunopathologic findings and CAS are presented in Table III.

**Correlation of the Immunopathologic Findings With the Follow-Up CAS**

There was no significant relationship between the preceding month’s immunopathologic findings and the follow-up CAS ($P>.05$) (Table III).

**Immunofluorescent Test Results and the Development of Relapse**

Remission duration in our patients ranged from 2 to 19 months in 26 patients (45%). Relapse developed in 69% of the patients whose DIF test result was positive and in 73% of the patients whose IIF test result was positive. Relapse developed in 69% of the patients whose DIF test result was negative and 55% of the patients whose IIF test result was negative.

**Discussion**

In this study, we evaluated the clinical and immunopathologic findings of pemphigus patients in the East Mediterranean region of Turkey. PV was the most common subtype of the disease in this region. A total of 14.75% of the patients with pemphigus had linear IgG and C3 deposition on the basement membrane zone. Antinuclear antibody test results were negative in these patients. The patients’ diagnoses of PE depended on the known criteria.24 This was found to be higher than in Bulgaria25 but similar in eastern Sicily.26 We believe that sun exposure may cause the development of PE in our region. The same feature in the southern region of Saudi Arabia27; however, is not higher than our prevalence of PE. Other than UV exposure, genetic factors may also play a role in the development of PE in our region.28–30 A total of 13.79% of PV patients with mucosal and skin lesions had only scalp lesions. This may be related to the high antigenic expression on the dense follicular area31 that is susceptible to the anti–Dsg antibodies.

CAS of skin disease correlated with Dsg 1 antibody titer and CAS of mucosal disease correlated with Dsg 3 antibody titer, but there were discrepancies in the results of ELISA and clinical involvement in two patients. One patient with PV had only a skin lesion on the nose; however, Dsg 3 and Dsg 1 antibodies were detected.
in his serum. A second patient with PV had only one lesion on the larynx on clinical examination and a suprabasal separation on histological examination. She had DIF +3 but no Dsg 3 antibody in her serum. There was also a discrepancy between the results of ELISA and histologic findings in the second patient. These results suggest that: (1) there was individual and regional variation in the expression of the antigens targeted by Dsg antibodies; (2) there was a presence of intercellular antibodies for Dsg 4, pemphaxin, and Ach receptor in pemphigus patients; and (3) different Dsg epitopes were not included in the ELISA kit.

**LIMITATIONS**

We were unable to apply IB (denaturating techniques) and IP (using non-denaturating detergents), diluted the sera for true index values, and performed ELISA each month similar to IF tests. Due to this fact, there were also some limitations of ELISA for routine processing with (1) obtaining true index values, and (2) detecting antibodies that targeted non–Dsg 1 and non–Dsg 3 antigens or different Dsg epitopes.

There was a significant correlation between CAS and IgG antibody titer in IF and ELISA tests in all patients. In addition to this, DIF C3 scale correlated with CAS. The antibody titers and C3 scale were not predictive of exacerbations and relapse; therefore, the usefulness of the tests and monitoring of therapy and prognostic value remains to be elucidated. On the other hand, ELISA is a diagnostic tool that measures circulating autoantibodies against Dsg 1 and Dsg 3; therefore, this assay is able to identify disease activity as well as differentiate subtypes as PV and PF. A previous study used ELISA index values to determine the initial dose of glucocorticoid therapy for 8 patients with PF. Further studies will be required to determine the choice of treatment modalities and its influence on disease prognosis.

**CONCLUSIONS**

Our results indicate that IgG antibody titers in IF and ELISA tests of patients with pemphigus correlated with CAS. They are not useful, however, in predicting exacerbations and relapses of the disease. To prevent the limitation of ELISA for detecting target antigens in atypical cases, further studies are needed in our region that apply another technique such as IB and/or IP in the first visit and/or clinical shift. Then, if antibodies against Dsg 1 and Dsg 3 are detectable by these techniques, ELISA could be useful in monitoring disease activity by monthly intervals with appropriate dilutions.

**Disclosure:** This study was supported by Cukurova University Scientific Research Projects Unit.

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ORIGINAL CONTRIBUTION

Community Study of Fixed-Combination Adapalene 0.1% and Benzoyl Peroxide 2.5% in Acne

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ABSTRACT

A new fixed-dose combination formulation of adapalene 0.1% and benzoyl peroxide (BPO) 2.5% has shown excellent efficacy and safety in registration studies; however, it can be difficult to judge the real-world performance of a product using only the results from controlled clinical trials. This 12-week, open-label, community-based study evaluated adapalene/BPO in 91 patients with mild to moderate acne (20–50 inflammatory lesions and 30–100 noninflammatory lesions) who were treated at dermatology centers throughout Argentina. The study evaluated efficacy, described the most common side effects, determined tolerability, and assessed the level of patient satisfaction with treatment. By week 12, there were statistically significant reductions in both inflammatory and noninflammatory lesions (80.6% and 69.3% from baseline, respectively; \( P < .001 \)); there were also significant improvements in the Investigator’s Global Assessment scores (median score, 2.9 at baseline and 1.0 at week 12; \( P < .001 \)). By week 12, 67% of patients were rated clear or almost clear by investigators. Local tolerability was good overall. When cutaneous irritation was present, it typically occurred in the first 2 weeks of treatment and improved or resolved with continuing therapy. Patients were highly satisfied with the results of treatment, and 74% of patients felt that they had marked or total improvement by week 12. Patient survey also revealed that 94% rated the efficacy as good or very good and 87.5% rated tolerability as good or very good. A significant majority (81%) felt that the treatment met expectations, and 62% perceived that improvement had been rapid during adapalene/BPO therapy. These results demonstrate that adapalene/BPO has good efficacy and tolerability in routine practice, resulting in continuous reductions in lesion counts throughout the study. Adapalene/BPO therapy is also associated with high patient satisfaction, which is important for therapeutic adherence and satisfaction with the physician’s care. (SKINmed. 2010;8:17–22)

Acne accounts for approximately 15% to 25% of dermatologic visits and affects the majority of teenaged persons (up to 85%), as well as a significant proportion of adults. There are few data on the prevalence and/or presentation of acne in Argentina; however, the Argentina Society of Dermatology conducted a descriptive study of 1616 patients with acne and reported that most patients were aged 13 to 26 years (mean age, 14.7 years) and had inflammatory acne (84%) on the face (90%). Mild to moderate disease was most common, with severe acne present in only 16% of the study group. For a substantial number of patients, acne is a long-lasting chronic disorder that requires treatment over a period of years. Because of the patient population (often adolescents and young adults) and duration of disease, using simple, efficacious, and well-tolerated treatment regimens is essential for achieving optimal results and maximizing the potential for adherence. The new once-daily formulation of adapalene/benzoyl peroxide (BPO) offers a convenient acne therapy that targets multiple pathogenic factors in acne and thus warrants consideration as a first-line therapy.

To enhance knowledge of acne therapies and help guide clinicians in selecting medications, it is important to evaluate products in the real-world setting and in different ethnic groups and populations. This study was conducted to assess a new formulation of adapalene 0.1% and BPO 2.5% (Epiduo, Galderma S.A., Paris, France) in Argentina, which has a somewhat atypical Latin American population. The Argentine population is dominated by people of European ancestry, and there is a high proportion of individuals with white skin (>85%) compared with other Latin American countries.
Acne has a multifactorial pathophysiology, with 4 major factors that influence the development of the microcomedone, the precursor to all acne lesions. These include:

- Hyperkeratinization and hyperproliferation of the cells in the follicular canal
- The hormonal influence of androgens and increased secretion of the sebaceous glands
- Colonization and proliferation of *Propionibacterium acnes*
- Inflammation involving both the innate immune system and local inflammatory mediators.

The recommended therapeutic approach for most patients with acne is to combine a topical retinoid plus an antimicrobial agent. This allows targeting of 3 of the 4 major pathophysiologic factors and has been shown in numerous studies to be an efficacious and well-tolerated therapeutic strategy. Combination retinoid-based therapy was first recommended in 2003 by the Global Alliance to Improve Outcomes in Acne; since that time, it has become a standard first-line therapeutic approach.

In recent years, the problem of antimicrobial resistance has been increasingly recognized in medicine. Thus, while antibiotics were once considered a cornerstone of acne therapy, now experts recommend that the use of antibiotics in acne be limited as much as possible. In addition, current acne management recommendations stress the use of BPO as an antimicrobial agent due to its rapid bactericidal effect on *P. acnes* and the lack of reports about development of resistance in pathogenic organisms. Using a topical retinoid in addition to BPO increases both the speed and extent of acne clearing.

Adapalene is a derivative of naphthoic acid, which is chemically stable with BPO and stable in the presence of light. It has comedolytic, antimcomedogenic, and anti-inflammatory actions and also acts as an immunoregulator. The safety and effectiveness of adapalene has been demonstrated in numerous clinical trials. BPO is an effective antimicrobial agent for acne, with a powerful and rapid bactericidal effect on *P. acnes*. It has been widely used for several decades with no evidence of development of bacterial resistance. In a controlled comparative study, researchers demonstrated that 2.5% BPO was as effective against mild to moderate inflammatory acne as higher concentrations (5% and 10%) but was associated with better cutaneous tolerability.

The new fixed-dose combination of adapalene 0.1% and BPO 2.5% is an aqueous gel that has been approved for once-daily use in treating acne. Adapalene/BPO has been evaluated in several large-scale clinical trials lasting up to 1 year that have shown an excellent safety profile. Reductions in both inflammatory and noninflammatory lesions are apparent as early as 1 week after treatment is initiated and continue over a prolonged period.

This study included patients from 19 dermatology centers in various cities of Argentina. The primary objective was to evaluate the efficacy and safety of the fixed-dose combination of adapalene/BPO in the treatment of mild to moderate acne over 12 weeks in clinical practice, as well as to assess the level of patient satisfaction with treatment.

**METHODS**

**Study Design**

This was an open-label, community-based, 12-week interventional study performed in multiple centers. A total of 105 patients with mild to moderate acne were enrolled in the study from December 12, 2007, through February 2008. A total of 91 patients were treated with the adapalene/BPO combination and 14 patients were excluded due to protocol violations during the pre-study washout phase.

Patients who met the inclusion/exclusion criteria described below applied fixed-dose adapalene/BPO gel to the face once daily at nighttime. Photographs were taken at baseline and at visit 5 (or the last study visit). At each visit, efficacy and safety evaluations were performed.

**Study Population**

Eligible patients included men and women of any race and ethnicity, aged 15 years or older, with mild to moderate facial acne (20–50 inflammatory lesions and 30–100 noninflammatory lesions). A washout period of up to 6 weeks was required for patients who had used prescription and over-the-counter acne treatments. Specifically, the following washout periods were applied: topical corticosteroids and systemic nonsteroidal anti-inflammatory drugs (15 days); systemic antibiotics, corticosteroids, or hormone treatment (4 weeks); oral isotretinoin (6 weeks); and anti-acne soaps and astringents (1 week).

Approximately 100 patients were planned for enrollment into the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, good clinical practice, and local regulations. All patients provided informed consent before entering the study.

**Efficacy Evaluation**

Efficacy evaluations of the face comprised inflammatory, noninflammatory, and total lesion counts and an Investigator’s Global Assessment (IGA) at screening, baseline, and during treatment (days 15, 30, 60, and 90). Facial lesion counts of open and closed comedones (noninflammatory lesions) and pustules, papules, and
nodules (inflammatory lesions) were taken from the forehead, left and right cheeks, and chin.

**SAFETY EVALUATION**

Cutaneous safety and tolerability were assessed by the investigator at each study visit. Cutaneous safety evaluations included erythema and scaling and tolerability evaluations included itching, burning, and stinging. Each was scored on a scale of 0 (none) to 3 (severe) at each visit. Erythema and scaling were assessed by the investigator at the time of the study visit; itching, burning, and stinging were assessed by patient report. Safety was also evaluated by reported adverse events, which were summarized by severity and relationship to study medication.

**PATIENT SELF-ASSESSMENT**

Patients rated the severity of their acne during the study by providing a global improvement score (0=total, 1=marked, 2=moderate, 3=mild, 4=no change, 5=worse) at 30, 60, and 90 days of treatment. In addition, patients completed a satisfaction survey at the end of treatment. This survey included 5 questions about the therapeutic results in terms of efficacy, tolerability, speed of the therapeutic response, and adherence; each variable was rated as excellent, very good, good, regular, or bad.

**STATISTICAL ANALYSES**

The safety population included all patients enrolled who were presumed to have used the study medication at least once and who had at least one postbaseline evaluation. The per protocol population included all patients who completed the 12-week evaluation period without significant study protocol violations.

Data were collected by each physician on a precoded format for each of the visits and for adverse events. Descriptive statistics were calculated, including frequencies, percentages, and cumulative percentages for qualitative variables. Continuous variables were summarized by the number of cases evaluated, arithmetic means, and standard deviation. Changes in lesion counts and IGA scores were evaluated by Student t test for paired samples with a level of significance P<.05. All statistical tests were two-tailed. SPSS version 13 software (SPSS Inc, College Station, TX) was used for statistical calculations.

**RESULTS**

**BASELINE CHARACTERISTICS**

A total of 105 patients were enrolled and 91 patients were treated with adapalene/BPO. The majority of patients (69.2%) were women and the mean age was 19.86±5.76 (range, 13–41) years. The mean duration of acne was 32.4±32.0 (range, 3–240) months. Most patients were light-skinned (81% had Fitzpatrick II or III skin types, 12% had Fitzpatrick IV skin type, and 4.4% had Fitzpatrick skin type I).

**EFFICACY**

Representative clinical results are shown in Figure 1 and Figure 2. The majority of patients in the study had a good response to therapy as indicated by lesion counts and global assessment scores.

*Lesion Counts.* Lesion counts significantly decreased during the 12-week treatment period, with a mean reduction in inflammatory lesions of 80.6% and noninflammatory lesions of 69.3% from baseline (P<.001). Reductions in all types of lesions (inflammatory and noninflammatory) began soon after initiation of adapalene/BPO therapy and continued throughout the duration of the evaluation period (Figure 3).

*Investigator’s Global Assessment.* The improvements in IGA score at day 90 indicated that the therapeutic response to adapalene/BPO was considerable (P<.001; Figure 4). At study end, only 12% of cases were classified as moderate in severity (vs 73% at baseline). At baseline, the mean IGA was 2.9 (moderately severe acne); the mean IGA was reduced to 1.1 (almost clear) at study
end ($p < 0.001$). As with the reduction in lesion counts, improvements in IGA continued throughout the duration of the study, suggesting that treatment should be maintained for at least 90 days. At the final visit, 67% of patients were judged to be clear or almost clear.

**SAFETY**

*Cutaneous Tolerability.* Tolerability of adapalene/BPO was good overall. As expected, tolerability problems were most likely in the first 15 days of the study. In this time, 14% of patients had moderate to severe erythema, 12% had burning at the application site, and 20% had desquamation or dry skin. After the initial period, the frequency of these tolerability problems declined. By day 30, 6% of patients had erythema, 7% had dry skin, 4% had desquamation, and 5% had burning. By the end of the study, only 2% had experienced moderate erythema at some point in the third month; 4% had dry skin, 3% had desquamation, and 1% had burning.

*Adverse Effects.* Burning at the application site was reported by 14.3% of patients. One case (1.1%) was considered moderate in severity and the remaining 13 cases were mild; however, 5 patients (5.5%) discontinued treatment due to application site reactions. No other types of adverse reactions were reported during the study.

**PATIENT SELF-ASSESSMENT**

By day 30 of treatment, 38% of patients reported that they believed their overall improvement in acne was complete or marked. An additional 32% reported moderate improvement and 22% reported mild improvement. Only 3% reported no change in their acne, and 4% thought that their acne had worsened. By day 60, 10% reported complete improvement, with an additional 42% reporting marked improvement; 27% reported moderate improvement, 18% mild improvement, and 3% no change or worsening. Finally, at day 90, improvement was complete in 18% or marked in 56% of patients, with just 4% reporting worsening or no change.

At study end, effectiveness was evaluated as good or very good by 94% of patients; 4% considered treatment to be negative (resulted in no change or worsening). A total of 87.5% of patients rated the tolerability as good or very good, 10% rated it as acceptable, and the remaining 2.5% rated it as poor. The speed of response was judged to be good or very good by 86% of patients. Of the remaining patients, 11% felt that the time to response was normal and 3% felt it was poor. Overall patient satisfaction was similar to the effectiveness rating, with 94% of patients indicating that they were very satisfied or satisfied with treatment. The majority (81%) felt that adapalene/BPO treatment met their expectations, and 95% felt the regimen was easy to follow.
DISCUSSION

The fixed-dose combination of adapalene 0.1% and BPO 2.5% in the topical treatment of mild to moderate acne for 12 weeks in our population was effective in 93% of cases, with marked improvement in 74% of cases and moderate improvement in the remainder. Acne lesion counts were reduced by the first study visit and continued to decline throughout the study. Tolerability was also good. When side effects occurred, they were typically reported in the first month of treatment and diminished over time. Patients should be counseled that side effects are generally transient and not severe.

These data are in line with the results of the adapalene/BPO clinical development program, which included cutaneous tolerability studies, phase II and III studies, and a 12-month safety study. Study of adapalene/BPO cutaneous tolerability showed that the fixed-dose combination product is as well tolerated as BPO 2.5% gel or adapalene 0.1% gel alone. The phase II and III clinical studies of a once-daily fixed formulation of adapalene gel 0.1% and BPO 2.5% were recently completed. The fixed-combination product had consistently greater efficacy than monotherapy, with differences in lesion counts observed after 1 week. It is likely that adapalene and BPO are synergistic: BPO is a very potent bactericidal agent against *P. acnes* and adapalene down-regulates the cell-surface receptor (toll-like receptor 2) that is used by *P. acnes* to stimulate cytokine production. Researchers have shown that the effect of adapalene on toll-like receptor 2 increases CD1d expression and decreases interleukin 10 expression by keratinocytes. These actions could increase interactions between dendritic cells and T lymphocytes, allowing BPO to have greater antimicrobial activity against *P. acnes*. Like other retinoids, adapalene is comedolytic and anticomedogenic; thus, adapalene likely enhances the penetration of BPO by helping to unclog the pore.

The registration trials of adapalene/BPO had similar designs comparing the fixed-dose combination product with the individual monotherapies or vehicle over a 12-week period. The studies showed statistically significant differences in success rates at week 8, week 12, and end point (P<.05). In addition, lesion counts were significantly lower in the group treated with adapalene/BPO as early as week 1. The frequency of adverse events and cutaneous tolerability for adapalene/BPO were comparable with that observed with adapalene monotherapy. While approximately 15% of patients in these studies were of Hispanic origin, no subgroup analysis by ethnic group has been published. Data on acne management in patients with Hispanic ethnic origin are exceptionally sparse in the literature.

Our results compare favorably with other real-world studies of acne treatments. At study end, 67% of patients were assessed to be clear or almost clear by investigators. In comparison, 25% of patients were rated clear or almost clear in a recent community-based study of tretinoin gel microsphere 0.04% or 0.1% in a pump dispenser. In 2003, results from the community-based BenzaClin Efficacy and Satisfaction Trial (BEST) were reported. On physician assessment, 39% of participants in the BEST study experienced marked improvement in acne, with an additional 35% rated as having moderate improvement. A total of 8% of patients in the BEST study were of Hispanic origin (N=93), and the physician global assessment was analyzed by ethnic origin. Within this subgroup, 55% of patients had marked improvement during the BEST study.

CONCLUSIONS

The results of this real-world study demonstrate a significant improvement in acne during a 12-week treatment period and good patient satisfaction. The efficacy data are consistent with results of clinical trials. The rapid onset of an effect and convenience of the therapeutic regimen may have had a significant role in patient satisfaction and may translate to improved patient adherence with therapy.

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ORIGINAL CONTRIBUTION

“Quitting Smoking Rejuvenates the Skin”: Results of a Pilot Project on Smoking Cessation Conducted in Milan, Italy

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ABSTRACT

This study reports the results obtained during the “Quitting Smoking Rejuvenates the Skin” campaign, a pilot project in favor of the fight against nicotine addiction in women promoted by the Municipality of Milan jointly with other organizations. The initiative allowed researchers to evaluate the benefits on the skin obtained by cessation of smoking in a sample of 64 Caucasian women who smoked and who, in the period between February 2007 and November 2007, were followed by a team of dermatologists, psychologists, and nutritionists. During the dermatologic program, clinical and instrumental evaluations were made at the beginning of the study and at 3, 6, and 9 months. The state of skin aging was evaluated visually by giving a clinical score to each sign of skin aging (lines, vascular and pigmentation state, elasticity, brightness, texture of the skin). These signs were then correlated using a particular “spider web” graph called Spiderming, the result of Derming research that allows the monitoring of results obtained over time. Taking into account that a wider area of the graph coincides with more advanced skin aging, the graph of mean values observed in the study patients narrowed as time went by; reaching certain statistically significant values in as little as 6 months of observation. The patients’ biological skin age was also calculated so as to better quantify the benefits they obtained by giving up smoking. It was possible to measure the biological age of the skin using noninvasive instrumental measurements of parameters such as skin smoothness, brightness, coloring, and elasticity. A complex mathematic algorithm processed the results obtained for each patient and, on this basis, calculated the biological age of the patient’s skin. At the end of the program, an average reduction of about 13 years in the biological age of the patients’ skin was found, while, at the beginning of the study, patients had presented with an average biological age of 9 years older than their chronologic age. This pilot project not only demonstrated that quitting smoking improves skin conditions, and above all skin-aging effects, but for the first time it afforded the opportunity to produce data that quantify this benefit. (SKINmed. 2010;8:23–29)

The project “Quitting Smoking Rejuvenates the Skin,” amply publicized and promoted in the media, was held on February 16th, 17th, and 18th in the major square of Milan, Piazza del Duomo, Italy, seeking habitual smokers who seriously wanted to give up smoking. All the candidates who came to the special mobile unit set up for the study were offered a skin test to evaluate the biological age of their skin preparatory to being included in the study, which was completely free for smokers aged between 30 and 65 years. During the 3 days, 183 women signed up for the initiative. After a preselection of candidates by the commission, 64 women were invited to take part in a psychological program of weaning from smoking, which would last 9 months. The participants, all Caucasian, gave their written informed consent before inclusion, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The candidates were followed by specialists from the Derming Institute for periodic checkups of their skin and were supported by a dietetic program to control their body weight. At the end of the program, the candidates who managed to stop smoking as a result of the program were contacted again to monitor their abstinence from smoking. With the further aim of gratifying and reinforcing their choice of giving up smoking, the candidates were awarded a certificate from the Municipality of Milan during a public ceremony.

MATERIALS AND METHODS

During the dermatologic program, clinical and instrumental evaluations of the skin were made at the beginning of the study and at 3, 6, and 9 months. The state of skin aging was visually evaluated by giving a clinical score to the various signs of skin aging (eg, wrinkles, vascular and pigmented status, skin elasticity, brightness, and texture).

Wrinkles (at nasolabial folds level and in the area around the eyes), surface microrelief, skin tone/elasticity, brightness, and dryness, as well as vascular and pigmented homogeneity, are described below (visual score).
Wrinkles
To determine wrinkles’ grade around the eyes and at the level of nasolabial folds, the following clinical and photographic reference scale was used: 0 = no wrinkles; 1 = very weak wrinkles; 2 = weak wrinkles; 3 = quite evident wrinkles; 4 = evident wrinkles; 5 = very evident wrinkles; 6 = marked wrinkles; and 7 = very marked wrinkles.

Surface Microrelief
Based on a photographic scale, the cheek surface microrelief was evaluated according to the following score: 1 = very regular: all the primary lines present the same depth. The secondary lines are well demarcated and form star-like shapes (made by convergent apexes of several triangles). 2 = regular: hiding and loss of secondary lines demarcation. Star-like shapes are still present, although with less-demarcated secondary lines. 3 = Irregular primary lines irregularity: strong hiding of lines with low presence of star-like shapes. 4 = Very irregular: strong deterioration of skin. Deep primary lines distortion and loss of secondary lines.

Skin Tonicity/Elasticity
Skin resistance to pinching, resistance to traction, and recovery after pinching were performed at cheek’s level (malar region), according to the following score: 0 = very important; 1 = important; 2 = moderate; 3 = weak; and 4 = very weak.

Skin Brightness
Skin brightness was calculated as 1 = very opaque; 2 = opaque; 3 = normal; and 4 = luminous.

Skin Dryness
Dryness of the skin was evaluated as: 0 = very hydrated skin; 1 = hydrated skin; 2 = normal skin; 3 = slightly dry skin; 4 = dry skin; and 5 = very dry skin.

Vascular and Pigmentary Homogeneity
Homogeneity grade was assessed according to specific clinical and photographic reference scales and to the following clinical scores: 0 = very homogeneous; 1 = homogeneous; 2 = slightly...
nonhomogeneous; 3 = nonhomogeneous; 4 = rather nonhomogeneous; and 5 = markedly nonhomogeneous.

**SPIDERMING SKIN AGING GRADE EVALUATION**

To determine the anti-age efficacy of nonsmoking, the data (mean values) relevant to all the clinical parameters considered were correlated by means of a particular graph called Spiderming (Derming srl, Monza Milan, Italy), which represents an innovative method for the description and visualization of skin aging grade.

Spiderming allows visualization of the global aging grade, also as a function of age range and sex of the individual included (in the graph, a wider area corresponds to a more marked aging grade of skin). Moreover, comparing the data obtained with Spiderming during the study period, it was possible to evaluate changes in the aging grade of the population under study.

**BIOLICAL AGE OF THE SKIN**

We could assess the biological age of the skin using noninvasive instrumental measurements of parameters such as skin smoothness, brightness, color, and elasticity. These parameters were chosen because they change as the state of skin aging changes. Calculating the biological age of the skin was performed on the basis of the above-mentioned parameters and with complex statistical methods compared with a standard control group previously studied so as to prepare the mathematic model.

The definition of biological age of the skin offers the advantage of also being readily understood by patients. We have previously developed a method for calculating skin biological age based on the measurement of various skin parameters and on the mathematic elaboration of the data obtained.

The assessment site was the participants’ medium third of the forearm, volar surface, and face (right or left randomly).

**MEASUREMENTS**

To perform the following measurements, a model system (Figure 1) was assembled:

- Electrical capacitance, sebum transmittance, and pH (*Derming Tester*, Derming srl, Monza Milan, Italy)
- Microrelief analysis on skin replicas (*FFT sector 2003*, Derming Hardware and Software, Monza Milan, Italy)
- Remittance spectrophotometry (*Spectra Win, Version 5*, Avantes, The Netherlands, Europe)

**MICRORELIEF ANALYSIS**

Skin replicas (5 × 5 cm) were taken using silicone rubber (Optosil; Heraeus Kulzer, Dormagen, Germany). The skin was wiped with a cleansing tissue and then allowed to dry. A fixed quantity (9 mL) of silicone polymer, mixed with 10 drops of catalyst, was applied on the skin and distributed on the test site. After a few minutes, the hardened replica was peeled from the skin site. After a drying and hardening time of at least 24 hours, the image of the replica (circular area of 90 mm²) was acquired by a stereomicroscope (Olympus SZ-404STR; Olympus, Tokyo, Japan) connected to a charge coupled device camera.1–3 To ensure reproducible and comparable data, the image acquisition was made under standardized conditions: position of replicas on the horizontal plane, magnification (×7), and intensity of two fiberoptic illumination sources (in east-west position), by 45° illumination incidence. A dedicated software to perform fast Fourier transform on skin texture was used. Two different grades of skin texture regularity are matched in Figure 2, with the corresponding frequency domains: the disposition of pixels varies from a dispersed pattern, representing a very regular texture (a), to a directional one (b).

**REMITTANCE SPECTROPHOTOMETRY**

The skin was illuminated by a Deuterium-halogen light source (DH-2000) through a flexible light guide containing 6 optical fibers and a central fiber optical system collecting the reflected light and guiding it to a wavelength scanner and a light detection device.4–5 Remittance was instantly recorded by a linear array of
photodiodes covered by an optical filter allowing only the passage of a specific wavelength range to each underlying photodiode. Measurements were taken in a 194- to 1100-nm wavelength range, taking into account the behavior of the considered spectrum as a whole and dividing it into 9 subgroups with shorter ranges. For each participant, the integral of the spectrum corresponding to 194 nm to 1100 nm as well as the integrals of the 9 previously selected subintervals were considered.

**Biological Age Calculation**

In a previous study carried out on a population of 170 non-smoking healthy women, it was possible to evaluate how the X variables (skin measurements) were related to Y (biological age), by ranking the X variables in order of their influence on Y and considering the interpretations and the implications of the sizes and signs of the respective coefficients. The linear regression model for the n variables is:

\[ Y = b_0 + b_1X_1 + b_2X_2 + \ldots + b_nX_n \]

The estimate of \( b \) (matrix notation) was the solution to the system:

\[ b = (X^\top X)^{-1}X^\top Y \]

The results of the measurements showed clear-cut correlations to microrelief, remittance, and plastoelasticity parameters, while electrical capacitance, sebum transmittance, and pH did not show any significant correlation. Based on the sample of the healthy population, it was possible to obtain the coefficients for microrelief, remittance, and plastoelasticity. This allows us to calculate the biological age of the skin.

**RESULTS**

Of 64 women included in the project, 28.12% withdrew at the beginning stage, and the remaining 71.88% completed the entire program. Of these, 63.06% managed to give up smoking and 17.39% consistently reduced the number of cigarettes they smoked every day, while only 19.46% did not change their smoking habits.

**Clinical Evaluation: Spiderming Graphs**

Remembering that a wider area in the graph coincides with more advanced skin aging, the graph of the average values obtained for each participant narrowed as time went by, reaching certain statistically significant values in as little as 6 months from the start of the observations (Figure 3).
Instrumental Evaluation: Biological Age

A complex mathematic algorithm processed the results obtained for each participant and calculated their biological age on this basis. At the end of the program, the study found an average reduction of about 13 years in the biological age of the participants, while, at the beginning of the study, they had presented with an average biological age of 9 years older than their chronologic age (Figure 4).

Dietetic Program

During the project, a dietician had the role of monitoring the participant’s weight and body composition, taking note of any changes in their eating habits, supporting them during the program, and intervening with a diet scheme only if required. A total of 63 candidates turned up for the first visit. When asked whether they feared they would put on weight while giving up smoking, 49.2% confirmed that it was a concern.

Most of the candidates, in a good state of health, had a normal weight and waist circumference, but their total body fat percentage was above average, the probable consequence of a constant lack of physical activity. All the candidates showed that they were well motivated to follow the program, and from the dietetic aspect, they were not following particularly incorrect or unbalanced diets. They were not interested in following a hypocaloric diet to lose weight, but were interested in receiving practical tips about nutrition as well as advice about physical activity. At the end of the first visit, nutritional and lifestyle advice was given to the participants for them to refer to during the program and a food diary to fill in for 1 week of their choice, with the only stipulation that they had stopped smoking or at least significantly reduced the number of cigarettes smoked daily. Between the first visit and the last checkup, intermediate checkups were carried out at 3 and 6 months. A total of 24 candidates turned up for the last checkup.

As for the other measurements, the total percentage of body fat presented an average increase of 2.8% in 25% of the cases. These results show that giving up smoking does not necessarily mean putting on weight. Where there is a tendency to gain weight (eg, for emotional hunger), adopting correct eating habits and correct lifestyles can certainly significantly contribute to controlling or at least reducing such a tendency.

Discussion

Clinical experience teaches that tobacco smoking has a negative effect on the skin. Heavy smokers present clinical signs of early skin aging compared with nonsmokers: parchment-like intensification of lines, dull coloring, and typical purse-like lines around the lips. But what impact does exposure to smoking have on skin disorders, and what is the biochemical mechanism of these effects? Dermatologic research is increasingly focusing on addressing this issue, and many studies have been recently published on this topic. Because smoking is a well-known risk factor for different types of cancer, an interesting case-control study investigated the possible correlation between smoking and skin cancer. The study was performed on a total of 1126 participants, of whom 161 had squamous cell carcinoma (malignant and invasive, metastasizing), 301 had basal cell carcinoma (only locally malignant and invasive, no remote metastases), 125 had melanoma (well-known to be malignant and metastasizing), and 386 served as healthy controls. The habits and exposure to tobacco smoke of all the participants were thoroughly investigated. An association was discovered between active smoking and squamous cell carcinoma, with a higher risk for habitual smokers than for past smokers, while there was no evidence of dose response on the basis of number of cigarettes smoked, just as there was no evidence of an increased risk of melanoma or of basal cell carcinoma in the participants who smoked. Although the possible association between smoking and basal cell carcinoma has never been found in the literature, after re-examining the clinical records of 200 patients who underwent surgical treatment for basal cell carcinoma at the Mayo Clinic in Rochester, Minnesota, it was observed that among the patients with a tumor with a diameter ≤1 cm, 30% were smokers; between 1.1 cm and 2 cm, 42% were smokers; between 2.1 cm and 4.9 cm the percentage of smokers went up to 56%; and >5.0 cm, the percentage was 50%. The authors of the study concluded that cigarette smoking can be associated with an increased prevalence of basal cell carcinomas with a diameter >1 cm. Other skin disorders that have been correlated with smoking are psoriasis, which seems to present more severely in women who smoke compared with those who don’t.
and lupus erythematosus, discoid lupus, and subacute lupus, which smoking makes less responsive to common treatments.11

From a purely aesthetic point of view, it is important to point out that the hair of persons who smoke prematurely turns white and thins out early. In effect, the genotoxic substances contained in cigarette smoke are metabolized in the cells of the hair follicle, where they can damage DNA. A study conducted on guinea pigs overexposed to cigarette smoke for 3 months revealed the appearance of areas of alopecia and pigment reduction compared with the nontreated controls and to guinea pigs who underwent treatment with a chemopreventive agent, N-Acetylcysteine.12 Induced alopecia was of the anagen dystrophic type, so the damage occurred in active growing stage hair. It is interesting to note that the guinea pigs exposed to smoke also developed massive skin atrophy, reduced thickness of the subcutaneous adipose tissue, and reduction in the number of hair follicles. From a cosmetic point of view, for the purpose of prevention, reduction, and recovery of skin damage from nicotine, it is essential to understand the mechanism with which smoking affects the skin.

In an article in *Lancet*, researchers compared the concentrations of the enzyme metalloproteinases 1 in the skin of the gluteal region of smokers and nonsmokers.13 Metalloproteinases 1 damages collagen, which comprises at least 70% of the skin dry weight. In fact, the authors found a statistically significant increase in messenger RNA (mRNA) for metalloproteinases in the skin of smokers compared with nonsmokers. This could be one of the factors responsible for the premature skin aging found in smokers. In addition, Japanese authors investigated the changes in collagen in the metalloproteinases of the extracellular matrix and in the tissue inhibitors of metalloproteinases in cultured human fibroblasts treated with different concentrations of hydrosoluble extracts of tobacco.14 As a positive control they used human fibroblast cultures irradiated with long-wave UV-A-1, since the mechanism of the expression of metalloproteinases mediated by the UV-A-1 is well-defined. Following treatment with extracts of tobacco smoke or with UV-A-1 irradiation, the authors found a significant dose-dependent increase in the expression of mRNA for 1 and 3 metalloproteinases, while no variation was found in the equivalent tissue inhibitors of the metalloproteinases. Type I and III collagen appeared decreased, as did the collagen biosynthesis, significantly reduced by 40.1%. On the other hand, L-ascorbic acid and hydrosoluble vitamin E could prevent the alterations of metalloproteinases 1 induced by both smoke extracts and UV-A-1. These observations suggest that the imbalance of the extracellular matrix components of the connective tissue might represent one of the molecular bases of premature skin aging in smokers. The authors also suggested that this process could be mediated by the reactive oxygen species.

Another molecular mechanism of smoking-induced skin alteration seems to have the effect of inhibiting keratinocytic migration, after exposure to nicotine, with consequent reduction of the skin’s ability to re-epithelialize wounds in persons who are smokers.15 This seems to happen because keratinocyte migration is reduced by the activation, caused by nicotine, of the cholinergic nicotinic receptors present on the keratinocytes.16 In the near future, the identification of these and other molecular damage mechanisms could help to clarify the pathogenetic mechanisms and to better identify the prevention and cure of harmful effects of smoking on the skin. In the meantime, we believe that the clinical observation of damages induced by smoking and the potential reversibility of the precocious signs of aging deserve to be further investigated through standardized clinical evaluations,
photographic documentation (Figure 5), and objective and non-invasive instrumental measurements. Furthermore, the message that we wanted to send out with this campaign was a positive one. Instead of performing a sort of psychological terrorism by listing all the possible illnesses—including the fatal ones—that smoking can cause, we have emphasized the opportunity of improving the appearance of one’s skin simply by quitting smoking.

CONCLUSIONS
This pilot project has not only demonstrated that stopping smoking improves skin conditions and above all the state of skin aging, but for the first time it has also afforded the opportunity of producing data that quantifies this benefit.

Acknowledgment: The “Quitting Smoking Rejuvenates the Skin” campaign is promoted by the Municipality of Milan jointly with other organizations, including Lega Italiana per la Lotta ai Tumori, Manageritalia, and Donne Dermatologhe Italia.

REFERENCES

FORMULARY OF DR. GEORGE C. ANDREWS
Deodorant Powder: Formula #21
• Boric acid – 30.0
• Zinc peroxide – 10.0
• Zinc stearate – 15.0
• Talcum – 45.0
Submitted by Douglas D. Altchek, MD, New York, NY
Common Herbal Remedies, Adverse Reactions, and Dermatologic Effects
Marc S. Micozzi, MD, PhD;1,2 Edmund A. Pribitkin, MD3

ABSTRACT
Herbal remedies (phytomedicines) possess significant biological activity and pharmacologic efficacy. Consequently, they may manifest potential adverse effects and drug interactions. The expansion in sales of herbal remedies has brought products to the marketplace that do not always conform to the standards of safety and efficacy that physicians and patients have come to expect. Relatively few physicians inquire about herbal medicine use, and up to 70% of patients do not reveal their use of herbal medicines to their physicians and pharmacists. All physicians should question patients regarding their use of herbal remedies and document their responses in the medical record. Patients should be aware that potentially limited standardization and quality control, and somewhat circumscribed regulation, may result in variability in content, efficacy, and potential contamination of herbal remedies. Physicians in general, and specifically dermatologists, should be aware of potential adverse reactions related to the use of certain herbal remedies. Specific cautions exist with regard to dermatologic side effects such as contact dermatitis, blisters, urticaria, angioedema, ulceration, photosensitization, and changes in skin pigmentation. (SKINmed. 2010;8:30–36)

Herbal remedies (or herbal medicines) are natural products marketed and regulated as dietary supplements. They contain plant constituents (phytochemicals or, in this context, phytomedicines) as their pharmacologically active components. For some herbal medicines, all of the specific ingredients that may account for their pharmacologic activity(s) are as yet incompletely characterized. While herbal remedies possess many beneficial effects, they may also result in adverse effects or drug interactions.

Recent articles in peer-reviewed medical journals have acknowledged herbal medicine’s importance in the growing field of complementary, alternative, and integrative medicine and have provided a context for clinicians to approach patients regarding the use of herbal medicines.1 Too few physicians query patients regarding their use of herbal medicines, however, and up to 70% of patients do not reveal their use of herbal medicines to their physicians and/or pharmacists.1 Many herbal medications, moreover, are now seemingly randomly added to micronutrient dietary supplements (presumably for marketing and promotional reasons) and may be taken without full awareness by much of the consumer population.

Herbal medicine use is common among surgical patients, as in the general population. For example, reports estimate its prevalence from 22% to 60% among select adult surgical populations and nearly 13% in pediatric surgical patients.1 The use of herbal medicines may increase the risk of adverse effects through several mechanisms, including direct pharmacologic effects, interactions with conventional prescribed drugs, and through the effects of unknown or unlisted contaminants in herbal preparations. The use of polypharmacy, as well as the physiologic alterations characteristic of various medical conditions, moreover, may increase the risk of morbidity and mortality associated with the use of herbal medicines. This review presents data on known and suspected dermatologic side effects of herbal medicines.

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTIONS
Many herb-drug interactions are speculative and remain unproven. Nonetheless, a growing body of scientific literature has highlighted the pharmacokinetic and pharmacodynamic interactions between herbal and prescription medicines.2 When an interaction between an herb and a drug is documented to occur, there is a tendency in the medical literature to hold the herb accountable for the adverse effect although it is just as likely that the adverse effect is due to the drug. When such cases reach the legal arena, however, it is unlikely that drug manufacturers are held accountable in the event of herb-drug interactions.

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Herbal supplements are generally intended to be taken over long periods of time (with the exception, for example, of echinacea and goldenseal \([\text{Hydrastis canadensis}]\)), and enzyme inductions (most notably of the cytochrome P450 \([\text{CYP}]\) isoenzymes) and other interactions may occur. Even a commonly used supplement such as goldenseal has the potential to increase the effects of antihypertensives and calcium channel blockers and to decrease the effects of anticoagulants.

**PHOTOSENSITIZATION EFFECTS**

Numerous herbal medicines may impact the skin and may potentially adversely affect wound healing, particularly in cosmetic procedures involving skin resurfacing. St John’s wort poses a risk of photosensitivity reaction attributed to its hypericin component.³ Concomitant use with other photosensitizing agents such as tetracycline hydrochloride, fluoroquinolones, and sulfonamides should be avoided. Retinoids such as tretinoin and similar dermal irritants should be administered with caution in conjunction with St John’s wort because of the possibility of augmented phototoxicity. Certain medicinal plants of the carrot family \((\text{Apiaceae})\) contain furanocoumarins and can also cause a photodermatitis in humans from sensitization of the skin to UV light. Use of any herbal medicines containing furanocoumarins should be avoided while undergoing cosmetic surgery, during UV light exposure, or in conjunction with other photosensitizing agents or dermal irritants.⁴

**DIRECT PHARMACOLOGIC EFFECTS**

**Garlic**

Garlic \((\text{Allium sativum})\) has been widely promoted as a remedy for colds, coughs, flu, chronic bronchitis, whooping cough, ringworm, asthma, intestinal worms, fever, and digestive, gallbladder, and liver disorders (Figure). Investigators have explored its use as a treatment for mild hypertension and hyperlipidemia. Heavy consumption may lead to elevated clotting times, perioperative bleeding, and spontaneous hemorrhage. Numerous studies have long documented garlic’s irreversible inhibitory effect on platelet aggregation and fibrinolytic activity in humans, which occurs within 5 days of oral administration.⁵

Unlike most of the other herbs discussed in this review, garlic is also a biologically active food with presumed medicinal effects, including possible anticancer effects. Clinical studies of garlic in humans address 3 areas: (1) effect on cardiovascular-related disease and risk factors such as lipids, blood pressure, glucose, atherosclerosis, and thrombosis; (2) protective associations with cancer; and (3) clinical adverse effects. There are multiple clinical studies with promising but conflicting results. There is high consumer usage of garlic as a health supplement.

Scant data, primarily from case-control studies, suggest that dietary garlic consumption is associated with decreased risk of laryngeal, gastric, colorectal, and endometrial cancers and adenomatous colorectal polyps. Single case-control studies suggest that dietary garlic consumption is not associated with breast or prostate cancer. No epidemiologic study has assessed whether using particular types of garlic supplements is associated with any particular benefit that questions the claims made by particular brands on the market.

Cholesterol levels have been related to the use of garlic as well. Thirty-seven randomized trials, all but one in adults, consistently showed that compared with placebo, various garlic preparations led to a small, statistically significant reduction in total cholesterol at 1 month (range of average pooled reductions, 1.2 mg/dL to 17.3 mg/dL). Garlic preparations studied included standardized dehydrated tablets, “aged garlic extract,” oil macerates, distillates, raw garlic, and combination tablets. Statistically significant reductions in low-density lipoprotein levels (range, 0 mg/dL to 13.5 mg/dL) and triglycerides (range, 7.6 mg/dL to 34.0 mg/dL) were
also found. One multicenter trial involving 100 adults with hyperlipidemia found no difference in lipid outcomes at 3 months between persons who were given an antilipidemic agent and persons who were given a standardized dehydrated garlic preparation.

Garlic has a range of biological activities. Twenty-seven small, randomized, placebo-controlled trials, all but one in adults and of short duration, reported mixed (but never large) effects of various garlic preparations on blood pressure outcomes. Most studies did not find significant differences between persons randomized to garlic compared with persons randomized to placebo.

Adverse effects of oral ingestion of garlic are halitosis and body odor. Other possible, but not proven, adverse effects include flatulence, esophageal and abdominal pain, small intestinal obstruction, contact dermatitis, rhinitis, asthma, bleeding, and myocardial infarction. The frequency of adverse effects with oral ingestion of garlic as a food and whether they vary by particular preparations are not established. Adverse effects of inhaled garlic dust include allergic reactions such as asthma, rhinitis, urticaria, angioedema, and anaphylaxis. Adverse effects of topical exposure to raw garlic include contact dermatitis, skin blisters, and ulcerative lesions. Frequency of reactions in inhaled garlic dust or topical exposures of garlic is not established.

The frequency and severity of adverse effects related to garlic should be quantified. Whether adverse effects are specific to particular preparations, constituents, or doses should be elucidated. In particular, adverse effects related to bleeding and interactions with other drugs such as aspirin and anticoagulants warrant further study (Table II).

GINKGO
Ginkgo (Ginkgo biloba) was recognized by the 1994 German Commission E for treatment of cognitive disorders, including dementia, intermittent claudication, and tinnitus or vertigo of vascular or involutional origin. Ginkgo is useful as treatment for Alzheimer disease and improves memory in patients with documented memory impairment. It is included in many geriatric vitamin supplements. Consistent with historical usage, G biloba does not demonstrate improvement in the cognitive function of healthy adults. While ginkgo is well established as an effective treatment for mild dementia and has been demonstrated to improve memory in persons with documented memory impairment, it has been irresponsibly marketed as a generic memory enhancer. A misguided study of ginkgo was conducted using standard tests of memory in patients without cognitive impairment. The subsequent promotion of the study findings has led to great confusion about the benefits of ginkgo.

Reports of spontaneous hyphema, spontaneous bilateral subdural hematomas, fatal intracerebral mass bleeding, and one case of bleeding following laparoscopic cholecystectomy illustrate ginkgo’s possible bleeding potential, theoretically through its inhibitory effect on platelet-activating factor and consequently on platelet aggregation. The elimination half-lives of ginkgo’s constituent terpenoids suggest that its use should be discontinued at least 36 hours before surgery.

GINGER
Ginger (Zingiber officinale) has been used for millennia in China as a digestive aid and to remedy stomach upset, gassy indigestion, bloating, and cramping. Recent studies have demonstrated its benefits as a treatment for nausea during chemotherapy and in motion sickness. Ginger is a potent inhibitor of thromboxane synthetase, arachidonic acid, epinephrine, adenosine diphosphate, and collagen. No cases of bleeding problems have been reported with ginger, and a recent placebo-controlled crossover trial in healthy men showed no effect of 2-g ginger ingestion on bleeding time, platelet count, or platelet function 3 or 24 hours after ingestion. Prolonged or heavy use of ginger has been reported to affect platelet aggregation, however, and may theoretically prolong bleeding times if used long-term. Ginger causes topical irritation.

PLANT SALICYLATES
Salicylates are found in numerous plants and should be used with caution, although some authors have contended that natural sources of salicylates appear to lack aspirin’s effect of inhibiting platelet aggregation. These plants include black cohosh rhizome (Cimicifuga racemosa), meadowsweet flower (Filipendula ulmaria = Spiraea ulmaria), poplar bark and/or buds (Populus spp.), sweet birch bark (Betula lenta, Betula pendula), willow bark (Salix spp.), and wintergreen leaves (Gaultheria procumbens). Other medicinal herbs such as dong quai (Angelica sinensis syn A polymorpha) and danshen (Salvia miltiorrhiza) contain coumarins and their use should be strictly avoided perioperatively (Table I). Herbal medicines such as kava (Piper methysticum), chaparral (Larea divaricata), and germander (Teucrium chamaedrys) have also been associated with liver toxicity. Plant salicylates may cause topical irritation. Capsaicin, a popular remedy for joint pain, made from green and red peppers, may also cause skin irritation due to its effects as a countercurrent irritant.

EPHEDRA
Ephedra, or ma huang (Ephedra sinica, E equisetina, E intermedia), although banned for sale as a supplement by the US Food and Drug Administration (FDA) since April 12, 2004, may still be obtained through various means. Ephedra has been used by millions of persons for weight loss, but it was also inappropriately used as a performance enhancer—in the latter case, leading
it to be listed on numerous autopsy reports as contributory to several fatalities among otherwise healthy individuals. An FDA-commissioned report in 2003 stated in its final ruling that 5 deaths could be directly attributed to ephedra. To put this number in perspective, the American Herbal Products Association reports that about 12 to 17 million people took ephedra in 1999, their latest numbers. The Nutrition Business Journal estimated that 2002 ephedra sales were $1.25 billion. These fatality reports led to ephedra being taken off the market in 2004, although the ban didn’t affect sales of over-the-counter cold medications such as decongestants, which often contain ephedrine in synthetic form. Such over-the-counter medications, however, must now be obtained from behind the pharmacy retail counter and sales must be registered and amounts restricted.

Ephedra causes dose-dependent increases in blood pressure and heart rate through the sympathomimetic effects of its predominant active component, ephedrine, and other constituent alkaloids, including pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine. Use of ephedra by prospective patients may complicate the perioperative administration of vasopressors, leading to hypertension, palpitations, tachycardia, seizure, and stroke. Ephedra may cause development of hypersensitivity myocarditis. It may result in life-threatening hyperpyrexia, hypertension, and coma when used in association with monoamine oxidase inhibitors. Concomitant use of ephedra with oxytocin or ephedra with ergot alkaloids may result in hypertension. Although ephedra is quickly cleared (elimination half-life, 5.2 hours), its use should be avoided, most certainly perioperatively.7

**Licorice**

Licorice (*Glycyrrhiza glabra*) root consumption may also increase hypertension and may result in hypokalemia. Case reports have documented instances of licorice-induced pseudoaldosteronism, hypokalemic myopathy, and hypokalemia-induced cardiac arrest. Herbal stimulant laxatives and herbal diuretics may also reduce serum potassium and should be used with caution in the perioperative period.

**Kava**

Kava preparations represent an herbal alternative to synthetic anxiolytics and tranquilizers and are frequently found in herbal beverages. In 2002, many European countries suspended kava sales following reports of severe and even fatal liver toxicities, although the attribution of this finding specifically to kava remains controversial. Kava has been well accepted for its use as a muscle relaxant and sleep inducer. After its use by approximately 70 million people, however, kava was claimed to manifest occasional severe liver toxicity (a situation also not uncommon with many prescription and over-the-counter drugs). This circumstance led to the question of whether kava should be banned as an effective treatment for anxiety. Or could a responsible approach to risk-benefit be developed, as with other antianxiety and sedative treatments that manifest side effects? A case-by-case analysis by researchers found alternative explanations for persons taking

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**Table I. Medicinal Plants Associated With Increased Risk of Bleeding**

<table>
<thead>
<tr>
<th>Coumarin-containing plants</th>
<th>Salicylate-containing plants</th>
<th>Plants that inhibit platelet function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danshen (<em>Salvia miltiorrhiza</em>)</td>
<td>Black cohosh rhizome (<em>Cimicifuga racemosa</em>)</td>
<td>Bromelain (<em>Ananas comosus</em>)</td>
</tr>
<tr>
<td>Dong quai (<em>Angelica sinensis</em> syn. <em>A polymorpha</em>)</td>
<td>Meadowsweet flower (<em>Filipendula ulmaria</em> = <em>Spiraea ulmaria</em>)</td>
<td>Cayenne fruit (<em>Capsicum frutescens</em>)</td>
</tr>
<tr>
<td>Horse chestnut bark (<em>Aesculus hippocastanum</em>)</td>
<td>Poplar bark and/or buds (<em>Populus</em> spp.)</td>
<td>Chinese skullcap root (<em>Scutellaria baicalensis</em>)</td>
</tr>
<tr>
<td>Sweet clover plant (<em>Melilotus officinalis</em>, <em>Melilotus alba</em>)</td>
<td>Sweet birch bark (<em>Betula lenta</em>, <em>Betula pendula</em>)</td>
<td>Dan shen root (<em>Salvia miltiorrhiza</em>)</td>
</tr>
<tr>
<td>Sweet vernal grass leaves (<em>Anthoxanthum odoratum</em>)</td>
<td>Willow bark (<em>Salix</em> spp.)</td>
<td>Feverfew (<em>Tanacetum parthenium</em>)</td>
</tr>
<tr>
<td>Sweet-scented bedstraw plant (<em>Galium triflorum</em>)</td>
<td>Wintergreen leaves (<em>Gaultheria procumbens</em>)</td>
<td>Garlic (<em>Allium sativum</em>)</td>
</tr>
<tr>
<td>Tonka bean seeds (<em>Dipteryx odorata</em>, <em>Dipteryx oppositifolia</em>)</td>
<td></td>
<td>Ginger rhizome (<em>Zingiber officinale</em>)</td>
</tr>
<tr>
<td>Vanilla leaf leaves (<em>Trilisa odoratissima</em>)</td>
<td></td>
<td>Ginseng, Asian (<em>Panax ginseng</em>)</td>
</tr>
<tr>
<td>Woodruff plant (<em>Asperula odorata</em>)</td>
<td></td>
<td>Onion (<em>Allium cepa</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papain from leaves and unripe fruit (<em>Carica papaya</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reishi fruit bodies (<em>Ganoderma lucidum</em>)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Turmeric root (<em>Curcuma longa</em>, <em>Curcuma aromatica</em>)</td>
</tr>
</tbody>
</table>
kava who experienced liver toxicity and concluded that the kava ban was highly questionable.\textsuperscript{10} Nonetheless, many retailers have voluntarily taken kava off the shelves.

Kava may still be obtained through traditional herbalists and through online distributors. Kavalactones in kava are believed to achieve their sedative-hypnotic effect by potentiating γ-aminobutyric acid inhibitory neurotransmission. Kava’s potential for interaction with anesthetic agents warrants its discontinuation at least 24 hours before surgery. A side effect of a characteristic reversible “kava dermatopathy” may develop if the herb is continuously used in high doses for several months. Symptoms include reddened eyes, scaly skin eruptions, and a yellowish discoloration of the skin, hair, and nails attributed to two yellow pigments in the plant.\textsuperscript{11}

A characteristic yellowish discoloration of the skin, carotenodermia, may also result from excessive ingestion of β-carotene supplements or foods containing high levels of β-carotene, such as carrot juice, or high levels of carotenoids in general, such as tomato juice.\textsuperscript{12}

**PLANT ESTROGENS (PHYTOESTROGENS) AND ESTROGENIC EFFECTS**

Many perimenopausal and postmenopausal women have turned to herbal remedies following the adverse outcomes of hormone replacement therapy reported by the Women’s Health Initiative.\textsuperscript{13} More than 500 plant species including soy (Glycine max) contain phytoestrogens, naturally occurring substances functionally similar to estradiol. Although much less potent than estradiol, phytoestrogens may potentiate or antagonize estrogen effects. Accordingly, these compounds may contribute to changes in skin pigmentation following plastic surgery procedures such as dermabrasion, laser skin resurfacing, microdermabrasion, and scar revisions. Use of some phytoestrogens in conjunction with estrogen replacement therapies, moreover, may result in symptoms such as nausea, bloating, hypotension, breast fullness or tenderness, migraine headaches, and edema. Among the more commonly used phytoestrogen-containing herbs are dong quai, red clover (Trifolium pratense), alfalfa (Medicago sativa var. italicca), licorice, and black cohosh.

**ST JOHN’S WORT**

St John’s wort (Hypericum perforatum) is approved for use in Germany for the treatment of mild depressive states, anxiety, nervous unrest, and sleep disorders. Although one multicenter trial has not confirmed its efficacy in the treatment of major depression, St John’s wort remains a popular short-term treatment for mild to moderate depression.\textsuperscript{7} St John’s wort is historically considered an effective treatment for mild to moderate depression. The negative study tested St John’s wort on patients with depression severe enough to warrant hospitalization. A major problem is that there has been no practical experience on what the appropriate St John’s wort dosage or regimen might be in such patients. The study found St John’s wort to be ineffective (the conventional antidepressant was also ineffective), and patients were deprived of needed mainstream psychotherapy when there was initially no plausible reason to believe that St John’s wort might be appropriately used in this population.

It is important not to ignore “historic use” when moving herbal remedies into the mainstream and conducting mainstream biomedical research on herbs. Another study reported in spring 2002 showed no difference between placebo and conventional medication in severely depressed patients who were also given 14 to 16 hours of intensive personal care from highly trained mental health professionals.\textsuperscript{7} Perhaps the real message for severe depression is that neither herbs nor drugs can effectively substitute for “hands-on” therapeutic care.

St John’s wort elevates mood by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons. St John’s wort induces the CYP isoform 3A4, however, and may thereby alter the pharmacokinetics of many commonly prescribed drugs including oral contraceptives, theophylline, alfentanil, midazolam hydrochloride, lidocaine, calcium channel blockers, and serotonin receptor antagonists. Reduced cyclosporine levels in St John’s wort users have been implicated in organ transplant rejection. The CYP isoform C is also induced by St John’s wort and can decrease levels of warfarin and nonsteroidal anti-inflammatory drugs. Finally, St John’s wort can decrease digoxin levels by inducing the P-glycoprotein transporter. St John’s wort’s pharmacokinetics suggest that its use should be stopped at least 5 days before surgery and postoperatively discontinued should patients require anticoagulation or immunosuppression. In patients whose affected drug levels are stabilized while taking St John’s wort, however, sudden discontinuation of the herbal remedy can result in elevation of drug levels and must be cautiously approached. St John’s wort may induce photosensitivity.\textsuperscript{14}

**CONTAMINANTS IN HERBAL MEDICINES**

The expansion of sales of herbal therapies has brought products to the marketplace that do not conform to the standards of safety and efficacy that physicians and patients expect. The Dietary Supplement Health and Education Act of 1994 (DSHEA) classified herbs as “dietary supplements,” and made the FDA responsible for demonstrating that a product is unsafe before it may be removed from the market. Because there is no direct proactive FDA regulation of herbs as there is for drugs, there is limited control over product standardization, either in terms of potency.
or contamination. The Good Manufacturing Practices (GMPs) guidelines mandated by the 1993 DSHEA legislation were not implemented by the FDA until 2007, 14 years later! Therefore, even potentially safe and effective herbal remedies without the direct adverse effects or conventional drug interactions outlined above may show inconsistencies in their production.

Studies have demonstrated contamination of herbal medicines with potent synthetic medications. Systematic reviews of Chinese herbal medicines have revealed reports of contamination with chloramphenicol, dexamethasone, phenytoin, digitalis, and hypoglycemic agents. Some herbal remedies may also contain hazardous levels of arsenic, mercury, and lead, all of which may manifest in dermatologic effects. Not all herbal extracts are the same, moreover, and commercially available extracts vary greatly in their quality. Variability in ginseng products, for example, showed that preparations contained as little as 11% and as much as 328% of the labeled concentrations of active ingredients. The United States Pharmacopeia (USP) and National Formulary (NF, currently USP28-NF23) works closely with the FDA and has published authoritative standards for numerous botanical supplements. Physicians may advise patients to purchase products carrying NF or USP on their labels. Alternately, patients may be advised to select manufacturers from countries, including those in Europe as well as Japan and Australia, where herbal medicines must, by law, be made according to the code of pharmaceutical GMP.

**CONCLUSIONS**

Herbal medicines continue to be used by many patients. All patients should be asked about the use of herbal medicines and should have their responses documented in the medical record. Studies have shown, however, that some patients do not adequately report their use of alternative therapies even when directly questioned. Physicians should, therefore, be aware of potential adverse reactions associated with herbal medicine use. Physicians and pharmacists should caution patients that lack of standardization, quality control, and regulation may result in variability in herbal content, efficacy, and possible contamination.

Well-controlled clinical trials are needed to better delineate herb-drug interactions, yield valuable new herbal medicines, or validate ancient remedies. Each physician, however, should consider advising patients to temporarily discontinue their use of herbal therapies prior to surgical procedures and general anesthesia. Few guidelines as to the specific schedule for discontinuation of herbal therapies exist. Physicians should consider individual patient circumstances when offering such advice, however, especially if discontinuation of herbal treatments may result in withdrawal symptoms or in fluctuations of currently stabilized conventional drug levels.

**REFERENCES**

8. Bordia A, Verma SK, Srivastava KC. Effects of ginger (Zingiber officinal Rosc.) and fenugreek (Trigonella foenum-graecum L)

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**Table II. Medical Plants and Their Dermatologic Side Effects by Topical and Oral Administration**

<table>
<thead>
<tr>
<th>Plant</th>
<th>Administration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apiaceae (carrot family)</td>
<td>Oral</td>
<td>Carotenodermia, photosensitization</td>
</tr>
<tr>
<td>Epedra (Chinese Ma huang)</td>
<td>Oral</td>
<td>Hyperpyrexia</td>
</tr>
<tr>
<td>Garlic</td>
<td>Oral</td>
<td>Angioedema, dermatitis, urticaria, topical, blisters, contact dermatitis, ulcers</td>
</tr>
<tr>
<td>Ginger</td>
<td>Topical</td>
<td>Irritation</td>
</tr>
<tr>
<td>Kava kava</td>
<td>Oral</td>
<td>“Kava dermatopathy”</td>
</tr>
<tr>
<td>Plant salicylates</td>
<td>Topical</td>
<td>Irritation</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td>Oral</td>
<td>Changes in pigmentation</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Oral</td>
<td>Photosensitization</td>
</tr>
</tbody>
</table>


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) Ingestion of which of the following may contribute to hyperpigmentation following a plastic or dermatological surgery procedure?
   a. Alfalfa.
   b. Carrot juice.
   c. Garlic.
   d. Ginger.
   e. None of these.

2) Signs/symptoms of kava dermatopathy include:
   a. reddening of the eyes.
   b. scaly skin eruptions.
   c. yellow discoloration of the skin.
   d. yellow discoloration of hair and nails.
   e. All of these.

3) A characteristic yellow discoloration of the skin (excluding the sclera) may occur in individuals who ingest excessive amounts of:
   a. arugula.
   b. onions.
   c. soy milk.
   d. tomato juice.
   e. yams.

4) Which of the following has been shown in multiple randomized trials to reduce serum cholesterol levels?
   a. Dong quai.
   b. Garlic.
   c. Ginger.
   d. Ginkgo.
   e. Licorice.

5) Which of the following elevates mood by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons?
   a. Ephedra.
   b. Garlic.
   c. Ginkgo.
   d. Ginseng.
   e. St John’s wort.

ANSWERS TO SELF TEST REVIEW QUESTIONS:
   a  e  d  b  a
Onychomycosis: An Asian Perspective

Virendra N. Sehgal, MD;1,2 Govind Srivastava, MD;2 Sunil Dogra, MD, DNB;3 Anuradha Chaudhary, MD;4 Tulsi Adhikari, MSC, PhD5

ABSTRACT

Extrapolated data from epidemiologic studies of onychomycosis unique to Asia have produced intriguing revelations and opened new lines of inquiry; however, the usefulness of this research is compromised by lack of uniformity in data collection. It is proposed that a common protocol be constructed to facilitate the study of onychomycosis, in Asia, as elsewhere, the most common disease of the nails. (SKINmed. 2010;8:37–45)

Onychomycosis is a widespread nail dystrophy that constitutes a major public health problem on the Asian continent. While observed in children and adults of both sexes, it is found most frequently in men and in patients older than 60 years. Primary onychomycosis caused by nail pathogens invading the healthy nail plate is as common as secondary onychomycosis, in which a preexisting disorder facilitates invasion by fungi. Onychomycosis is the most common of all nail disorders, accounting for up to 50% of all onychopathies and about 30% of all cutaneous fungal infections. The incidence is particularly high in warm and humid climates, such as in India. Onychomycosis is as much a psychosocial problem as a medical issue. In addition to serving as a reservoir of pathogens that may spread to other sites, onychomycosis can impact patients’ quality of life.

Because of the importance of the subject and its increasing prevalence on the continent, it would be useful to organize a uniform protocol for the evaluation of research in onychomycosis in Asia. Such a protocol would facilitate further medical studies and underscore the public health importance of this condition for policy makers.

EPIDEMIOLOGY

Although detailed studies on the epidemiology of onychomycosis in Asian countries are limited, they imply that the prevalence of onychomycosis is lower than in Western countries. Factors that increase the prevalence of onychomycosis include increasing age; male sex; genetic factors; underlying conditions such as diabetes, immunodeficiency, peripheral arterial disease, and psoriasis; environmental and behavioral factors such as sporting and religious practices; and certain professions. In one study, the prevalence of onychomycosis in tropical countries (3.8%) was lower than in subtropical countries and countries in the temperate zone. In another study from Indonesia, the average incidence of onychomycosis among fungal disease ranged from 3.5% to 4.7%. Researchers recorded the condition as more prevalent in young adult men than in women (82% vs 18%). In this study, the average female patient was a decade older than the male patients. Other studies from India, however, did not show such a drastic contrast between men and women. Women outnumbered men (1:5–2:1) in Indonesia and Pakistan, while the ratio was nearly equal in a study from Taiwan. These findings contrast with those in European countries, while in Brazil, researchers conducting an extensive study that lasted 3 years and 9 months, recorded a female ratio of more than 3:1. The salient features of some important studies in onychomycosis from Asian countries and other parts of the world have been shown in the literature (Table 1).

CLINICAL CONNOTATION

Presenting complaints are largely related to the disfigurement of the nails, although patients may seek treatment because of pain or infection. Toenails are involved in the majority of cases. This may be partly because toenails grow 50% to 66% more

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slowly than fingernails, giving the fungus more time to establish infection. The variations in symptoms can be due to the clinical type of the nail affection. Researchers\(^1\) have recorded certain predisposing habits of patients in the Indian subcontinent, such as walking barefoot, wearing ill-fitting shoes, nail-biting (onychophagia), and working with chemicals. Among the types of onychomycosis, distal and lateral subungual onychomycosis (DLSO; Figure 1) appear to be most frequent in Asian countries, followed by candidal onychomycosis, superficial white onychomycosis (SWO; Figure 2), proximal subungual onychomycosis (PSO; Figure 3), and total dystrophic (destructive) onychomycosis (TDO; Figure 4).\(^1,10\) Depending on the affection of nails of the hands or the feet, however, a minor variation can often be observed.\(^2,13\) Further, various permutations and combinations may occur in a single patient; this often depends on the occupation of the patient.\(^1\) Researchers\(^16\) recorded the association of the disease with trauma (14.14%), chronic paronychia (12.22%), diabetes (4.4%), leprosy (2.2%), and psoriasis (1.1%). They also stressed the significance of fungal infections elsewhere in the body, hyperhidrosis (24%) and hypothyroidism/hyperthyroidism, as important associated conditions. Investigators in Taiwan,\(^11\) however, in their study of 182 patients, recorded TDO to be the second most common form of onychomycosis. A similar observation was recently made by researchers\(^16\) in a study from central India. In Thailand, after observing 2000 patients at an outpatient dermatology clinic, researchers\(^23\) recorded fungal diseases in only 6% of patients (119), 33 of whom had onychomycosis. Researchers\(^24\) studied fungal infections of the feet in athletes (soccer players) and nonathletes of corresponding age and sex groups and found a paradoxically low incidence of tinea pedis and onychomycosis in the athletes.

Immunosuppression, poor peripheral circulation, nail trauma, diabetes mellitus, poor hygiene, and autoimmunity can often be found in patients with onychomycosis.\(^1,25\) In a study of the prevalence of skin disorders in patients with human immunodeficiency virus (HIV) infection in Bangkok, researchers\(^26\) found that 9.3% of patients had onychomycosis. In a study in India, researchers\(^27\) recorded a significantly higher prevalence of onychomycosis in the diabetic than in the control group (17% vs 6.8%), and toenail affliction was 4 times higher in diabetics in comparison with fingernails. Even where onychomycosis is no more common in diabetics than in the general population, it poses a greater risk because of the possible sequelae.

### POTASSIUM HYDROXIDE MOUNT AND ISOLATION OF FUNGI IN VITRO/CULTURE

The demonstration of the causative fungi of onychomycosis has been the ultimate step in confirmation of the diagnosis. Mycologic examination is currently the preferred diagnostic method, despite a false-negative rate of 30%. Yet all patients with a positive result on potassium hydroxide mount do not have positive fungal culture results. Certain specimens that are negative for fungal elements in direct microscopy, however, may yield positive fungal culture results. Researchers\(^17\) studied 439 of 878 nail specimens that were positive for fungal elements on direct microscopy, 35 of which subsequently remained fungal culture–negative (a very high positive culture result rate). Notably, of the remaining 439 specimens that were negative for fungi on direct microscopy, as many as 86 were culture-positive. Thus, both direct microscopy and fungal culture are recommended for diagnosis.\(^1,10,17,28-31\) The prevalence of the galaxy of fungi isolated from nail clippings recorded in several Asian studies is given in Table III. There is a wide variety of causative fungi from one geographic area to another,\(^32-34\) as well as from different studies in the same area.\(^35-40\) Climate, hot and humid or cold and dry, influence the pathogenicity of the causative fungi. Researchers\(^35\) reiterated that changing climate conditions and human behavioral patterns are critical to the habitat and growth/spread of different fungi. They found that dermatophytes were influenced by the changing climate and that yeasts were more endemic in Hong Kong. Some
investigators\(^1\) found a major pathogen of onychomycosis to be dermatophytes in diabetic men and Candida in diabetic women. Others\(^1\) reported that the spectrum of fungi that cause onychomycosis and concomitant superficial fungus infections in other parts of the body of the same patients can sometimes be different, meaning that they may have been acquired in different seasons that favor the various fungi. This is especially true in the geographic areas of Asia where extremes of seasons occurs (eg, Delhi, India). In contrast, in the temperate Western countries (eg, the United Kingdom and Canada), major pathogens that cause onychomycosis were dermatophytes (80%–90%), followed by Candida (5%–17%) and nondermatophytic molds (2%–3%).\(^{41,42}\) In southern Europe (eg, Italy and southern Greece) where there is a warm climate, the proportion of dermatophytes decreases (40%–68%) and that of Candida increases (21%–55%).\(^{33,44}\) In Asian and Middle Eastern countries (eg, Iran, Pakistan, and India),\(^45\) the proportion of dermatophytes further declines (40%–48%), and Candida is the major gainer (43%–46%), along with nondermatophyte molds (8%–11%). With more hot and humid environments, as in African countries such as Libya, onychomycosis is mainly caused by Candida (84%), while dermatophytes account for around 14% of cases.\(^46\)

Recent epidemiologic surveys on onychomycosis show that dermatophytes are the most common isolates in all geographic zones, whereas a higher incidence of Candida fingernail infections is generally found in more tropical climates. In the Achilles project\(^47\) with more than 96,000 patients in 20 European countries, onychomycosis was diagnosed in 29.6% of the population. In more than 70% of the diagnoses confirmed by culture, dermatophytes were the fungus that caused infection. In the Asian Achilles project, surveys of patients from China, Hong Kong, the Philippines, Korea, Indonesia, and Taiwan revealed that dermatophytes represented the majority of onychomycosis infections: Trichophyton rubrum was isolated in 53.6% of cases and Trichophyton mentagrophytes was isolated in 14.9% of cases. There appeared to be a higher incidence of dermatophytes in subtropical/temperate areas as well.\(^47\) Newer diagnostic approaches include calcofluor, which stains fungi in nails, and molecular genetic techniques for species recognition (eg, restriction fragment length polymorphism).

**ONYCHOMYCOSIS AND HIV**

Cutaneous fungal infections, including onychomycosis, are an important source of morbidity in individuals infected with HIV. Although it is not among the most severe infections that affect HIV-positive patients, it has a unique clinical presentation and tends to be more extensive and refractory to treatment. Onychomycosis is most likely to develop in HIV-positive individuals when the CD4 count drops below 450. Therefore, the presence of onychomycosis, in particular proximal SWO, may be a visible marker of the degree of immunodeficiency. The clinical presentation of onychomycosis consist of DLSO, SWO, and PSO in descending order in most of the published reports.\(^48\) Among the causative fungal organisms, the most common is dermatophytes followed by nondermatophyte molds or Candida species. Among dermatophytes, T rubrum is the most commonly isolated pathogen.
Table I. Epidemiologic: Salient Features in Some Important Asian Studies Compared With Other Parts of the World

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>CENTRAL INDIA</th>
<th>AIIMS</th>
<th>MAORAS (tropics)</th>
<th>NEW DELHI</th>
<th>MALAYSIA</th>
<th>SOUTHERN THAILAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for inclusion</td>
<td>Nail abnormality and suspected abnormality</td>
<td>Abnormal nails</td>
<td>Diagnosed/ suspected mycosis</td>
<td>Nail changes</td>
<td>Clinically diagnosed as onychomycosis</td>
<td>Established onychomycosis and positive culture results</td>
</tr>
<tr>
<td>Presenting complaints</td>
<td>Nail abnormalities and suspected onychomycosis</td>
<td>Abnormal nails</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Nail abnormalities</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>6 months</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Socioeconomic factors</td>
<td>Age, sex, occupation</td>
<td>Age, sex</td>
<td>Age, sex</td>
<td>Age, sex, occupation, income, education, hobbies, work habit</td>
<td>–</td>
<td>Age, sex, occupation</td>
</tr>
<tr>
<td>Hobbies and work habits</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Habit of cutting nails themselves, nail biting, wearing shoes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Family history of fungal infection</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Family history of fungal infection, contact with cattle and pets</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>History of trauma</td>
<td>Trauma, chronic paronychia, diabetes, leprosy, and psoriasis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Cellulitis on leg or foot, hepatitis B, hepatitis C, diabetes</td>
</tr>
<tr>
<td>Climate</td>
<td>–</td>
<td>–</td>
<td>High temperature and humidity and rain fall</td>
<td>–</td>
<td>Geographic differences in epidemiologic and etiology of onychomycosis</td>
<td>–</td>
</tr>
<tr>
<td>Site of nail affliction</td>
<td>Given</td>
<td>Correlated</td>
<td>Given</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fasting and postprandial blood sugar test</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Done</td>
<td>–</td>
</tr>
<tr>
<td>Potassium hydroxide examination</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Done</td>
<td>Done</td>
<td>–</td>
</tr>
<tr>
<td>Clinical variants of onychomycosis (DLSO, TDO, SWO, paronychia of nailfold–frequency)</td>
<td>Given</td>
<td>–</td>
<td>–</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
<tr>
<td>Associated and/or concomitant diseases</td>
<td>–</td>
<td>–</td>
<td>Considered</td>
<td>Considered</td>
<td>–</td>
<td>Considered</td>
</tr>
<tr>
<td>Frequency of isolation of fungi on culture–T. rubrum, etc</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
<td>Given</td>
</tr>
</tbody>
</table>

Abbreviations: DLSO, distal and lateral subungual onychomycosis; PSO, proximal subungual onychomycosis; SWO, superficial white onychomycosis; TDO, molds are the prevailing pathogens in Mediterranean and tropical countries (including Taiwan) with a warmer and more humid climate.
The major pathogens in temperate Western countries are dermatophytes. Candida and nondermatophyte fungi are the prevailing pathogens in Mediterranean and tropical countries (including Taiwan) with a warmer and more humid climate. Abbreviations: DLSO, distal and lateral subungual onychomycosis; PSO, proximal subungual onychomycosis; SWO, etc.

<table>
<thead>
<tr>
<th>DENMARK</th>
<th>TURKEY</th>
<th>ITALY</th>
<th>GREECE</th>
<th>TAIWAN</th>
<th>NORTHEAST BRAZIL</th>
<th>HONG KONG</th>
<th>PAKISTAN LAHORE</th>
</tr>
</thead>
</table>

- Microscopy and histopathology
- Abnormal nail
- Age, sex, height, weight, ethnic background
- Absent, present
- Diabetes mellitus, human immunodeficiency virus
- Environmental conditions cause higher isolation rates of dermatophytes
- Concomitant diseases such as tinea corporis, T. manuum

<table>
<thead>
<tr>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
<th>Seen</th>
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- Dermatophytes
- Concomitant diseases such as tinea corporis, T. manuum
- Tinea unguium, tinea pedis
- Total dystrophic (destructive) onychomycosis.

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- Clinical, microscopic, culture examination
- Clinical, microscopic, and culture examination
- Work habits--wet, footwear, synthetic tights
- Work habits--wet
- Family history of tinea unguium
- Family history

- Abnormal nails
- Abnormal-appearing nail, histopathologic examination
- Abnormal nails
- Abnormal nails
- Abnormal nails
- Abnormal nails
prevalence of onychomycosis in HIV-infected patients was reported to be 9.3%\(^3\) in Thailand and 9.9%\(^3\) in Malaysia.

**CONCLUSIONS**

Detailed studies of the incidence, presentation, diagnosis and treatment of onychomycosis in Asia can further illuminate and help alleviate this important public health problem. While there is a ubiquitous occurrence of the condition, there is a need for different strategies in therapeutic and preventive measures especially designed for different geographic areas. Nonuniform assessment, such as varying methods of sampling for potassium hydroxide mount and culture, variable clinical criteria for diagnosis, and limited availability of newer diagnostic techniques, compromise the usefulness of epidemiologic data related to onychomycosis. These conditions underline the need for a uniform protocol to facilitate data collection and ultimately produce future studies that provide germane comparisons across Asia.

**REFERENCES**

Table III. Fungi Recorded From Prominent Asian Studies

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NEW THERAPY UPDATE
William Abramovits, MD; Aditya K. Gupta, MD, Section Editors

Veregen (Sinecatechins Ointment) 15%
William Abramovits, MD;1,2,3 Aditya K. Gupta, MD4,5

DESCRIPTION
In October 2006, the US Food and Drug Administration (FDA) approved the use of kunecatechins ointment (Veregen) for the treatment of external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years and older. Marketing (Bradley Pharmaceuticals, Inc. Fairfield, NJ) started in January 2007 (currently marketed by PharmaDerm, a division of Nycomed US, Melville, NY). The ointment (manufactured by C.P.M. Contract Pharma GmbH, Feldkirchen-Westerham, Germany) is a botanical drug product for topical use. The drug in it is sinecatechins, formerly kunecatechins, a proprietary, partially purified fraction of the water extract of green tea leaves from Camellia sinensis (L.) O Kuntze and is a mixture of catechins and other green tea components. Catechins constitute 85% to 95% (by weight) of the total drug substance, which includes more than 55% of Epigallocatechin gallate; other catechin derivatives such as epicatechin, epigallocatechin, and epicatechin gallate; and some minor catechin derivatives, ie, gallo catechin gallate, gallo catechin, catechin gallate, and catechin. It also contains gallic acid, caffeine, and theobromine, which together constitute about 2.5% of the drug substance. The remaining drug substance contains undefined botanical constituents of green tea leaves.

Each gram of the ointment contains 150 mg of sinecatechins in a water-free ointment consisting of isopropyl myristate, white petrolatum, white wax, propylene glycol palmitostearate, and oleyl alcohol.1

CLINICAL PHARMACOLOGY
The mode of action of sinecatechins ointment in the clearance of genital and perianal warts is unknown. Catechins are bioflavonoids, polyphenols linked to evidence of fighting tumors as well as enhancing immune system function. In vitro, sinecatechins have antioxidative activity; however, the clinical significance of this is unknown. Antiviral and antiproliferative actions are matter for speculation.

The pharmacokinetics of topically applied sinecatechins ointment has not sufficiently been characterized. Data suggest that systemic exposure to catechins after repeat topical application of sinecatechins 15% ointment is likely to be less than observed after a single oral intake of 400 mL of green tea.

CLINICAL STUDIES
FDA approval was based on the pooled results of two randomized, double-blind, vehicle-controlled phase III clinical studies that enrolled a combined 1005 patients to investigate the safety and efficacy of sinecatechins 15% ointment in the treatment of immunocompetent patients 18 years or older with external genital and perianal warts. Participants applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new occurring during treatment). During both studies, the median baseline wart area was 51 mm² (range, 12 mm² to 585 mm²) and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16 for all randomized patients dispensed medication. Of the patients treated with the sinecatechins 15% ointment, 53.6% reached complete clearance vs 35.3% taking placebo.

Median time to complete wart clearance in the two trials was 16 weeks and 10 weeks, respectively. The recurrence rate of external genital and perianal warts after treatment in patients with complete clearance is unknown.

In a recent study of 503 patients randomized to receive Polyphe non E (MediGene AG, Munich, Germany), a proprietary extract of green tea leaves 15%, 10% polyphenols/catechins, or placebo ointment was self-applied 3 times a day to all visible anogenital warts until complete clearance or up to 16 weeks, with recurrence evaluated at 12-week treatment-free follow-up for patients with complete clearance. A total of 53% cleared completely on the 15% ointment, 51% on the 10% ointment, and 37% on...
In the study of 503 patients taking Polyphenon E ointments, the majority of adverse events were mild or moderate application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, meatal stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

A total of 266 of 397 (67%) patients in the sinecatechins 15% ointment group had either a moderate or a severe reaction that was considered probably related; of these, 120 (30%) patients had a severe reaction. Severe reactions occurred in 37% (71 of 192) of women and in 24% (49 of 205) of men. The percentage of patients with at least one severe related adverse event was 26% (86 of 328) for patients with genital warts only, 42% (19 of 45) in patients with both genital and perianal warts, and 48% (11 of 23) of patients with perianal warts only. Phimosis occurred in 3% of uncircumcised men (5 of 174) treated with sinecatechins 15% ointment and in 1% (1 of 99) in vehicle. The maximum mean severity of erythema, erosion, edema, and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash, and staphylococccmia. In a dermal sensitization study of sinecatechins 15% ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 of 209 patients (2.4%) under occlusive conditions. The ointment is contraindicated in individuals with a history of sensitivity reactions to any of its components. In case of hypersensitivity, treatment should be discontinued. Its use on open wounds should be avoided.

In the study of 503 patients taking Polyphenon E ointments, the majority of adverse events were mild or moderate application site reactions that declined during continued treatment. In the study with 1400 patients, the majority of adverse events were also reported as mild to moderate, of short duration, and on application site only. Sinecatechin 15% ointment has not been evaluated for the treatment of urethral, intravaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions. Overdosage with sinecatechins 15% ointment has not been reported.

In the clinical trials, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19 of 397). These included application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, mental stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

The maximum recommended human dose (MRHD) of sinecatechins 15% ointment was set at 3 times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg sinecatechins for the animal multiple of human exposure calculations presented in its labeling. Dose multiples were calculated based on the human equivalent dose.

In an oral (gavage) carcinogenicity study, sinecatechins were administered to p53 transgenic mice at doses up to 500 mg/kg/d (22-fold MRHD) for 26 weeks. Treatment was not associated with increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Sinecatechins 15% ointment has not been evaluated in a dermal carcinogenicity study.

Sinecatechins 15% ointment is rated Pregnancy Category C. Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of sinecatechins during the period of organogenesis (gestational days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment-related effects on embryo-fetal development or teratogenicity at doses of up to 1000 mg/kg/d (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 mg/kg/d and 36 mg/kg/d of sinecatechins during organogenesis (gestational days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment-related effects on embryo-fetal development were noted at 4 mg/kg/d (0.7-fold MRHD). There was no evidence of teratogenic effects at the evaluated doses. A combined fertility/embryo-fetal development study using daily vaginal administration of
Sinecatechins 15% ointment is indicated for the topical treatment of external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years and older. Safety and efficacy in immunosuppressed patients have not been established, nor has it been established for the treatment of external genital and perianal warts beyond 16 weeks or for multiple treatment courses.

Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as the sinecatechins 15% ointment is excreted in breast milk.

SAFETY
Safety and efficacy in pediatric patients have not been established. Seven patients (1.4%) older than 65 years were treated with sinecatechins 15% ointment in clinical studies, not enough to determine whether older persons respond differently than younger persons.

INDICATIONS AND ADMINISTRATION
Sinecatechins 15% ointment is a brown ointment supplied in aluminum tubes containing 15 g and 30 g of ointment per tube.

COMMENTS
Human papilloma virus (HPV) infections remain the most common sexually transmitted disease of viral etiology. Viral DNA studies utilizing polymerase chain reaction methodology suggest a prevalence of 50% to 75% among sexually active individuals. Most infected individuals do not experience HPV-associated disease, and the infection usually spontaneously regresses as an effect of cell-mediated immunity. About 1% of sexually active adults have visible lesions at any time point.

All of these numbers are expected to decline with the recent introduction of a quadrivalent HPV vaccine, but that is in the mediate future. For the immediate, the currently available physically destructive and pharmacologic procedures remain relevant. At 6.8% (vs 5.8% placebo), the rate of recurrences at 12 weeks after the end of therapy among treated patients with complete clearing appears lower than for other modalities. Pooled data suggests that cryosurgical destruction is about 80% effective and carries a recurrence rate of about 30%, and some topically applied medications or other means be avoided while the ointment is on the skin, or the ointment should be washed off before these activities.

Sinecatechins 15% ointment may weaken condoms and vaginal diaphragms; therefore, their use in combination is not recommended. Women using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental intravaginal application must be avoided. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive. Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily. The ointment may stain clothing and bedding.

Sinecatechins 15% ointment is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16-week treatment period, these should also be treated with the ointment. The effect of sinecatechins ointment on the transmission of genital/perianal warts is unknown.

Sinecatechins 15% ointment is to be applied 3 times per day to all external genital and perianal warts. Wash the hands before and after application of Veregen. About a 0.5-cm strand of the ointment should be applied to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of ointment on the warts. Treatment should be continued until complete clearance of all warts, but no longer than 16 weeks. Local skin reactions are frequent. Treatment should be continued when the severity of the local skin reaction is acceptable.

Sinecatechins 15% is a brown ointment supplied in aluminum tubes containing 15 g and 30 g of ointment per tube.
for destruction fare worse, although caution interpreting non–head-to-head study data must be exerted. Most established treatment options carry unfavorable side-effect profiles and low efficacy with high recurrence rates and may unduly burden patients and partners.

Our personal experience (WA) with the product as adjuvant therapy to cryosurgery in perianal condylomata has been gratifying. This has led to off-label use for verruca vulgaris and for molluscum contagiosum with apparent success, but this is still anecdotal.

A cost-effectiveness analysis of sinecatechins in the treatment of external genital warts concluded that sinecatechins yield a lower cost of treatment than imiquimod for this indication.6

Because there is still room for an alternative in the treatment of this recalcitrant infection (condyloma acuminata), the sinecatechin 15% ointment option seems to be a useful one.

REFERENCES

Free radicals are involved in the pathogenesis of several diseases including inflammation, neurodegenerative conditions, skin and eye disorders, and various forms of cancer. Epidemiologic evidence correlating higher intake of certain foods, typically fruits and vegetables or food components containing antioxidants, with a lower incidence of human disease are documented in the literature. Specific examples of such foods are apples, pears, grapes, wine, and tea.

In the United States, the Center for Disease Control and Prevention (CDC) became the leading federal agency and national health authority for the National Fruit and Vegetable Program. In March 2007, a new public health initiative, “Fruits & Veggies: More Matters” was initiated. The program has emphasized the revised guideline, increasing the recommended servings of fruits and vegetables beyond 5 servings per day to 5 to 13 servings per day.

**SCIENTIFIC STUDY REVIEW**

**DIET AND WRINKLES**

A Melbourne, Australia study of diet and lifestyle involved 177 Greek-born individuals living in Melbourne, 69 Greek persons living in rural Greece, 48 elderly Anglo-Celts living in Melbourne, and 159 Swedish persons living in Sweden as participants. Results of the study concluded that less actinic skin damage correlated with a higher intake of vegetables, olive oil, fish, and legumes and lower intake of butter, margarine, milk products, and sugar products. Regression analysis produced similar findings, except that fish was no longer significant. High intake of vegetables, legumes, and olive oil appeared to be protective against cutaneous actinic damage. High intake of meat, dairy, and butter appeared to be adverse. Overall, the findings suggest that persons who consumed a higher intake of vegetables, olive oil, and monounsaturated fat and legumes but a lower intake of milk and milk products, butter, margarine, and sugar products had less wrinkling in sun-exposed sites, suggesting the possibility of a covariance between food categories in which a cuisine may operate on skin biology. One hypothesis is that the former food group may have partly contributed to reduced skin wrinkling due to high content of antioxidant vitamins and phytochemicals.

In Greek cuisine, vegetables and legumes are consumed with olive oil. This combination may enhance the benefit of preventing skin wrinkling if the oil promotes the absorption of fat-soluble antioxidant vitamins and phytochemicals. Fish intake was significantly correlated with less skin wrinkling; this association was not observed in the multiple regression analysis. The ability of fish to be protective against actinic damage may depend on what it is eaten with, eg, fish combined with salad or vegetables. For each ethnic population, vegetables, legumes, and fermented milk products were negatively correlated or predictive of photoaging. Diets with higher consumption of full-fat milk, red meat, potatoes, soft drinks, cakes, and pastries were associated with extensive skin wrinkling. Higher consumption of butter was particularly associated with skin wrinkling. Diets associated with higher consumption of eggs, yogurt, legumes, vegetables, eggplant, asparagus, celery, onions (leeks and garlic), nuts, olives, cherries, grapes, melon, dried fruits, prunes, apples, pears, multigrain breads, tea, and water were associated with reduced photoaging.

Intake of micronutrients such as iron, zinc, calcium, phosphorus, magnesium, and vitamins E and C appeared to be protective against actinic skin damage. Regression analysis indicated that vitamin C was positively associated with skin wrinkling. The study postulated that perhaps this is related to the possibility that the intake of vitamin C, 127 mg/d, may be at a level acting as a pro-oxidant.

**UV-INDUCED IMMUNE SUPPRESSION AND SKIN CANCER**

Studies of immune-suppressed transplant recipients and biopsy-proven skin cancer patients have confirmed that UV radiation-induced immune suppression is a risk factor for the development of skin cancer in humans. Dietary botanicals have been shown...
to inhibit UV-induced immune suppression and photocarcinogenesis. Retinoids, green tea polyphenols, grape seed proanthocyanidins, resveratrol, curcumin, and silymarin are examples of botanical components that have chemopreventative effects.5

**Phytochemicals as Strong Photoprotecting UV Absorbers and Antioxidants**

Flavonoids and chromone derivatives found in a variety of plants including fruits and vegetables can act as photoprotecting UV absorbers and potent antioxidants.6 Cumulative UV-A radiation is believed to generate reactive oxygen species and penetrates beyond the epidermis into the dermal layer of skin.7 Few UV-A sunscreens are available in the United States. Chemical structural similarities exist between UV-A/UV-B filters and polyphenolic compounds that are commonly found in plant flavonoids. In addition to photoprotection, flavonoids may provide antiallergenic, anti-inflammatory, antitumor, and antibacterial benefits.7,8 A flavonoid, rutin, combined with organic sunscreens, 7.0% weight for weight ethylhexyl methoxycinnamate and 2.0% weight for weight benzophenone-3 and 2.0% titanium dioxide was noted to increase sun protection factor. In this study, results appear to be formulation-dependent.7,9

**CONCLUSIONS**

Flavonoids are able to enhance the effectiveness of sunscreens. Their chemical structure makes them particularly suitable to help provide protection in the UV-A range when formulated with sunscreens intended to be effective in the UV-A spectrum (320–400 nm).

The polyphenolic structure of the flavonoid is believed to stabilize organic UV filter molecules, elevating the amount of energy between lower-energy molecular orbitals to a higher-energy orbital.7

**REFERENCES**

The word “conservative” has many meanings, depending on the context. In medicine, the definitions that are relevant are more limited, consisting of “conserving or tending to conserve,” “prudent,” and “safe,” according to Webster’s New Twentieth Century Dictionary; whereas, the verb “conserve,” referred to in the first of these definitions, is defined as “to keep in a safe or sound state.”

DEFINITIONS

Among the more frequent applications of this term in dermatology and dermatopathology is in describing excisions or re-excisions of melanocytic lesions. A “conservative excision” or “conservative re-excision” is taken by many, including professors in major referral centers, to indicate an excision or re-excision with an attempt to save as much tissue as possible. Thus, for a cutaneous neoplastic lesion such as a dysplastic nevus, a 1- to 3-mm margin is denoted by this term.

There is an alternate definition that satisfies Webster’s definition as well or better than this one: conservative excision or conservative re-excision may also denote an excision with much wider margins so as to conserve not the tissue immediately surrounding the lesion, but rather the patient’s life should the lesion prove capable of invasion and/or metastasis. Such an approach might well be understood to be more “prudent” and “safe” than one that conserves adjacent tissue but at the expense of greater long-term risk. It turns out that there are other physicians who define the terms conservative excision and conservative re-excision in the latter manner; some of these are also professors in major referral centers. Thus, we now have two contradictory definitions of these terms in common use in dermatology and dermatopathology.

Consulting medical dictionaries is of little help. Stedman’s Medical Dictionary does not give “conservative” as a modifier under “excision.” It defines conservative as “denoting treatment by gradual, limited, or well-established procedure, as opposed to radical.” Dorland’s also does not give conservative as a modifier under excision, although it does define “marginal excision” as “surgical removal of an entire lesion, including only a very small margin of surrounding tissue,” which would correspond to the former of the two definitions given above for conservative excision. Dorland’s defines conservative as “designed to preserve health, restore function, and repair structures by nonradical methods, as conservative surgery. Cf. radical.” Both of these definitions of conservative, used as a modifier of excision, could be interpreted to indicate excision with narrow margins.

One is then left to ponder why Dorland’s gives a different term to denote the same thing. Worse, both dictionaries specifically contrast “conservative” with the term radical, which is universally used in surgery to indicate much more extensive surgery than just excision with the 1- to 2-cm margins indicated for melanoma. For example, one current surgery textbook cites radical procedures 13 times in its index; all of these citations refer either to procedures that include lymph node dissection, pancreatectoduodenectomy, or both. As currently applied, “conservative excision” or “conservative re-excision” may be used to indicate either of these very conflicting definitions.

THE REPORT

This issue is of more than academic interest. For example, if a pathologist indicates that conservative re-excision of a suspicious lesion should be performed, indicating that margins appropriate for melanoma (eg, 2 cm) be taken, and the clinician interprets this to mean narrow margins, the patient may well receive inappropriate care. Such a miscommunication may also result in malpractice litigation. In one such case, a large award was given to the plaintiff after it became evident that the clinician, the primary pathologist, and the consultant pathologist used different definitions of conservative re-excision, compromising the care of the patient.

CONCLUSIONS

Physicians receiving a report recommending a “conservative excision” or a “conservative re-excision” must be certain which definition is intended, even if this requires separate communication and possibly a disruption in one’s practice routine. Physicians who use either term should define which definition is intended as “conservative excision (with narrow margins)” or “conservative excision (with 1- to 2-cm margins).” The best practice may be to avoid the term altogether.
HISTORICAL DIAGNOSIS & TREATMENT

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

Lupus Vulgaris
HISTORICAL VIGNETTE

Charles Steffen, MD, Section Editor

Dermatopathology in Historical Perspective:
The Montgomery Giant Cell of Lichen Simplex Chronicus

Svetlana Rubakovic, MD; Charles Steffen, MD

In this short historical review, we will discuss the origin and references to the giant cell that is sometimes histopathologically present in the dermis of lichen simplex chronicus that was first described by Hamilton Montgomery, MD. A photomicrograph of the giant cell was included by Montgomery in his text Dermatopathology published in 1967. We will then provide a short biography of Montgomery.

We recently sent a slide containing biopsy sections from a patient with an inflammatory skin disease to Philip E. LeBoit, MD, for his opinion as to the diagnosis. Dr LeBoit opined that the patient had lichen simplex chronicus. He mentioned as evidence that there were “Montgomery giant cells” in the dermis, a criterion for lichen simplex chronicus.

The knowledge that giant cells were a feature of lichen simplex chronicus may have been deeply buried in our memory banks, but not the eponym. Dr LeBoit could not source the eponym, nor could the medical library or dermatologists of the Mayo Clinic where Hamilton Montgomery practiced, nor the American or European dermatologic colleagues of ours.

In his discussion of the histopathology of lichen simplex chronicus in the 1954 edition of the text by Oliver Ormsby and Montgomery, he wrote: “At times there may be clumping of endothelial cells of the capillaries in the cutis. This must be distinguished from the clumping of cells seen in mycosis fungoides.”

Montgomery had this to say on the subject in his dermatopathology text published in 1967:

At times there is clumping of the endothelial cells [in lichen simplex chronicus as] seen in the early stages of mycosis fungoides or even simulating Sternberg-Reed cells of Hodgkin’s disease. However, the clumped endothelial cells in neurodermatitis of the localized or disseminate type reveal no evidence of immaturity.

Montgomery then illustrated this cell in a photomicrograph wherein he referred to the “clumped” cell as a “pseudogiant” cell (Figure 1).

A somewhat cursory review of dermatology texts and journals found no mention of the Montgomery giant cell of lichen simplex chronicus except for that by Ackerman. He mentioned that in lichen simplex chronicus: “Plump, stellate, and multinucleated fibroblasts [are found] in the thickened papillary dermis.” Ackerman later discussed this cell in his presentation on the internet:
There is nothing specific about the multinucleated fibroblast in the upper part of the dermis, they being encountered not only in lichen simplex chronicus, but in other long-standing processes associated with altered collagen, such as chronic discoid lupus erythematosus.  

HAMILTON MONTGOMERY

Hamilton Montgomery (Figure 2) was a founder of American dermatopathology, and among its preeminent practitioners. Born in Chicago in 1898, he was introduced early to medicine by his father, Dr Frank Montgomery, who had published one of the first dermatology textbooks in the United States. “Hammy” received his medical degree from Harvard and returned to Chicago for his training. He continued at the Mayo Clinic, with which he would be associated for the rest of his career. There, in the late 1920s, he attended a series of lectures by Oscar Gans, a pioneer in joining the disciplines of pathology and dermatology. Deeply influenced by the German professor, Montgomery devoted himself to the study, practice, and teaching of dermatopathology. He was an early champion of integrating dermatopathology into the practice of dermatology, rather than isolating it in pathology labs. As Professor of Dermatology, he mentored many students at the Mayo Graduate School of Medicine. He co-authored several editions of the standard reference, Diseases of the Skin, wrote the seminal Dermatopathology (1967), was associated with more than 128 publications, and tirelessly championed dermatopathology as a subspecialty. He was a founding member and first president of the American Society of Dermatopathology. In 1959 he was awarded Emeritus at Mayo. Hamilton Montgomery died in 1982.

REFERENCES


RECOMMENDED READING ON THE LIFE OF HAMILTON MONTGOMERY

Extranodal Natural Killer/T-Cell Lymphoma, Nasal-Type

Dimitrios Chorianopoulos, MD; Konstantinos Samitas, MD; Stylianos Vittorakis, MD; Vasiliki Kiriazi, MD; Dimitra Rondoyianni, PhD; Georgios Tsoulosis, MD; Athanasios Skoutelis, PhD

A 51-year-old previously healthy man, an ex-smoker, was admitted to the authors' medical department with a 3-month history of dry cough; intermittent fever; painless, ulcerated cutaneous lesions over the trunk and limbs (Figure 1); and progressive weight loss. He was of Greek descent. His medical history was remarkable for nasal polyps, which were surgically removed 15 years earlier. Initially, he had been treated with antibiotics, without improvement. Several days before admission, chest radiography revealed pulmonary infiltrates in the left lower lobe. On admission, physical examination revealed a well-oriented man in mild distress, with inspiratory rhonchi at the lower part of the left lung and scattered erythematous nodules of variable size, some of which were ulcerated. Laboratory values were notable for leukopenia, 3.3 × 10^9/L; total protein, 5.9 g/dL; globulin, 2.2 g/dL; serum glutamic oxaloacetic transaminase, 86 IU/L; serum glutamic pyruvic transaminase, 71 IU/L; and lactate dehydrogenase, 519 U/L. Computed tomography (CT) of the chest showed multiple alveolar opacities bilaterally (Figure 2). Fiberoptic bronchoscopy did not reveal any important pathologic findings. Results of bronchial biopsy, cytology of bronchoalveolar lavage, washing, brushing, and sputum following bronchoscopy were negative. CT of the brain and sinonasal area revealed an abnormal low-density mass in the left nasal area. CT findings of the abdomen were negative, as were results of a bone marrow biopsy. There was no evidence of immunosuppression. The differential diagnosis, considering the evidence described, included granulomatous or infectious diseases, angiocentric lymphoproliferative lesions, and lymphomas. Biopsy of a skin lesion showed lymphoproliferative infiltration of the dermis with a follicular and angiocentric growth pattern and regional epidermal necrosis. Immunohistochemical stains showed that the tumor cells were positive for CD56 and CD3 (cytoplasmic positivity) and expressed the cytotoxic proteins T-cell intracellular antigen and granzyme B (Figure 3). They lacked TdT, CD34, CD7, TCL-1, and CD123. Findings from an in situ hybridization study for Epstein-Barr virus were negative. Given this result, molecular analysis of T-cell receptor (TCR) gene rearrangements was performed using polymerase chain reaction–based TCR-γ gene, with negative results. The morphology and the immunophenotype were consistent with natural killer/T-cell lymphoma, nasal-type. Nasal involvement must be first excluded to proceed to the diagnosis of nasal-type natural killer–cell lymphoma. Indeed, histologic examination of the nasal mass revealed its polypoid nature. Thus, the authors were led to the diagnosis of extranodal extranasal natural killer/T-cell lymphoma, nasal-type, CD56-positive, Epstein-Barr virus–negative, TCR-negative. The patient received combination chemotherapy and completed 4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone every 14 days for 2 months. Skin lesions improved, and there was no fever soon after the initiation of therapy. Reevaluation after the fourth cycle, however, disclosed pulmonary infiltrations as well as leukemic infiltration of the central nervous system. The patient had received systemic salvage chemotherapy and intrathalcal infusions of methotrexate. Although the lung lesions had diminished at that time, the patient developed paraplegia, his clinical course rapidly deteriorated, and he eventually died.

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EBV is strongly associated with this type of lymphoma, particularly the nasal type, and the circulating DNA load is prognostically relevant. The proportion of extranasal NK/T-cell lymphomas that are found to be EBV-negative is low: about 30% of cases in some series. They usually present a clinically less aggressive course and less necrosis than CD56-positive EBV-positive lymphoma.

NK-cell neoplasms were first reported in the Revised European-American Lymphoma (REAL) classification, termed angiocentric T-cell lymphoma; the terms lethal midline granuloma and pleomorphic T-cell lymphoma were also used. Recently, they have been identified as distinct clinicopathologic entities in the classification introduced by the World Health Organization (WHO) in 2001.

There are very few reports in the literature regarding lung involvement in NK/T-cell lymphoma, nasal-type. In 1997, researchers reported the case of a CD56-positive (nasal-type NK/T-cell) lymphoma arising on the skin, with lung invasion. Other investigators reported a case of a 38-year-old man with an ulcerated tumor of this type at the left thigh, with bone marrow and right lower lung field infiltration. In addition, in a clinicopathologic study of 13 cases of nasal-type NK/T-cell lymphoma studied over 14 years, only one had disease progression to the lung. Finally, a case of primary NK/T-cell pulmonary lymphoma, most likely the first one, was published in 2006.

As mentioned, this type of lymphoma has an extremely poor prognosis; median survival is about 5 months for disseminated forms. Apart from the International Prognostic Index, other parameters have been proposed as important in predicting the disease outcome. A recent retrospective multicenter study proposed a different prognostic model (based on B symptoms, stage, lactate dehydrogenase level, and regional lymph node involvement) that appeared to define in a more effective way the high-risk group who need more aggressive therapy.

Innovative therapeutic strategies should be attempted, including immunotherapy or L-asparaginase, but rarity of these lymphomas does not permit access to large number of patients.

**REFERENCES**


Figure 2. Skin biopsy: focal infiltration of the dermis by the lymphoid cells (hematoxylin-eosin stain, original magnification ×100 [A]). Expression of cytoplasmic CD3 by the lymphoid cells (EnVision’s stain, original magnification ×200 [B]). Expression of CD56 antigen by the lymphoid cells (EnVision’s stain, original magnification ×200 [C]).

Figure 3. Computed tomographic scan of the thorax obtained on admission.
CASE STUDY

Atrophic Sarcoidosis:
An Unusual Presentation of Cutaneous Sarcoidosis

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A 66-year-old woman presented with asymptomatic skin-colored to hypopigmented scaly plaques over the extremities, reportedly of 12 years’ duration. The lesions started as well-defined erythematous scaly papules over the forearms, gradually followed by the appearance of similar lesions over both legs and dorsum of feet. During this period, the lesions increased in size, with peripheral extension and central clearing, leading to the present morphology. She is a known patient with coronary artery disease currently on treatment. There is history of exertional dyspnea, which has been related to her cardiologic ailment. She is not a known diabetic and has no other significant medical history.

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On cutaneous examination, the patient had multiple skin-colored to hypopigmented well-defined annular plaques with cigarette paper–like central atrophy and scaling at the periphery of the lesions (Figure 1). There was no sclerosis, telangiectasia, or ulceration in any of the lesions. There was loss of hair in all lesions; however, no sensory loss or nerve thickening was noted.

Hematoxylin and eosin staining of the skin biopsy specimen taken from the margin of one of these plaques showed multiple non-necrotizing granulomas comprising epithelioid cells and sparse Langhans giant cells without lymphocytic cuffing centered around appendages, consistent with sarcoidosis (Figure 2). There was no nerve twig invasion and no organism was found in special stains, including Ziehl Neelsen, Fite, and PAS.

Complete blood cell count and liver and renal function tests were within normal limits. Chest x-ray and x-rays of the hands were within normal limits. Mantoux test was negative. Serum angiotensin-converting enzyme and urinary Ca2+ levels were normal. Venereal disease research laboratory test result was nonreactive.

She was treated with prednisolone (30 mg/d) and hydroxychloroquine (400 mg/d), but, after 2 months of treatment she did not have much clinical improvement.

DISCUSSION

Sarcoidosis is a chronic granulomatous disease with multisystem involvement. Cutaneous involvement occurs in 20% to 35% of patients and consists of 2 clinicopathologic categories: granulomatous infiltration and reactive phenomenon. Specific lesions of sarcoidosis vary in manifestation. Erythema nodosum solely represents the reactive lesion. Atrophic sarcoidosis is one of the rare variants of specific types of cutaneous sarcoidosis.

Atrophic cutaneous sarcoidosis is a very rare variant. The first report of atrophic sarcoidosis in the English literature dates back to 1970, when a case was reported with lesions limited to the legs.1 Subsequently, researchers reported a case of a 53-year-old man who presented with generalized atrophic sarcoidosis.2 Both of these patients had associated ulceration. Purely atrophic sarcoidosis is extremely uncommon. There was another reported case of atrophic sarcoidosis with necrobiosis lipoidica–like lesions on the scalp of a diabetic patient.3

Researchers retrospectively reviewed 147 cases of cutaneous sarcoidosis, of which 7 (4.8%) had ulcerative lesions.4 All 7 patients were of African American origin. Six of these 7 patients had an atrophic base. Hence, it can be speculated that atrophic and ulcerative sarcoidosis are in the same spectrum of specific cutaneous manifestations of sarcoidosis, although there are reports of atrophic sarcoidosis alone without associated ulceration. There is even a reported case of cutaneous sarcoidosis resembling discoid lupus erythematosus with scaly atrophic plaques and cicatricial alopecia on the scalp.5 Ulcerative sarcoidosis is 3 times more common in men than in women.6

It may be difficult to clinically differentiate the lesions of atrophic sarcoidosis from those of patch stage mycosis fungoides and necrobiosis lipoidica, although they can be differentiated by histopathologic examination. In the majority of patients with ulcerative sarcoidosis,
ulceration develops over the atrophic base, which resembles necro-biosis lipoidica. They are more commonly located in the pretibial areas. The atrophic nature and location of these lesions implicate trauma as the possible etiology of ulceration. Extracutaneous findings are more common in patients with ulcerative sarcoidosis as suggested by several researchers. Even after investigation, however, we could not find any extracutaneous involvement in our patient, having long-standing cutaneous involvement.

Traditional treatment options in cutaneous sarcoidosis include corticosteroids, antimalarials, methotrexate, and combinations of these agents. The newer therapeutic options include pentoxifylline, tetracyclines, isotretonoin, leflunomide, thalidomide, cyclosporine, chlorambucil, and allopurinol. The anti–tumor necrosis factor α antibody infliximab has been found to be dramatically effective in the treatment of cutaneous sarcoidosis. Ulcerative sarcoidosis is relatively resistant to treatment. Treatment failures have been report-ed with the use of chloroquine, topical/intrareional triamcinolone, isotretonoin, allopurinol, antimicrobials, and radiation therapy. Methotrexate can be used as an alternative in treatment-resistant cases. Atrophic sarcoidosis appears to be even more treatment-resistant. In a case reported by researchers, ulcerative lesions healed with a 30- to 40-mg/d dose of prednisolone; however, atrophic lesions did not change with prednisolone therapy.

REFERENCES

EPIDUO™ (adapalene and benzoyl peroxide) Gel 0.1% / 2.5%  
Rx only  
For Topical Use Only  
Not For Ophthalmic, Oral, or Intravaginal Use.

BRIEF SUMMARY

INDICATIONS AND USAGE
EPIDUO Gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided.ERYTHEMA, SCALING, DRYNESS, AND STIRNG/BURNING MAY OCCUR WITH USE OF EPIDUO Gel.

ADVERSE REACTIONS
Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, and stinging/burning. Other most commonly reported adverse events (≥1%) in patients treated with EPIDUO Gel were dry skin, contact dermatitis, application site burning, application site irritation, skin irritation.

DRUG INTERACTIONS
Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid, medicated or abrasive soaps and cleansers and products with high concentrations of alcohol or astringents in combination with EPIDUO Gel. Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution.

Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO Gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO Gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

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

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

Nursing Mothers
It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO Gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of EPIDUO Gel in pediatric patients under the age of 12 have not been established.

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

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO Gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m2/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m2/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of EPIDUO Gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO Gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

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

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells. In rat oral studies, 20 mg adapalene/kg/day (120 mg/m2/day; 98 times the MRHD based on mg/m2/day comparison) did not affect the reproductive performance and fertility of F1 males and females, or growth, development and reproductive function of F1 offspring.

No fertility studies were conducted with benzoyl peroxide.

PATIENT COUNSELING INFORMATION
– Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO Gel as a thin layer, avoiding the eyes, lips and mucous membranes.
– Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.
– EPIDUO Gel may cause irritation such as erythema, scaling, dryness, stinging or burning.
– Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.
– EPIDUO Gel may bleach hair and colored fabric.


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*In a phase 3 clinical trial of 1670 patients, median reduction in inflammatory lesions was 70% and median reduction in comedonal lesions was 62% at week 12.

**Important Safety Information**

Epiduo® Gel is a retinoid and antimicrobial combination product indicated for the topical treatment of acne vulgaris in patients 12 years and older. The most common adverse events associated with use of Epiduo® Gel are erythema, scaling, dryness, stinging and burning. In addition, adverse events reported in greater than 1% of patients treated with the Gel included contact dermatitis and skin irritation. Excessive exposure to sunlight and sunlamps should be avoided during treatment, and use of sunscreen products and protective clothing is recommended. Concomitant use of irritating topical products (like products containing resorcinol, salicylic acid or sulfur) should be avoided. Epiduo® Gel has not been tested in pregnant or nursing women, or with the elderly. Pregnancy Category C.

Please see brief summary of Prescribing Information on next page.
C3
C4