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1 Draelos, Z. The ability of onion extract gel to improve the cosmetic appearance of post-surgical scars. Cosmetic Dermatology, June 2008.
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Granuloma Annulare: Not as Simple as It Seems
Lawrence Charles Parish, MD, MD (Hon);1 Joseph A. Witkowski, MD2

Granuloma annulare (GA), the ringed eruption, has also been termed lichen annularis and heloderma simplex et annularis, just to recount a few of the names for this “deeply seated nodule or a ring of closely grouped nodules of firm consistency, elevated, sharply circumscribed, whitish, pinkish, reddish, purplish or bluish red in color.” This is a description, presented by Ormsby and Montgomery in their definitive text of more than a half century ago.1 When first delineated in 1895 by T. Colcott Fox in London as a ringed eruption, GA was considered either of unknown cause or due to a tubercular infection.2 Despite decades of investigations, its etiology continues to remain obscure, even today.

Our reasons for discussing this morphologically distinct entity with vague etiology and pathogenesis are due to some recent unusual findings. A discussion of the traditional differential diagnoses of erythema elevatum diutinum and necrobiosis lipoidica diabetica would add little to our knowledge; however, a middle-aged man with stasis dermatitis and even elephantiasis raised our curiosity, when a cutaneous biopsy demonstrated GA among the areas, manifesting diffuse redness and thickening. Was this a coincidence or part of a dermatitis (Figure 1)? Could the diffuse presentation represent a Koebner phenomenon?

GA AND OTHER DISEASES
GA has been linked with a number of diseases. For example, there are case reports of its association with prostate carcinoma, breast malignancies, pulmonary adenocarcinoma, and cervical adenocarcinoma.3 GA has been found in patients with lymphomas, including Hodgkin’s disease, mycosis fungoides, and lymphoepithelioid cell lymphoma (Lennert’s lymphoma). Concerning Lennert’s lymphoma, the similarities with GA were raised due to the initial granulomatous presentation. Twenty percent of patients with lymphomas other than mycosis fungoides have been found to have a number of cutaneous signs, ranging from erythema nodosum to urticaria, so that a granulomatous picture might not be so strange.4

There are patients with morphea and systemic scleroderma who have coexisting GA. Both diseases have vascular injuries, altered collagen, and lymphohistiocytic infiltrates. Whereas GA has fragmented collagen bundles and inflammation, characterized by necrobiosis and granulomatous formation, morphea has dermal fibroblasts in excess.5

GA has been found following trauma, UV light exposure, insect bites, herpes zoster infection, mycobacterial infection, and even pressure applied to the hands. The list goes on and on with little documentation to prove a cause and effect.6 GA has been found in infants as young as 68 days,7 while senior citizens infrequently are afflicted.

ADDITIONAL CONSIDERATIONS
What is the pathogenesis of GA? No infectious origin has ever been confirmed. Periodically, the question of its being an

Figure 1. A 47-year-old man developed dermatitis on both legs. While the stasis dermatitis diagnosis seemed a reasonable clinical diagnosis, the dermatopathology revealed granuloma annulare.
inherited disease is raised. Some have suggested that allergic contact dermatitis reactions might precipitate GA. Fortunately, GA seems to have escaped the strange fables of etiology that have plagued sarcoidosis—pine tree pollen.

Categorizing GA into various types: localized (Figure 2), generalized (Figure 3), papular, subcutaneous, or even granuloma multiforme contributes little to the understanding of this condition. There are no internal manifestations, and rarely does it involve the face. A review of the histopathologic picture of palisading granulomas and necrobiosis does not make the background of this ringed eruption any clearer.

Various treatments have been suggested but none can give positive results for a pharmacologic proof. These might be considered in the eras in which they were proposed: arsenic administered by mouth, salicylic acid ointment, tuberculin injections, carbon dioxide snow, and radiation. A more contemporary approach would include topical corticosteroids, intralesional corticosteroids, oral antihistamines, psoralen–UV-A, cyclosporine, pentoxifylline, isotretinoin, fumaric acid, and topical immunomodulators. To add to the muddle, performing a biopsy sometimes results in clearing of the lesions.

CONCLUSIONS

GA continues to remain an enigma with revelations lacking about its cause and, more importantly, effective treatment. The patient can be reassured that the disease is self-limiting, but GA has been known to last at least 34 years.

As to its association with stasis dermatitis, it is most likely a coincidence. The facts remain that patients with GA usually do not have other strange diseases.

REFERENCES


Figure 2. The erythematous ringed lesion of granuloma annulare can appear alone.

Figure 3. Generalized granuloma annulare of several years’ duration in a middle-aged woman.
Patch testing remains a valuable technique in the diagnosis of allergic contact dermatitis. Ongoing analysis of our patch testing reaction rates allows for the surveillance of emerging trends in our patch test population.

As a cell-mediated hypersensitivity reaction occurring in the skin, allergic contact dermatitis (ACD) is mediated by antigen-specific T lymphocytes. To develop ACD, an individual must first be sensitized by an allergen of low molecular weight (<1000 Da) that can readily penetrate the stratum corneum.1 Since these chemicals are often too small to elicit an immunologic response on their own, they associate themselves with other proteins in the skin, thus formulating a hapten-protein antigen complex that may be recognized by certain immune cells. Langerhans cells, the professional antigen-presenting dendritic cells residing in the epidermis, process and uptake the antigen and present it to naïve T cells, which, in turn, produce two clonal populations of cells: antigen-specific effector and memory T cells. Upon an individual's re-exposure to the specific allergen, Langerhans cells bearing the antigen interact with antigen-specific T lymphocytes circulating in the skin. This elicits an inflammatory response through the release of cytokines and other potent mediators, ultimately resulting in varying degrees of erythema, edema, and vesiculation in patients.

Patch testing is an important diagnostic tool commonly used to identify allergens responsible for ACD. It is useful when the diagnosis is not clearly apparent. The authors report the patch test results from 2004–2008 and compare the results with the North American Contact Dermatitis Group and Mayo Clinic. Four hundred thirty-four patients with suspected allergic contact dermatitis underwent standardized patch testing with a tray consisting of 50 allergens at Mount Sinai Medical Center. Two hundred ninety patients (66.8%) had positive reactions to at least one allergen. The most frequent contact allergens included nickel sulfate (13%), fragrance mix (9.6%), propylene glycol (7.8%), neomycin sulfate (6.6%), thimerosal (6.4%), bacitracin (6.2%), and sodium gold thiosulfate (5.8%). (SKINmed. 2010;8:257–260)
in the Table. In our sample, 290 patients (66.8%) had a positive reaction to at least one allergen. The most frequent contact allergens included nickel sulfate (13%), fragrance mix (9.6%), propylene glycol (7.8%), neomycin sulfate (6.6%), thimerosal (6.4%), bacitracin (6.2%), and sodium gold thiosulfate (5.8%).

**DISCUSSION**

We compared our results with those of the most recent study conducted by the NACDG and the Mayo Clinic. The NACDG conducted a study in 2005–2006 of 4454 patients in which they found 2907 (65.3%) of patients had at least one allergic patch test reaction. The most frequent contact allergens were nickel sulfate (19%), balsam of peru (myroxylon pereirae) (11.9%), fragrance mix (11.5%), neomycin sulfate (10%), quaternium-15 (10.3%), bacitracin (9.2%), and cobalt (II) chloride hexahydrate (8.4%). The Mayo Clinic conducted a retrospective review of 3854 patients from 2001–2005 in which 2664 (69.1%) patients were positive for at least one reaction. The most frequent contact allergens were dermatophagoides mix 20% (27.4%), nickel sulfate (17.1%), balsam of peru (myroxylon pereirae) (13.7%), gold sodium thiosulfate (13.5%), neomycin sulfate (11.8%), fragrance mix (11.3%), and thimerosal (10.5%).

The prevalence of positive patch test reactions (66.8%) is consistent with the findings from the NACDG (65.3%) and the Mayo Clinic (69.1%). While the percentage of positive reactions for each allergen was consistently lower as compared with the NACDG and Mayo Clinic, this may have been a result of our small sample size. The patients who underwent patch testing between 2004 and 2008 underwent testing with a tray of 50 chemicals as opposed to the 65 chemicals tested by the NACDG and Mayo Clinic. The additional 15 allergens that were tested by the two groups were found to produce positive reactions in less than 2% of the specified populations. While increasing the number of antigens in a tray has been known to yield more positive reactions, it is important to determine the clinical relevance of these positive reactions. In one study, a standard tray with 65 allergens failed to detect ACD in 50.2% of patients. Therefore, testing for additional allergens beyond a standard series may be of great benefit when taking into consideration a patient’s history and environmental exposures.

Prior studies have consistently reported nickel sulfate hexahydrate, neomycin sulfate, fragrance mix, and balsam of Peru as common sensitizers. According to the NACDG, the frequency of positive patch test reactions to nickel continues to rise with time and persists to be the most frequently positive antigen. In this small study, nickel was reported to have the highest number of positive reactions, although the percentage of individuals with a positive reaction to this allergen was less compared with the NACDG and Mayo Clinic. As the most common allergen detected by patch test patients in the United States and as a major contact allergen in the world, there is strong evidence that its prevalence is rising. According to a recent report, nickel allergy is highest among women and patients younger than 18, affecting 35.8% of patch-tested patients in this demographic. Some countries in Europe, such as Denmark, have sought to regulate the release of nickel in consumer products, thus resulting in a decrease in prevalence of this allergy.

Fragrance allergy was the second common sensitizer. Fragrance allergy is consistently one of the most frequent patch test reactions reported by the NACDG, and there is some evidence that fragrance sensitization increases with age. Fragrances are widely found in perfumes, cosmetics, and other skin care products. The 8 constituents of fragrance mix I (all at 1%) include evernia prunastri (oak moss) extract, isoeugenol, eugenol, cinnamal, hydroxycitronellal, geraniol, cinnamyl alcohol, and amyln cinnamal. In 2005, a new fragrance mix was presented. The constituents of fragrance mix II include citronellol 0.5%, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyril) 2.5%, hexyl cinnamal 5%, citral 1%, coumarin 2.5%, and farnsrol 2.5%. One study found that 35% of individuals had positive reactions to fragrance mix II and negative reactions to fragrance mix I.

Neomycin sulfate and bacitracin were also common allergens in our patient population. While bacitracin was reported as a frequently positive allergen by the NACDG, neomycin sulfate was a common allergen presented by the Mayo Clinic. Neomycin sulfate and bacitracin are antibacterial agents that may be found in topical creams, ointments, and lotions and are used to treat a variety of skin, eye, and external ear infections. These two antibiotics are often paired in over-the-counter preparations because together they provide coverage against gram-positive cocci and aerobic gram-negative bacteria. There is evidence that ACD associated with these agents is becoming an increasing problem in postoperative wound care. As a result, white petrolatum may be a preferable alternative topical agent.

Thimerosal elicited a frequently positive reaction in our population and in the Mayo Clinic population. Thimerosal is a mercuric derivative used as a preservative in vaccines, ophthalmic and nasal products, and even tattoo inks. While 6.4% of our patients were positive for thimerosal, 10.5% of patients at the Mayo Clinic were positive for this allergen. There have been some reports that the reaction with thimerosal may lack relevance, as this allergen may not be responsible for contact allergy. Therefore, thimerosal has been removed from many standard screening series.

Likewise, gold sodium thiosulfate elicited a positive reaction in both our population and the Mayo Clinic. Gold is often found in jewelry, dental implants, and even intracoronary stents. A recent
investigation reported a correlation between contact allergy to gold and a gold concentration in the blood of patients with stents.25 As an increasing number of people with cardiovascular disease undergo stent procedures, it is important to note that metals such as gold can elicit a contact allergy in this population.

Propylene glycol was a frequent sensitizer unique to our patient population. Propylene glycol acts as a solvent, moisturizer, and emulsification agent for medicines, food, cosmetics, and other products. One retrospective study using the NACDG data identified the most common sources of this allergen: 53.8% were

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<tr>
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<tbody>
<tr>
<td>2.5% Nickel sulfate</td>
<td>13 (57)</td>
<td>19</td>
<td>17.1</td>
</tr>
<tr>
<td>8% Fragrance mix</td>
<td>9.6 (42)</td>
<td>11.5</td>
<td>11.3</td>
</tr>
<tr>
<td>30% Propylene glycol</td>
<td>7.8 (34)</td>
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<td>Not tested</td>
</tr>
<tr>
<td>20% Neomycin sulfate</td>
<td>6.6 (29)</td>
<td>10</td>
<td>11.8</td>
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<tr>
<td>0.1% Thimerosol</td>
<td>6.4 (28)</td>
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<td>10.5</td>
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<tr>
<td>20% Bacitracin</td>
<td>6.2 (27)</td>
<td>9.2</td>
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<tr>
<td>0.5% Sodium gold thiosulfate</td>
<td>5.8 (25)</td>
<td>Not tested</td>
<td>13.5</td>
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<td>1% Cobalt chloride</td>
<td>5 (22)</td>
<td>8.4</td>
<td>10.3</td>
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<tr>
<td>2.5% 12 Methylidibromo-glutaronitrile/phenoxethanol (Euxyl K-400)</td>
<td>4.6 (20)</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>25% Balsam of Peru</td>
<td>4.6 (20)</td>
<td>11.9</td>
<td>13.7</td>
</tr>
<tr>
<td>1% Formaldehyde</td>
<td>3.6 (16)</td>
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<td>3% Carba mix</td>
<td>3.4 (15)</td>
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<td>4.6</td>
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<tr>
<td>0.25% Potassium dichromate</td>
<td>3.2 (14)</td>
<td>4.8</td>
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<tr>
<td>2% Quaternium-15</td>
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<tr>
<td>1% Paraphenylenediamine</td>
<td>2.5 (11)</td>
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<tr>
<td>2% Methyl methacrylate</td>
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<tr>
<td>0.1% Sesquiterpene lactone mix</td>
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<tr>
<td>0.5% 2-Bromo-2-nitropropane-1,3-diol (Bronopol)</td>
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<tr>
<td>0.01% 5-Chloro-methyl-4-isothiazolin-3-one (KathonCG)</td>
<td>1.8 (8)</td>
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<tr>
<td>1% Thiuram mix</td>
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<td>20% Colophony</td>
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<tr>
<td>12% Paraben mix</td>
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<tr>
<td>1% Cinnamic aldehyde</td>
<td>0.9 (4)</td>
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<tr>
<td>1% 4-Chloro-3,5-xylenol (PCMX)</td>
<td>0.9 (4)</td>
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<tr>
<td>1% 4-tert-Butylphenolformaldehyde resin</td>
<td>0.9 (4)</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>1% 2, 5 Diazolidinylurea (Germall II)</td>
<td>0.9 (4)</td>
<td>3.7</td>
<td>3.5</td>
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<td>2% Imidazolidinyl urea (Germall 115)</td>
<td>0.9 (4)</td>
<td>2.9</td>
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<td>0.01% Budesonide</td>
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<td>0.1% Tixocortal-21-pivalate</td>
<td>0.6 (3)</td>
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<tr>
<td>5% Benzocaine</td>
<td>0.6 (3)</td>
<td>1.9</td>
<td>1.5</td>
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Abbreviations: MSSM, Mount Sinai School of Medicine; NACDG, North American Contact Dermatitis Group.
found in personal care products (creams, lotions, and cosmetics), 18.3% in topical corticosteroids, and 10.1% were found in other topical medications.26

Although most studies reported balsam of Peru as a common sensitizer, it elicited a reaction in only 4.6% of our patients. This was unusual, especially given the fact that this allergen is known to have some cross-reactivity to fragrance mix due to the overlap in chemicals.27

CONCLUSIONS

Patch testing remains a valuable tool in the identification of allergens contributing to dermatitis. While our study was limited with regard to sample size, our results were consistent with prior large-scale studies. Regional variation and changes in exposure patterns over time, however, may contribute toward shifts in positive allergen frequency. Identifying these changing trends will serve to better guide the treatment and care of patients with suspected ACD.

REFERENCES

Due to the importance of personal appearance in the university years, skin has a significant importance among the younger population. Therefore, even a slight change on the skin in this age group directs them to seek prompt medical advice. In this case, the physician is almost always a dermatologist. Our main objective in this research was to establish the reasons why students seek medical assistance at dermatology polyclinics and determine the most frequent diagnoses.

METHODS

University students who visited two dermatology polyclinics within the Ege University Health, Culture and Sports Office between April 2003 and March 2004 were included in the descriptive study. Each student was examined by two dermatologists. All dermatological diseases were recorded. Questions about demographic data and frequency of using the swimming pool were directed to the patients. Patients were asked to assess and give a score for the state of their mental wellness using the visual analog scale (0–100) during the past month. Chi-square and Student t tests were used for statistical analyses. A total of 1733 individuals, 750 (43.3%) men and 983 (56.7%) women, were included in the study. The most frequently seen diseases were acne vulgaris (40.1%) and fungal diseases (17.08%), whereas the least frequently seen were parasitic skin diseases (0.46%) and vascular diseases (0.51%). The mean mental wellness score was found to be 61.03±21.34 (0–100, median: 65.00). It can be concluded that students visit university dermatology outpatient clinics frequently and the most common complaints are acne vulgaris and fungal diseases.

RESULTS

A total of 1733 individuals were included in the study. Of these patients, 750 (43.3%) were men and 983 (56.7%) were women. The mean age was 21.14±2.52 years (median: 21.00; minimum–maximum: 16–45 years). A total of 33.7% of the students were living with their families, 30.9% shared an apartment with friends, and 29.9% lived in a dormitory. The most frequently seen diseases were acne vulgaris (40.1%) and related diseases (0.46%), followed by fungal diseases (17.08%). Parasitic skin diseases (0.46%) and vascular diseases (0.51%) were rarely detected (Table). The most frequently prescribed medicines were topical antifungals (17.8%), followed by acne vulgaris–related medicines (isotretinoin and other acne medicines) (15.7%). Of all the patients visiting dermatology outpatient clinics, the number of participants who used the swimming pool was 866 (41.5%) and the number of those who never used the pool was 1220 (58.5%).

Patients assessed their state of mental wellness during the past month on a scale of 100. The mean mental wellness score was 61.03±21.34 (0–100, median: 65.00). A total of 32.6% of the students stated that they needed psychological support in the past, whereas 17.6% said that they actually received such support. The relationship of occurrence of an allergic skin disease to need for receiving psychological support and actually

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Table: Skin Diseases of University Students

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne vulgaris and related diseases</td>
<td>696</td>
<td>40.1</td>
</tr>
<tr>
<td>Fungal diseases</td>
<td>296</td>
<td>17.08</td>
</tr>
<tr>
<td>Bacterial diseases</td>
<td>303</td>
<td>17.48</td>
</tr>
<tr>
<td>Viral diseases</td>
<td>113</td>
<td>6.5</td>
</tr>
<tr>
<td>Traumatic lesions</td>
<td>65</td>
<td>3.75</td>
</tr>
<tr>
<td>Nevi</td>
<td>29</td>
<td>1.67</td>
</tr>
<tr>
<td>Allergic diseases</td>
<td>135</td>
<td>7.78</td>
</tr>
<tr>
<td>Hair diseases</td>
<td>41</td>
<td>2.36</td>
</tr>
<tr>
<td>Pigmentary diseases</td>
<td>18</td>
<td>1.03</td>
</tr>
<tr>
<td>Parasitic skin diseases</td>
<td>8</td>
<td>0.46</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>9</td>
<td>0.51</td>
</tr>
<tr>
<td>Drug reactions</td>
<td>20</td>
<td>1.15</td>
</tr>
<tr>
<td>Total</td>
<td>1733</td>
<td>100</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Students frequently visit dermatology outpatient clinics. Acne vulgaris and fungal disorders are the most common complaints of the students. Parasitic skin diseases and vascular diseases were found to be rare in our study. Results of the present study revealed that almost half of the university students (50.2%) needed psychological support. Interestingly, there was no statistical relationship between the dermatologic diseases and psychological condition. It can be concluded that during the significant period of personal development in the college years, university students benefit from psychiatric assistance while undergoing medical therapy.

REFERENCES

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Although Paul Gerson Unna used principles of dermoscopy as early as 1893, it was Johann Saphier, another German dermatologist, who coined the term dermatoskopie in 1920 while employing a binocular device with a built-in light source to study the vessels of the skin.1 In the United States, Leonard Goldman was the early pioneer who reported the use of this diagnostic technique, which he referred to as surface microscopy, to evaluate melanocytic lesions in 1951.2 It was not until the 1980s, however, when dermatoscopy caught the attention of a broader audience. Since that time, the field of dermatology has witnessed an explosive number of publications regarding dermatoscopy, especially during the recent decade in which more than 1060 articles have been published on the subject. In Europe and Australia, the continents in which the major studies of dermatoscopy have originated during the past 2 decades, it has become the standard of care in evaluating pigmented skin lesions due in part to the wide availability of portable handheld dermatoscopes. In the United States, however, dermatoscopy is slowly gaining popularity. In 2010, approximately 50% of surveyed dermatologists used a dermatoscope on a regular basis,3 a noticeable increase from only 25% in 2002.4

A dermatoscope renders the cornified layer translucent, revealing subsurface structures within the epidermis and superficial dermis, providing additional morphologic criteria in diagnosing skin diseases. The widely available handheld pocket-size dermatoscopes have a light source with usually a 10-time magnification, some requiring contact with the skin while others offering the option of contact and noncontact. Immersion contact dermatoscopes usually employ a halogen light bulb as a light source, whereas polarized light dermatoscopes, which provide the option of contact and noncontact, are equipped with multiple light-emitting diode (LED) light bulbs. Immersion contact dermatoscopy allows slightly better visualization of superficial structures such as milia-like structures, comedo-like openings, and blue-white veils, while polarized light dermatoscopy, either contact or noncontact, allows slightly better visualization of deeper structures such as fibrosis and vascular structures.5,6 No study exists that demonstrates a difference in diagnostic accuracy between the two different methods of dermatoscopy in the clinical setting; thus, a dermatoscope should be chosen based on the user’s preferences.

The initial interest in dermatoscopy in the modern era focused on its ability to improve the diagnostic accuracy of melanoma, although, of late, it has been promoted to be useful in diagnosing a wide range of skin diseases that includes infections, infestations, and inflammatory diseases. Accordingly, there are two key objectives of dermatoscopy: (1) to decrease unnecessary harvesting of benign skin lesions, and (2) to increase the diagnostic accuracy of melanomas, especially early melanomas.7–9

Evaluation of a skin lesion with a dermatoscope involves a 2-step process (Figure 1). The first step is to determine whether the lesion is melanocytic. If the lesion is determined to be melanocytic, then the second step is to determine whether the melanocytic lesion is benign, malignant, or indeterminate using any one of the available algorithms. Expert dermatoscopists have developed simplified algorithms for the nonexperts, including primary care physicians and dermatologists, to facilitate the use of the dermatoscope.

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Simplified algorithms, however, do not allow an in-depth critical understanding of the dermatoscopic structures that are required to avoid some of the pitfalls and limitations of dermatoscopy.

An alternative to the simplified algorithms is the comprehensive analysis referred to as pattern analysis, a method that may be superior in learning and practicing dermatoscopy. Pattern analysis requires a methodical and sequential analysis of all of the observed dermatoscopic structures, requiring not only the correct recognition but also the understanding of the diagnostic significance of the observed dermatoscopic structures. In contrast to simplified algorithms, meaningful clinical application of pattern analysis requires more time in training and experience.

For the novice who is weighing the decision to use a dermatoscope, the sheer amount of available information and knowledge on dermatoscopy may be daunting. Just trying to make sense of the nomenclature of dermatoscopy is challenging. With experience, one learns to focus on the more relevant dermatoscopic structures in arriving at a diagnosis for the various entities. Indeed, the correct recognition of the relevant dermatoscopic structures is the key to becoming proficient in dermatoscopy no matter which method is employed, either a simplified algorithm or more comprehensive pattern analysis. In this review, the major dermatoscopic structures observed in a variety of entities are highlighted, especially concerning those entities that may simulate melanoma and/or entities in which application of dermatoscopy is particularly useful.

NONMELANOCYTIC LESIONS

Step one of the 2-step process of dermatoscopy consists of determining whether the lesion is melanocytic or nonmelanocytic. This initial triaging step may have a greater clinical impact than the second step of dermatoscopy. The additional morphologic criteria provided by dermatoscopy have the potential to increase the diagnostic accuracy of a variety of benign lesions such as the hemangioma, dermatofibroma, solar lentigo, and seborrheic keratosis that may simulate melanoma, thereby obviating the need for a biopsy confirmation of these benign lesions. Malignant lesions, especially basal cell carcinoma (BCC), can be diagnosed with more accuracy using a dermatoscope as well.

HEMORRHAGE

Dermatoscopic criteria of hemorrhage (Figure 2):

- “Blood spots”: oval to round islands of pigment that range from yellow, red, maroon, brown, purple, to black
- Concomitant presence of the color spectrum of blood spots
- Separate small islands of pigment with a red hue that have no connection to the main body of the pigment serve as a good clue

Hemorrhage within the cornified layer of skin and mucous membranes, as well as that within the nail apparatus, can be a deceitful simulator of a melanocytic lesion. Dermatoscopy can be helpful in discriminating true hemorrhage from a melanocytic lesion, especially on volar skin and nail apparatus, thus avoiding unnecessary biopsies. In hemorrhage, present are discrete sharply delineated...
round pigmented bodies, referred to as “blood spots” that range in hue from yellow, red, maroon, brown, purple, to black. Separate small islands of pigment with a yellow or red hue that have no connection to the main body of the pigment serve as a good clue that the pigmentation is due to blood and not aggregations of melanocytes. Since the presence of hemorrhage within the nail apparatus does not explicitly exclude an underlying neoplasm, a biopsy may still be necessary depending on the clinical context and the index of suspicion of an underlying neoplasm.

HEMANGIOMA

Dermatoscopic criteria of hemangioma (Figure 3):

- Multiple closely set lacunae (lagoons) that range in color from red, maroon, blue-red, to blue-black with or without subtle gray-white outline
- Dermatoscopic findings vary depending on the presence of:
  - Epidermal changes (e.g., hyperkeratosis, acanthosis)
  - Location of the vessels
  - Presence of thrombosis

With the naked eye, vascular lesions, especially thrombosed ones, may simulate a melanocytic lesion. The dermatoscopic structures in vascular lesions are relatively distinctive, enabling the clinician to readily distinguish them from other entities. Dermatoscopically, there are closely grouped round to oval pigmented structures, referred to as lagoons or lacunae, that are yellow, red, maroon, purple, blue-red, or blue-black.\(^\text{12,13}\)

The presence of a subtle gray-white peripheral outline surrounding each of the lacunae provides an additional clue. These lacunae or lagoons histologically correspond to dilated dermal blood vessels\(^\text{14}\) and therefore can appear more red when the offending vessels are more superficial or more purple or bluish if the vessels are located deeper within the dermis. The peripheral gray-white outline represents thin fibrous septae between the dilated vessels. Acanthosis and hyperkeratosis of the epidermis further accentuate the gray-white color. A frequent clinical finding is that of a thrombosed hemangioma, which can be a diagnostic challenge due to its jet-black clinical appearance. The concomitant presence of the color spectrum of lacunae, especially the presence of yellow and red hue in addition to the jet-black hue, is a good clue that the lesion is vascular in nature. A homogenous jet-black thrombosed vascular lesion with no discrete lacunae may not be dermatoscopically distinguishable from other pigmented lesions. When the vessels are present in the deep dermis, the dermatoscopic findings minimally contribute in the diagnostic evaluation.

SEBACEOUS GLAND HYPERPLASIA

Dermatoscopic criteria of sebaceous gland hyperplasia (Figure 4):

- White to yellow lobulation (“cumulus sign”) with a central umbilication
- Prominent vessels that surround the lesion (“crown vessels”)

Sebaceous gland hyperplasia usually does not pose a diagnostic difficulty for clinicians, owing to its characteristic size, distribution, color, and surface attributes. At times, however, the color and surface features are not readily visible with the naked eye, resulting in the need for biopsies to exclude, most frequently, BCCs. A view through a dermatoscope frequently reveals the white to yellowish lobulation (“cumulus sign”) with surrounding vessels (“crown vessels”) and central umbilication characteristic of a sebaceous gland hyperplasia,\(^\text{15,16}\) providing clinicians with a diagnostic confidence superior to that of the naked-eye examination alone, and thus potentially resulting in fewer biopsies.
DERMATOFIBROMA

Dermatoscopic criteria of dermatofibroma (Figure 5):

- White scar-like area or white network, often central
- Peripheral pigment network

Dermatofibromas are very common benign cutaneous lesions that are clinically firm papules, plaques, or nodules that vary in color from light brown, dark brown, reddish purple, to yellow. In many cases, the history, clinical context, and clinical examination readily differentiate these lesions from other entities, i.e., the firmness on palpation can consistently suggest the diagnosis of a dermatofibroma. In lesions that remain problematic despite clinical examination, dermatoscopy can be of value. The central white scar-like area with a peripheral pigment network comprises the most frequent dermatoscopic structures found in a dermatofibroma.17–19

The varying degree of fibrosis in the superficial dermis and the elongated pigmented thin rete-ridges represent the histopathologic correlate of the dermatoscopic structures. Sometimes the scar-like area may show a central white “pigment network” rather than a homogeneous white area, corresponding to the uneven fibrosis in the superficial dermis.19,20 Since the histopathologic findings vary widely in dermatofibromas, the dermatoscopic findings will mirror those dominant histopathologic findings that are present. For example, if foamy histiocytes predominate, the yellow hue becomes the dominant background color; if numerous erythrocytes and siderophages predominate, blue-gray becomes the background color, proving it difficult to differentiate from a blue nevus or nodular melanoma; if follicular induction is prominent, discrete foci of translucency may be present; and if sebaceous gland induction is prominent, small white to yellow globular structures may be present.17

BASAL CELL CARCINOMA

Dermatoscopy of BCC (Figure 6):

Nonpigmented

- Telangiectasia
- Arborizing vessels
- Short fine telangiectasias
- Arborizing microvessels
- White streaks/white areas (“chrysalis structures”)
- Translucency
- Milky-pink to red background
- Erosion/ulceration

Pigmented

In addition to the criteria above:

- Islands of pigment
  - Blue-gray globules
  - Blue-gray ovoid nests
- Pigment distribution pattern
  - Maple-leaf
  - Spoke-wheel

Initially, dermatoscopy had been enthusiastically promoted to be useful in detecting pigmented BCCs, but, more recently, the application of the diagnostic technique has been expanded to include detecting nonpigmented ones.21,22 Indeed, rather than attempting to understand the dermatoscopic criteria for pigmented BCCs, understanding the dermatoscopic criteria that are common to both pigmented and nonpigmented BCCs offers a more fundamental and compelling approach in differentiating BCCs from entities that may simulate them, such as solar keratosis, lichen planus-like keratosis, Bowen's disease, and both benign and malignant melanocytic lesions. Published dermatoscopic criteria for BCC, for the most part, apply to superficial and nodular BCC,21,23 although dermatoscopic findings of rare subtypes such as fibroepithelial tumor of Pinkus have been described.24

By understanding the repeatable histopathologic findings of BCCs, whether pigmented or not, one can predict the dermatoscopic findings. Prominent vascularization situated parallel to the surface, varying amounts and degree of fibromucinous stroma, and epithelial aggregations that vary in size are the usual histopathologic findings. The telangiectasias, white areas or streaks (“chrysalis” structures), and semi-translucency represent the corresponding dermatoscopic findings. The combination of histopathologic findings provides the
background milky-pink to reddish hue that is frequently present on dermatoscopy. Depending on the size and configuration, the telangiectatic vessels have been described as short fine telangiectasias, arborizing microvessels, and arborizing vessels.25

Larger caliber arborizing vessels are more frequently found in nodular BCCs, while short fine telangiectasias are more frequently found in superficial BCCs. Translucency on dermatoscopy may be subtle to obvious depending on the size and location of the neoplastic epithelial aggregations. Hence, translucency is more prevalent in nodular BCCs compared with the flatter superficial BCCs in which the translucency may be subtle to absent.

Islands of pigment varying in size are present in addition to the aforementioned dermatoscopic findings in clinically pigmented BCCs. Pigment ranges from tan to brown to blue-gray. Small islands of blue-gray pigment have been referred to as blue-gray globules, while the large islands of blue-gray pigment have been referred to as blue-gray ovoid nests.26 Rarely, the pigment may be distributed in a “maple leaf”– or “spoke-wheel”–like pattern.26 For the pigmented BCCs, the challenge for the clinician is to differentiate pigmented structures of epithelial aggregations from pigmented structures of melanocytic aggregations, which may be difficult and at times impossible if other dermatoscopic features of BCC are subtle to absent.

Most of the dermatoscopic findings of BCC (eg, prominent vessels, white streaks, blue-gray globules) are not specific, but these findings in concert with clinical examination and context lead to a more accurate diagnosis or, at least, narrow the diagnostic possibilities. For the experienced dermatologist, dermatoscopy has limited utility in diagnosing typical superficial and nodular BCCs. For clinically subtle or atypical-appearing lesions, however, even the most seasoned dermatologist will appreciate some of the advantages that a dermatoscope offers, as it often reveals the characteristic BCC subsurface structures that were not apparent with the naked-eye examination.

**SEBORRHEIC KERATOSIS**

Dermatoscopic criteria of seborrheic keratoses (Figure 7):

- Comedo-like openings and milia-like cysts
- Sulci and gyri (fissures)
  - Cerebriform or brain-like structures
  - “Fat fingers”
  - Network-like structures
- Hairpin vessels
- Sharply demarcated

Seborrheic keratoses are common benign keratinocytic growths that typically present as waxy brown lesions, predominantly on the trunk but also on the face and extremities. Because these lesions are so widespread among the population, their clinical appearance can vary greatly, especially depending on the age of the lesion. While
some seborrheic keratoses appear as benign "stuck-on" keratotic papules, others can present as asymmetric papules or plaques with a multitude of colors and even whitish areas within, often raising suspicion of a melanoma. The use of a dermatoscope may reveal the characteristic subsurface structures leading to a more appropriate management of this very common benign epithelial lesion.

The classic dermatoscopic features of seborrheic keratoses include a sharply demarcated lesion with comedo-like openings, milia-like cysts, hairpin vessels, and sulci and gyri within a background color that usually ranges from tan to brown-black.27-29

Comedo-like openings refer to well-defined brown or black circular areas within the lesion,27 and milia-like cysts are whitish circular areas that are less well-demarcated.27 These structures histologically correspond to widened infundibulae and infundibular tunnels, respectively.28 Hairpin blood vessels refer to superficial telangiectasias arranged in loops that present in some seborrheic keratoses.28 The sulci and gyri or fissures represent the epithelial undulation that is frequently present in seborrheic keratoses. The widths of the sulci and gyri may significantly vary. Narrow-width sulci and gyri may appear as thick grids of pigment network, referred to as network-like structures, while the thicker sulci and gyri at the periphery of some seborrheic keratoses may resemble "fat fingers."31 Because milia-like cysts, comedo-like openings, hairpin vessels, and fissures may be observed in melanocytic lesions, absence of major melanocytic dermatoscopic structures should be confirmed.

Additional dermatoscopic features, namely signs, have been described, but their relevance and contribution in making the diagnosis seborrheic keratoses are unclear. The “wobble sign” has been described in reference to seborrheic keratoses, as these lesions do not wobble from side to side when the dermatoscope is moved (in contrast to papillomatous melanocytic nevi).29 The “jelly sign,” or jelly-like border, has been defined as peripheral subtle pigment appearing on the skin surface much as jelly would be spread over a piece of bread.32 Consistent reproducible descriptions and images of a jelly sign and the histologic correlate are lacking, and thus the reproducibility and utility of the sign requires further validation.

**SOLAR LENTIGO**

Dermatoscopic criteria of solar lentigo (Figure 8):

- Sharp demarcation
- Scalloped border (“moth-eaten”)
- Hypopigmented areas
- Light brown structureless areas
- Faint pigment network
- Linearly striated pigment network (“fingerprint” appearance)
- Pigment “psuedonetwork” (head and neck area only)

Dermatologists frequently encounter solar lentigines in the daily practice owing to their high prevalence and clinical variability in appearance. Solar lentigines are not infrequently biopsied by dermatologists because melanoma cannot be excluded with confidence by naked-eye examination. The diagnostic difficulty arises when solar lentigines are inflamed, heavily pigmented, or unevenly pigmented. The diagnostic difficulty may be compounded when the lesion occurs on the face and is accompanied by any of these atypical features. Sharply marginalized scalloped borders, hypopigmented areas, and light brown areas, characteristic of a solar lentigo, are better delineated through a dermatoscope.29,33,34
When pigment network is present in solar lentigines, it is regularly meshed, but faint and patchy. A more characteristic pigment network pattern may be present, namely linearly striated pigment network that has been likened to a “fingerprint” pattern. Histopathologically, this characteristic pigment network represents thin elongated rete-ridges (likened to “hockey sticks”) that are heavily pigmented at the basal layer. As there is some relationship between solar lentigo and seborrheic keratoses, the linearly striated pigment network can also be found in flat or “macular” seborrheic keratoses.

On the face, especially on a severely sun-damaged one, a different kind of pigment network may be observed. A network of pigment may be formed when closely set follicular openings that are spared of pigment are found within a background of an interfollicular interconnecting epidermis that is pigmented. The resulting pigment network has been referred to as pigment “pseudonetwork” of the face, since the network is not a manifestation of hyperpigmented ridges as in a conventional pigment network. One caveat is that if the follicles are sufficiently apart, a conventional pigment network may also be present. Pigmented solar (actinic) keratoses, flat seborrheic keratoses, lichen planus–like keratoses, and solar lentigines occurring on the face may exhibit this particular pigment network pattern. While these lesions usually have symmetric pigmentation around the follicular openings with a relatively even pigment pattern between them, early melanomas may have perifollicular asymmetric pigmentation and gray to brown granules within the interfollicular epithelium (annular-granular pattern). In advanced melanomas, sparing of the pigment around the follicular openings is no longer preserved, resulting in foci of homogenous black areas. Diagnostic difficulties arise when the nonmelanocytic pigmented lesions present with asymmetric pigmentation around the follicular openings surrounded by brown granules, making the differentiation from melanoma difficult and therefore necessitating a histologic confirmation if other dermatoscopic features of the benign lesion are not present.

CONCLUSIONS
Diagnostic evaluation of a skin lesion depends on multiple considerations that include history, context, naked-eye examination, and now dermatoscopic examination. Each of these factors may have a different impact depending on the clinical situation. In addition, the extent to which the dermatoscopic findings play a role in the diagnostic evaluation also depend on the user’s clinical experience as well as the entities to which they are being applied. For the novice, recognition of the more relevant and reproducible dermatoscopic structures and the limitation of their specificity offers a more fundamental approach to learning dermatoscopy. Attempting to simply memorize the colorful and metaphorical signs and names of the dermatoscopic structures may lead to inappropriate application of the diagnostic technique, as many of the dermatoscopic structures have not been fully validated, even the major ones, which have limitations on interobserver reproducibility.

Every dermatologist strives to become proficient in recognizing melanomas, but to become proficient, it is equally important to recognize all the simulators of melanoma and not only the
melanomas themselves. Dermatoscopy has the potential to increase the diagnostic accuracy of melanomas by increasing the diagnostic accuracy of pigmented and nonpigmented skin lesions that simulate melanoma. In other words, dermatoscopy has the potential to increase the specificity in diagnosing melanomas. Hence, step one of dermatoscopy may well have just as much of a clinically relevant role as the second step of dermatoscopy, a subject of the next issue. The importance and relevance of the first step are being recognized as additional algorithms in reference to step one are being formulated.\(^\text{36}\)

**REFERENCES**

SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

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

1) Compared to immersion contact dermatoscopy, polarized light dermatoscopy, either contact or noncontact, allows slightly better:
   a. diagnostic accuracy
   b. visualization of milia-like structures and comedo-like openings
   c. visualization of blue-white veils
   d. visualization of fibrosis and vascular structures
   e. All of the above
   f. None of the above

2) Which of the following layers is rendered translucent by dermatoscopy?
   a. Stratum corneum
   b. Stratum granulosum
   c. Stratum spinosum
   d. Stratum basale
   e. Stratum malpighii

3) Which of the following is (are) found on dermatoscopic examination in seborrheic keratoses but not in melanocytic lesions?
   a. Milia-like cysts
   b. Comedo-like openings
   c. Hairpin vessels
   d. Fissures
   e. All of the above
   f. None of the above

4) Which of the following findings on dermatoscopic examination is (are) specific for basal cell carcinoma?
   a. Prominent vessels
   b. White streaks
   c. Blue-gray lobules
   d. All of the above
   e. None of the above

5) Which of the following patterns, seen on dermatoscopic examination of solar lentigos and some seborrheic keratoses, corresponds to thin elongated rete ridges heavily pigmented at the basal layer likened to “hockey sticks” seen on histopathologic examination?
   a. “Fingerprint” pattern
   b. “Moth-eaten” pattern
   c. “Wobble sign”
   d. “Jelly sign”
   e. “Maple-leaf” pattern
   f. “Spoke-wheel” pattern
   g. “Chrysalis structures”
   h. “Blood spots”

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

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Sporotrichosis is the only subcutaneous mycosis for which direct examination or histology is of little or no value for diagnosis. The diagnosis solely rests on the isolation of *Sporothrix schenckii* in culture. On pathologic examination, causative organisms are rarely seen. Staining with fluorescent-labeled antibodies may aid in visualizing the cigar-shaped yeast forms; however, the organisms are still difficult to identify. Topical therapy is not effective. Potassium iodide is an effective treatment for sporotrichosis, but this agent has not been subjected to specific treatment trials comparing its efficacy against azoles or allylamine alternatives. Itraconazole is generally safe and well tolerated, and the relapse rate is low. Terbinafine could be another therapeutic alternative to treat the disease. Since 1998, researchers from Brazil suggested that feline transmission of sporotrichosis in Rio de Janeiro city was associated with a large and long-lasting outbreak of the disease. To understand the outbreak, there have been studies on the epidemiology and antifungal susceptibility of the *S. schenckii* strains through molecular diagnosis. Data suggest that all isolated strains were genetically related. (*SKINmed.* 2010;8:275–280)
arranged in flower-like groups (Figure 2). The conidia become detached from the conidiophores, sometimes being arranged side by side in a row bilaterally to the hyphae. The yeast parasitic phase is pleomorphic, showing spindle-shaped and/or oval cells measuring 2.5 to 5 μm in diameter and resembling a "cigar."

**Pathology**

Histologic, both suppurative and granulomatous, inflammation is seen in the dermis and subcutis. The causative organisms are rarely seen. Staining with fluorescent-labeled antibodies may aid in visualizing the cigar-shaped yeast forms; however, the organisms are still difficult to identify. Asteroid bodies are also seen. When numerous fungi are present, as in the immunocompromised host, budding yeast to cigar-shaped organisms are often identified by periodic acid-Schiff or silver stains.

**TREATMENT**

Topical therapy is not effective. Saturated solution of potassium iodide (SSKI) has been used with success. Although neither fungistatic nor fungicidal, SSKI is thought to affect the host’s immune reaction to the organism. Its cost is low, but it has a bitter taste as well as potential side effects (eg, iododerma, gastrointestinal upset, thyroid suppression). SSKI clearly is effective but has not been subjected to specific treatment trials comparing its efficacy against azoles or allylamine alternatives. Many factors can contribute to the shortage of relevant literature. The duration of therapy in patients taking SSKI will also depend on drug compliance. Treatment is limited by side effects and the therapeutic dose should be maintained for up to 4 weeks beyond the time of total clinical cure. Itraconazole, for example, is quite effective against sporotrichosis, compared with ketoconazole, which is ineffective. In a study of 17 patients with lymphangitic and cutaneous sporotrichosis, all had significant clinical improvement and mycological cure when treated with 90 to 180 days of oral itraconazole (100 mg/d). The drug is generally safe and well tolerated, and the relapse rate is low. Amphotericin B may be indicated in severe or disseminated disease. Fluconazole is thought to be effective in fixed cutaneous sporotrichosis and disseminated disease with bone and joint involvement. Terbinafine may be another therapeutic alternative to treat the disease. Some investigators found that patients have demonstrated good response with terbinafine with few adverse reactions. The dosage of terbinafine to treat sporotrichosis can range from 250 mg/d to 1000 mg/d, according to different studies.

**THE EPIDEMIC IN BRAZIL**

In Rio de Janeiro city, Brazil, the first case of human sporotrichosis transmitted by cats was reported at the Clinical Research Institute Evandro Chagas, Fiocruz, between 1994 and 1997. From 1998 until today, the number of zoonotic sporotrichosis cases has exponentially increased and investigators have characterized the beginning of an epidemic outbreak of zoonotic sporotrichosis transmitted by cats. This is the largest epidemic of sporotrichosis due to zoonotic transmission described in Rio de Janeiro.

Between 1998 and 2004, at the Evandro Chagas Clinical Research Institute, 1503 cats, 64 dogs, and 759 humans have been diagnosed with sporotrichosis by isolation of *S. schenckii* in culture. As a rule, feline disease preceded human and canine diseases, and persons most frequently affected included housewives taking care of cats with sporotrichosis. Domiciliary or professional contact with sick cats was observed in 84.1% of the canine cases and in 84.7% of the human cases. Among the latter, 57.1% reported a history of a scratch or bite. In one study, women were most commonly affected (n=122, 68%) and the age range was 5 to 89 years, with a median of 39 years. Among a group of 178 patients, 156 reported domiciliary or professional contact with cats with a suspected or confirmed diagnosis of sporotrichosis and 97 reported a history of a scratch or bite. The most frequent occupations were domestic activities (30%) and students (18%). Five percent of the patients were veterinarians and veterinary assistants. The disease was frequent in women involved in domestic activities and animal care.

**MOLECULAR DIAGNOSIS**

To understand the outbreak in Rio de Janeiro, Brazilian investigators have been studying the epidemiology and antifungal susceptibility of the *S. schenckii* strains cultivated from humans and cats involved in the sporotrichosis epidemic through fingerprinting.
analysis. They found 9 subtypes of S. schenckii, but none were associated with specific clinical forms. Their data suggest that all strains isolated from patients and cats with sporotrichosis originated from a common source and were genetically related.\textsuperscript{16,17}

**Clinical, Histopathologic, and Serologic Features**

The lymphocutaneous form was the most frequent clinical form (n=95, 55.6%), followed by the fixed cutaneous form (n=45, 25.3%) and multiple cutaneous lesions (n=29, 16.3%).\textsuperscript{15,18} Mucosal involvement was observed in 5 patients (2.8%), affecting the nasal cavity in 1 and the conjunctiva in 4.\textsuperscript{15,19,20} The lesions varied in morphology, including nodules, tubercles, pustules, cysts, gummas, ulcers, vegetating lesions, verrucous lesions, and plaques accompanied or not by lymphangitis. The predominant sites affected were the upper limbs (65.2%), followed by the lower limbs (12.9%) and the face (6.2%).\textsuperscript{13} Histopathologic examination of 73 biopsy fragments revealed a granulomatous infiltrate in 66 (90.4%), and the fungus was detected in 21 (28.8%), corresponding to a high frequency.\textsuperscript{13}

Arthralgia was a symptom reported by 53 (29.8%) patients, of whom 5 had signs of arthritis.\textsuperscript{13,21} According to investigators,\textsuperscript{13,15,18} in places with a large number of cases of the disease, reports of spontaneous regression are not rare, nor are the occurrence of hypersensitivity reactions such as erythema nodosum/multiforme.

For the first time, erythema nodosum\textsuperscript{22} and erythema multiforme\textsuperscript{23} were associated with sporotrichosis. These uncommon manifestations might be explained by different mechanisms, such as repeated inoculation during prolonged contact with sick animals, self-inoculation, dissemination of the fungus through the bloodstream, or aspiration of conidia and/or yeasts originating from lesion exudates or respiratory particles released by sneezing of the infected cats.\textsuperscript{18,24} In addition, continuous exposure to large amounts of fungus-contaminated materials and subclinical reinfections may result in hypersensitivity.\textsuperscript{22}

In 2004, investigators\textsuperscript{13} studied 52 patients with sporotrichosis confirmed by isolation of S. schenckii and reactivity to Montenegro skin test during the ongoing outbreak of this mycosis in Rio de Janeiro. The authors emphasized the importance of parasitologic confirmation and the possibility of incorrect diagnosis based on the lesion's appearance, epidemiologic information, and immunologic tests. The antigen used for the Montenegro skin test was conserved in either thimerosal 1:10,000 (group 1) or 0.4% phenol (group 2). Nineteen patients (39%) in group 1 and 7 (12%) in group 2 presented an induration >10 mm (P<.001). Sera from 3 patients (6.7%) reacted to indirect immunofluorescence for leishmaniasis, while sera from 10 patients (22%) reacted to enzyme-like immunosorbent assay. Fifteen patients (28.8%) presented with up to 2 lesions, with a predominance of ulcers. Forty-four patients (84.6%) were treated with itraconazole. The authors suggest that in the differential diagnosis between sporotrichosis and leishmaniasis, the possibility of coinfection, allergy to the reagent diluents, and cross-reactions should be investigated.

Thirteen (7.3%) of the 178 patients showed spontaneous regression of the cutaneous lesions, whereas 165 (92.7%) required specific treatment with itraconazole orally administered at 100 mg/d for 4 to 36 weeks (median = 12 weeks). Of these 165 patients, 49 (90.3%) were cured and 16 (9.7%) abandoned treatment. Five of the 9 diabetic patients required a longer treatment (16 to 24 weeks) and the itraconazole dose needed to be increased to 200 mg/d to 400 mg/d in 3 patients. Four other patients with chronic obstructive pulmonary disease and 9 with a history of alcohol abuse responded well to treatment of itraconazole 100 mg/d. All patients were followed up for 6 months to 1 year after the end of treatment and many remained in contact with cats with sporotrichosis. Lesion reactivation was observed in only 2 patients, who were successfully treated.

**Sporotrichosis in Cats and Dogs**

The first case of sporotrichosis disease in cats was described in 1956. The same investigators described other cases of sporotrichosis in cats and dogs between 1963 and 1964.\textsuperscript{25}

In 2002, researchers investigated the potential of cats as a possible source of infection. A total of 148 cats with sporotrichosis and 84 apparently healthy cats in domiciliary contact with the affected animals were studied regarding the presence of S. schenckii.
schenckii in different biological materials. The fungus was isolated from 100% of cutaneous lesions, 47 (n=71, 66.2%) nasal cavity swabs, 33 (n=79, 41.8%) oral cavity swabs, and 15 (n=38, 39.5%) pools of nail fragments from cats with sporotrichosis. S. schenckii was also isolated from oral swabs of 3 (n=84, 3.57%) apparently healthy cats in domiciliary contact with the affected animals (Figure 3). Isolation of the fungus from the nails and oral cavities of cats reinforces evidence indicating that transmission can occur through a scratch or bite, whereas isolation from nasal fossae and cutaneous lesions, together with the wealth of yeast-like elements observed in histologic sections of skin biopsies, demonstrates the possibility of contamination through secretions. The results of molecular typing of S. schenckii isolated from humans and animals support this hypothesis.

Until the 1990s, the largest series of cases involving dogs consisted of only 12 animals. Since 1998, a sporotrichosis epidemic affecting domestic pets and humans has been observed in Rio de Janeiro. In 2006, naturally acquired sporotrichosis resulting from an epidemic outbreak in the Metropolitan area of Rio de Janeiro was diagnosed in 44 dogs during a period of 5 years. Present knowledge about canine sporotrichosis is derived from a few reports of isolated cases. The large number of dogs with sporotrichosis observed in this epidemic might be attributed to cats acting as the main source of infection. In that study, sporotrichosis in cats preceded its occurrence among their owners and dogs with which they had contact. The majority of infected dogs probably did not have systemic manifestations, and cutaneous lesions may have resolved without treatment. Although the cutaneous lymphatic form is the most frequent clinical presentation in humans, the same does not apply to cats or, according to this study, to dogs. It is likely that the habit of dogs to sniff their environment is related to acquisition of the fungus through the nose. The presence of cats in the homes of humans and dogs with sporotrichosis was observed in 82.9% of cases. Findings suggest that sporotrichosis in dogs has a good prognosis and is easily treated, in contrast to cats in which the disease is usually severe, often systemic, and difficult to treat. According to investigators, dogs are probably not directly involved in the transmission of sporotrichosis in view of the scarcity of viable fungal elements in lesions and the absence of S. schenckii in the oral cavity. Apart from that, there were no reports of human cases associated with transmission from dogs in the epidemic in Rio de Janeiro. Other investigators have also suggested that cats are the most important vector in the transmission of sporotrichosis.

At the Instituto de Dermatologia Prof Azulay, Rio de Janeiro, Brazil, there were 78 cases of sporotrichosis associated with cat scratch and/or contact with cats (Figure 4) from 2000 until 2006. They have accomplished an extensive bibliographic review from published cases based on journals included in Medline and Lilacs. All data included were collected from cases reported of cat-transmitted sporotrichosis (CTS) between the years of 1980 and 2006 in Brazil. The main objective of their study was to investigate the epidemiology of CTS and confirm the Rio de Janeiro epidemic outbreak of CTS as well as to compare it with data from other states of Brazil (Figure 5). While there were no cases described in the north, northeast, and central west regions of the country, there were a few cases in the south and other states of the southeast region, apart from the state of Rio de Janeiro. An epidemic outbreak in Rio de Janeiro was confirmed by Fiocruz researchers from the year of 1998 to the present. According to these investigators, cases of CTS were revealed to be increasing with time. It is important to call public attention as
well as governmental authorities to improve the early diagnosis and treatment of sporotrichosis. A multidisciplinary team of health workers, including physicians, social workers, and veterinary personnel, is necessary to properly control the sporotrichosis outbreak. Moreover, Rio de Janeiro is a tourist town and therefore foreign travelers should be advised about this outbreak and physicians should learn to prevent and treat it properly.30

**IMPORTANT QUESTIONS, DISCUSSION, AND CONCLUSIONS**

There are still some very important questions to be answered: is it possible that the successive passages in those animals (cats) could have increased the virulence of the fungus? Has the organism of the cats worked as a filtering system to naturally select the more aggressive strains of *S. schenckii*? On the other hand, certain strains of a genotypic more aggressive *S. schenckii* might have occurred and contributed to suppression of the immune response, leading to an increased number of widespread cutaneous cases. Does it explain the high percentage of cutaneous disseminated cutaneous lesions compared with the normal population? What makes the Brazilian outbreak different?

There are many possible explanations on this matter. First of all, it is not considered at the present time to be an outbreak. That is because this outbreak has been going on since 1998. It can be characterized as an epidemic of sporotrichosis. The number of patients affected in addition to cats is steadily increasing each year without any focus from the authorities, despite the numerous notifications from the local health system. The cats affected with sporotrichosis carry a large number of parasites, and if the disease is not treated, it can be fatal. Humans and dogs behave differently. Both develop a localized form of the disease if there is no underlying immunosuppression. They usually carry fewer parasites and their immune systems can deal with them in a better way. Cats acquire the disease when they scratch themselves onto vegetation and when they fight with other street cats. Nevertheless, we still do not know why this epidemic is confined to Rio de Janeiro. Possibly it is because of the number of street cats in this city as well as the hygienic conditions of the population affected.11,12

There are important actions to be taken: to study the human and animal cases by an integrated team of physicians, veterinarians, and mycologists. Another step is to thoroughly investigate the environment, preferably by a team of biologists and ecologists, to examine the soil and vegetation conditions that propagate the infection and learn how to interrupt the chain of transmission of the disease to cats, dogs, and humans.

To control the outbreak in Rio de Janeiro, it is crucial to create a suitable system to notify public health authorities and identify potential risk groups and areas of high prevalence of CTS.

The general population should learn through educational actions about the potential risks of the infection. Moreover, medical, health, and veterinary professionals need to be properly trained to diagnose and treat the disease.

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

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Modern physicians harbor the notion that scientific dermatology originated and developed in Western Europe from the 17th century onwards. It is not true. In India, the therapeutics of dermatoses have been practiced by physicians for centuries. Several ancient Indian texts have discussed traditional methods of treating skin diseases, including the Charaka Samhita (6th century BC), which contains detailed descriptions of the causes, symptoms, signs, and prognoses of skin diseases.

CLASSIFICATION

According to Atreya Punarvasu, there are 18 types of dermatoses: 7 of them are major (Kepala, Udumbara, Mandala, Rishiyajiva, Punderika, Sidhma, and Kakana), while 11 are minor (Ekakushtha, Charamakushtha, Kitima, Vipadika, Alasaaka, Dadru, Charmadala, Pama, Visuphota, Sataru, and Vicharchika). The etiology of dermatoses, according to ancient Indian dermatologic literature, was related to 3 complexions (humors), whose morbidity vitiates the skin, blood, flesh, and the body fluids.

BODY HUMORS BALANCE AS SIGN OF HEALTH

According to Ayurveda, the factors responsible for causing skin diseases can pollute all the humors (Vata, Pitta, and Kapha), thus resulting in affliction of the skin, blood, flesh, and body fluids (Table). By the diagnosis of a particular dermatosis, the underlying humoral morbidity can easily be identified and vice versa. Dryness, atrophy, prickling pain, aching pain, contraction, dilation, hardness, roughness, horripilation, and dusky red colorations are the signs and symptoms of dermatoses of the Vata type. Burning, redness, exudation, suppuration, smell of raw meat, softening, and sloughing are the symptoms of dermatoses of the Pitta type. Discordance of the Kapha humor produces whiteness, coldness, pruritus, heaviness, sliminess, and softening. These concepts are still valid and form the basis of Ayurvedic treatment. Thus, the therapy of dermatoses consists of purification of the whole body system, along with systemic and/or local medication.

CERTAIN NOTEWORTHY PRINCIPLES

CONCEPT OF SENSE OF HEAT

In dermatologic practice, heat in the blood, or sense of heat (SOH), is not an uncommon complaint. It may manifest as eruptions, urticaria, toxicallergic dermatitis, reaction to medicine, erythroderma, genital eruptions, and acne. Discussing the origin of SOH, some experts maintain that temperament is the pattern of activity and reactivity of the body and is expressed in terms of elementary qualities: heat, coldness, pruritus, heaviness, sliminess, and softening. These concepts are still valid and form the basis of Ayurvedic treatment. Thus, the therapy of dermatoses consists of purification of the whole body system, along with systemic and/or local medication.
complex was studied in several skin diseases such as urticaria, drug-related dermatitis, and eczemas; SOH covering the entire body was also observed in acne, seborrheic dermatitis, melanodermatitis toxica, and rosacea. Certain Ayurvedic preparations such as khus (Vetiveria zizanioides) are particularly helpful in alleviating SOH and thus relieving the symptoms of dermatoses.

**Concept of Phagocytic Index Modification**

Phagocytes (polymorphonuclear leucocytes) of blood play an important role in the control and cure of skin infections. *Swerita Chiraita*, a bitter herb, was found to increase the phagocytic coefficients of the polymorphonuclear leucocytes, and may thus be invaluable in treatment of infective disorders such as chronic pyoderma, furunculosis, fungal, bacterial, and viral infections.9,10

**Role of Trace Elements**

Essential trace elements such as zinc, copper, selenium, and magnesium have been found to be rich in certain herbs. They are often an integral part of the enzyme systems that regulate major metabolic events in the body. In a number of skin diseases, alterations of several trace elements are observed. During inflammatory processes, a large number of free radicals are produced. The scavenger enzymes of free radicals, including superoxide dismutase and glutathione peroxidase, are dependent on these trace elements. Further, zinc plays an important role in the normal functioning of skin and hair. It has also been associated with a number of skin conditions, including acrodermatitis enteropathica, acne vulgaris, wound healing of leg ulcers, and pustular psoriasis. Several herbs that are rich in zinc, such as *Swerita chiraita*, are known to provide dramatic results in such disorders.9

**Blood Purification Concept**

Purification of blood is another important area that may help in amelioration of many skin and systemic disorders. Several Ayurvedic preparations have been used as blood purifiers. In addition, if properly selected and stored, they are believed to be less toxic and more useful in clearing dermatoses. Psychosomatic factors are important in several skin disorders such as psoriasis, lichen simplex chronicus, trichotillomania, neurotic excoriations, factitial dermatitis, parasitic delusions, and vulvodynia. Several herbal preparations such as Bacopa monniri, Nardostachys Jata mansi, and Withania somnifera have distinct anti-stress and neuropharmacologic effects. Ashwagandha (*Withania somnifera*) can be an effective adjuvant therapy for the treatment and prevention of neurocutaneous disorders.9,10

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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.

**DIAGNOSIS:** Erythema bullosum is to be differentiated by the presence of other lesions of erythema multiforme, the development of the bullae from erythematous macules, the distribution and comparatively acute course. In urticaria bullosa the blebs arise from wheals.

**TREATMENT:** Arsenic given to the limit of tolerance and long continued, often, but not invariably, produces good results. The greatest effort should be directed toward improving the patient’s general health. The bullae are to be evacuated, covered with pulvis talci salicylates N.F. and protected with dry compresses. Or a 2 per cent boric acid wet dressing may be employed. In severe, extensive cases the continuous warm bath gives the patient the most comfort.
Pitfalls abound in the diagnosis of melanomas, especially in differentiating between them and benign melanocytic lesions. One lesion in particular is diagnostically troublesome and was therefore given the designation of “pseudomelanoma” by Kornberg and Ackerman in 1975; however, true melanomas may be misdiagnosed under this term. There are other ways in which nevi may mimic melanomas, as the following will demonstrate.

**PSEUDOMELANOMA**

Pseudomelanoma consists of a recurrent nevocellular nevus in which, following incomplete surgical excision, most likely saucerization (i.e., “scoop,” “scallop,” or “shave” excisional biopsy, or “shave excision”), or partial destruction by other means, such as laser, the lesion recurs due to proliferation and/or migration of remaining nevocellular cells into the cicatrix (scar) that resulted from the destructive procedure. These melanocytic cells tend to grow irregularly in streaks of variable dimensions often accompanied by, in addition to scar tissue, inflammation and proliferation of blood vessels. In typical lesions, an irregular pigmented lesion in the site of a previously treated nevocellular nevus is seen clinically. The clinical appearance is, therefore, disturbing and may be reinforced by dermatoscopic findings that also resemble a melanoma or a dysplastic nevus. The diligent dermatologist may be unaware of the previous procedure and, in turn, sees a melanocytic lesion that indeed looks histopathologically worrisome. The typical lesion shows an irregular proliferation of melanocytes in or adjacent to scar tissue (Figure 1). These often line the dermoepidermal interface, but may occur within the scar. The tendency to line the interface is apparently due to an epidermotropism inherent in cutaneous melanocytes.

The diagnosis is confirmed by recognition that the connective tissue fibrosis is due to the procedure and does not represent a stromal reaction to the melanocytic lesion, when finding one or more nests of typical nevus cells within or adjacent to the scar tissue (Figure 2). This may represent a significant pitfall.

**PSEUDO-PSEUDOMELANOMA**

Wallace H. Clark, Jr, MD, renowned dermatopathologist who introduced both multivariate analysis and the variable of tumor thickness into the melanoma field, is said to have famously remarked upon learning of the newly coined term pseudomelanoma, “Melanomas recur, too.” Indeed they do.

This may happen if the initial lesion was not recognized as a melanoma. We refer to this lesion as a “pseudo-pseudomelanoma” (Figure 3). Because melanomas may arise in nevi, the residual nevocellular tissue may appear benign, even though the recurrent tissue is not (Figure 4). Simply recognizing that the lesion is recurring in a scar and identifying benign nevus tissue deep within the scar tissue is not sufficient to rule out a melanoma. This represents a situation where “a little knowledge is a dangerous thing.” Either lesion may occur in scar tissue in which deep nests of bland nevus cells are not visible on the histopathologic sections examined, further complicating the diagnosis.

**PSEUDOMETASTASIZING PSEUDOMELANOMA**

Lesions other than recurrent nevi may resemble melanoma, both clinically (with or without dermatoscopy) and histologically. One such lesion is the cellular blue nevus. Cellular blue nevi are also prone to undergo a process known as benign metastasis, in which tissue from an otherwise benign lesion or even some normal tissue disseminates to a local lymph node and then does not proceed further.

Nevi are especially prone to undergo this phenomenon, as is thyroid tissue. One of us (WCL) has previously reported this process in a 20-year-old woman who developed a metastatic lesion from a cellular blue nevus of the dorsum of her foot. Unfortunately, she had been previously misdiagnosed as having metastatic melanoma, leading to extensive surgery and morbidity with massive lymphedema of a lower extremity, when we first saw her. We coined the term *pseudometastasizing pseudomelanoma* to denote this type of lesion.
Nevi may also occur in lymph nodes and other internal tissue because of an error in histogenesis, in which melanocytes migrating from the neural crest in embryogenesis fail to reach their target tissue and then give rise to nevi. Most such lesions are simply never discovered. They may be found in a lymph node dissection or sentinel lymph node biopsy, following excision of a primary lesion, leading to confusion.

**Figure 1.** Case 1: Pseudomelanoma: Recurrent nevus cells in a "saucerization" excision cicatrix. (Hematoxylin and eosin stain, original magnification ×340).

**Figure 2.** Case 1: Pseudomelanoma: Nest of bland nevus cells deep within excision cicatrix. (Hematoxylin and eosin stain, original magnification ×340).

**Figure 3.** Case 2: Pseudo-pseudomelanoma: Melanoma cells within the epidermis following melanoma excision. (Hematoxylin and eosin stain, original magnification ×340).

**Figure 4.** Case 2: Pseudo-pseudomelanoma: Nest of bland nevus cells deep within excision cicatrix. (Hematoxylin and eosin stain, original magnification ×340).
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WAX MOULAGE


Courtesy of Michael Geiges, MD
Brooke Spiegler syndrome is an autosomal dominant genodermatosis that is characterized by the growth of multiple adnexal neoplasms including spiradenoma, trichoblastoma, trichoepithelioma, and cylindroma. The syndrome has been linked to a mutation in the tumor suppressor gene CYLD1, located on chromosome 16q12–13.1 The clinical phenotype is quite variable and may be characterized by the presence of one or all of these neoplasms. Familial cylindromatosis can be particularly disfiguring since the so-called turban tumors can be numerous and grow quite large.

Because of the superficial nature of trichoepitheliomas, destruction or ablation using CO2, Erb: YAG laser, or radiofrequency devices is often effective.2 Ablative therapies are generally not effective for cylindromas, however, because of their depth. In addition, because the growth of cylindromas generally spans the full thickness of the dermis, they cannot be shelled out like a cyst. Surgical management of cylindromas generally consists of deep excision of large or painful tumors to deep fat. Incomplete excision and recurrence are typical due in part to the multifocal nature of tumor development. Malignant transformation of cylindromas is fortunately rare,3 but the progressive growth of tumors is nonetheless a serious therapeutic and cosmetic problem for some patients. The presence of large confluent tumors can lead to complications such as infection, bleeding, and even chronic anemia.3

Agminated plaques of cylindromas tend to occur in the central portion of the forehead (Figure 1). The patient depicted in Figure 1 demonstrates cumulative tumor development on the forehead over the course of 35 years. Because of the wide area of involvement and the likelihood of recurrence, we chose to excise the problematic area in toto to the level of the frontalis muscle and graft with skin from an unaffected area of the body.
(posterior upper arm, Figure 2A). Since the patient was reluctant to undergo excision of the entire cosmetic unit of the forehead, a rectangular area of excision was designed to encompass the most concentrated area of tumor growth and allow placement of suture lines in preexisting horizontal skin lines of the forehead for best cosmesis. A full thickness skin graft was sutured to the recipient bed (Figure 2B) and a bolster dressing was applied (Figure 2C). The patient tolerated the procedure well, and the color and texture of the grafted skin is a satisfactory match to the uninvolved skin on the forehead after 2 months (Figure 3). There have been no new tumors within the grafted site to date (18 months post-operatively). The rectilinear design of the flap within the borders of the horizontal forehead lines allows for future subsequent excisions with grafting to be performed on adjacent tissue while respecting relaxed skin tension lines.

In summary, solitary cylindromas can be managed with conservative excision while large areas of recurrent agminated tumor may be best managed with full thickness skin grafting.

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A 56-year-old diabetic woman underwent total abdominal hysterectomy for stage IV clear cell endometrial carcinoma 4 months before presentation. After receiving the third cycle of chemotherapy (carboplatin, liposomal doxorubicin, and paclitaxel), she developed intestinal perforation that required emergent bowel resection and colostomy. Her hospital course was complicated by heparin-induced thrombocytopenia and development of ischemic gangrene involving both feet. Conservative treatment with local wound care was recommended. Three weeks later, the patient was readmitted for resumption of chemotherapy. On examination, both feet showed mummified toes with dry gangrene with a mold-like coating over the plantar aspect of her foot (Figure 1). The patient underwent debridement followed by bilateral transmetatarsal amputations. Multiple tissue cultures grew the fungus shown in Figure 2.

**CLINICAL COURSE**

The fungus was identified as *Paecilomyces lilacinus*. The patient was treated with intravenous voriconazole and wound lavage with amphotericin B; however, her clinical condition rapidly deteriorated with the development of intra-abdominal sepsis, which was poorly responsive to conservative treatment. The decision was made to withhold aggressive measures and she was discharged to hospice care, where she died. No fungi were isolated from fungal blood cultures.

**DISCUSSION**

*Paecilomyces* species are saprophytic filamentous fungi that are found worldwide in soil and as air and water contaminants. Although *Paecilomyces* species are uncommon pathogens, they can produce serious infections in immunocompromised patients, and the incidence of infections in immunocompetent hosts has been increasing in recent years. The majority of cases described in the literature involve patients with identified predisposing factors. The most common predisposing factors for cutaneous and subcutaneous infections are solid organ and bone marrow transplant, malignancy, and corticosteroid therapy.

*P. lilacinus* and *Paecilomyces variotii* are the two species associated most frequently with human disease. The differentiation between these two species is clinically important, since there is a marked difference in their in vitro susceptibilities to the antifungal agents. *P. lilacinus* grows rapidly on Sabouraud's dextrose agar and develops colonies with a violet appearance when mature. The identification of *Paecilomyces* is difficult for most clinical microbiological laboratories because it can be morphologically confused with other fungi.
such as Penicillium. Assistance of a reference laboratory is often required. The optimal treatment for *P. lilacinus* infections has not yet been established. In localized infections, removal of the infected foci and elimination of any foreign body should be attempted, if feasible. Amphotericin B, itraconazole, and echinocandins have shown poor activity against *P. lilacinus*, while the new triazoles are active against it. *P. variotii* on the other hand has exhibited a different susceptibility pattern, being susceptible to most antifungal agents apart from voriconazole and ravuconazole. Optimal duration of treatment is unknown, but a minimum of 3 months of potent antifungal treatment is suggested by some authors.

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Born in Bačko Dobro Polje (Kis Kér/Klein-Ker) in the then Kingdom of Hungary, Austrian Empire, David Gruby was schooled in Budapest, attended medical school in Vienna, and received his medical degree in 1839. Shortly after, he moved to Paris and continued his microscopic research, started in Vienna. He would have been required to change his Mosaic denomination to pursue a career in Austria.1

BACKGROUND
He discovered many fungi, eg, Candida albicans and Trichophyton ectothrix. Gruby also described the propagation of puerperal infection via lymph and blood vessels, thereby anticipating Ignaz Philip Semmelweis’ clinical observation a few years later. As a practitioner, he counted among his patients Frédéric Chopin, Franz Liszt, Alexandre Dumas père, Heinrich Heine, Alphonse Lamartine, and other celebrities.

Heinrich Heine, Jewish-German poet in France, caustically joked that he has a doctor so small that somebody might think he has no doctor. Well, Gruby was short in stature but big in brain. When he died, he left a fortune of $300,000 to his kinship of several dozen persons in the Gruby mishpakhah. Sure, this was a bit less than the £200,000 Sir Erasmus Wilson had left a few years earlier, and more than the 51,000 fl. Salomon Stricker left to his widow (still a lordly sum) in the very same year. Wilson was of Scottish-Norwegian descent, while Gruby and Stricker were Hungarian Jews.

During the nineties of two centuries ago, another Serbian gentleman Dr Milroad Obradović dedicated much time to investigate the background of the master and the Gruby clan. I knew of this endeavor through Professor Kovać, but, alas, before Obradović could finish and publish, he met his untimely death. Professor Nikola Gaćeša, together with a foreword by Professor Kovać, published part of it posthumously in Serbian in 2006. More details of the Gruby story will emerge in the history seminar at the Seoul World Congress of Dermatology in 2011 by Professor Sarolta Kárpáti, head and chairwoman of dermatology at the Semmelweis University in Budapest. Why then? There is some suspicion that Gruby was in fact born in 1811 and not in 1810.

On occasion of the forthcoming bicentennial of Gruby’s birth (August 20), a bronze portrait bust was unveiled in his birthplace, a small community on the right bank of the lower Danube about 200 km south of Budapest, in Serbia of today (Figure). This move was initiated by Professor Teodor Kovać, erstwhile president of the Jewish Community in Novi Sad (Úvidék/Neusatz/Neoplanta), regional capital of the Vojvodina, and by the local administrative authorities.

HUMANITIES AND SCIENCE
Still another point to be emphasized: 200 years ago, the humanities and the sciences developed alongside education. The above-mentioned Agostino Bassi for instance, as much as his teacher Lazzaro Spallanzani (born 1729) (the portraits of both hung in Louis Pasteur’s laboratory), were both law graduates. Imagine the polyglot capabilities a man such as Gruby must have had: Yiddish and Hebrew as much as Hungarian were sung at his cradle; countless years of Latin, Greek, and German followed during the classes of gymnasium; then medical school; followed by 50 years of French (which he probably had to learn earlier since many at the time, including Kaposi, insisted that French
be spoken at the table in the home regularly, as confided to me [KH] by his granddaughter Hildegard).

Admittedly, a PhD in medicine/biology today may be much more knowledgeable than Gruby was in this field. What immeasurable flexibility, however, the study of more than half a dozen languages (and cultures) must have conferred to his thinking, a far cry from the monolingual Anglo-Saxon of today.

Scientific thinking, including planning handwork, needs both the humanities and the sciences. This is neglected today, deplorably so. The late giant of our field, Darrel Wilkinson, and I [KH] discussed this topic time and again over the decades, eg, comparing the number of lines we had to learn by heart of one or the other classical poets, and the influence such background has on our present-day activities.

Gruby was an early hero of microscopy, before the developments of Ernst Abbé, Carl Zeiss, Carl Weigert, Ira van Gieson, Oskar Israel, and Robert Remak, to haphazardly name just a few. They facilitated the application of microscopic techniques, until the star in mycology appeared on the scene, Raymond Sabouraud, who was born in the year when Johann Lucas Schönlein died (1864).

DEDICATION

Being invited to remove the cloth from the memorial bust and place a wreath, together with the local dignitary in the name of the Vienna and Budapest medical schools, was a signal honor for the authors. These lines may serve to stimulate our memory of the early microscopic researcher and enliven the overabundance of the medico-Judean heritage of Central Europe, the date, April 12, 2010 (28 Nissan), Holocaust Day, being conducive to this act.

REFERENCE

A 35-year-old male prisoner presented with a 9-month history of an enlarging, asymptomatic plaque on the chin, which later ulcerated and became secondarily infected. The patient was positive for the human immunodeficiency virus, with a CD4 cell count of 135.

The Mantoux test was positive and blistering, and findings on chest x-ray were normal.

Skin biopsy and tuberculosis culture confirmed Lupus vulgaris. The patient was commenced on antituberculosis treatment and responded very well.

From the Department of Dermatology, Nelson R. Mandela School of Medicine, Durban, South Africa

STOMATOPYROSIS

Also known as burning mouth/tongue syndrome (BMS), stomatodynia, glossopyrosis, or glossodynia, stomatopyrosis represents burning in the mouth and may be caused by the following medications:

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- Penicillin
- Atacand
- Prinivil
- Cephalosporins
- Sinequan
- Chloroptic
- Sustива
- Gold
- Teveten
- Klonopin
- Vasotec
- Mercury
- Viramune
- Neurontin
- Zephrex
- Pamelor
- Zestril

Adapted from Litt, JZ. Curious, Odd, Rare, and Abnormal Reactions to Medications. Fort Lee, NJ: Barricade Books; 2009:165–168.
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Klippel-Trenaunay syndrome (KTS or angio-osteohyper trophy) is a sporadic vascular malformation with no confirmed genotype that consists of a triad of superficial vascular malformation of the skin in association with venous varicosities and underlying bony and soft tissue hypertrophy. The distribution of the vascular stain in a mosaic pattern led Happle to postulate that the disorder would only occur in the setting of a somatic mutation. Genetic analysis has identified several cases of KTS associated with an upregulation of VG5Q, an angiogenic factor. Vascular birthmarks are classified into 2 major categories, which include hemangiomas and the rarer vascular malformations. Hemangiomas are characterized by endothelial cell hyperplasia, a rapid proliferative phase, followed by a period of involution. In contrast, vascular malformations lack endothelial hyperplasia, do not involute, and are categorized according to the type of vessel involved and hemodynamic features.

The condition acne keloidalis nuchae describes keloidal papules often coalescing into plaques arising on the posterior scalp and neck. The lesions are thought to be secondary to chronic perifolliculitis and folliculitis that results in destruction of the follicle and liberation of hair shafts with ensuing fibrosis and ultimately keloid formation. Acne keloidalis nuchae typically occurs in men of African descent but also occurs in Hispanics, Asians, and less often in Caucasians. Patients present with suppurative inflammation of the follicular unit that heals with keloid papules which may coalesce into plaques over time.

We present a patient with KTS and a 10-year history of acne keloidalis nuchae with massive keloidal hypertrophy on the occipital scalp in the distribution of his congenital capillary malformation. Literature searches were performed to assess previous cases demonstrating a connection between keloid
formation and underlying vascular malformations. Cross reference of “Kippel-Trenaunay” and “keloid,” “vascular malformation” and “keloid,” “port-wine stain” and “keloid,” and “Sturge Weber” and “keloid” in both OvidMedline and PubMed yielded no results. Similar growth factors and abnormal structural elements, however, are involved in the etiology of both vascular malformations and keloids.

One of the major hypotheses for the pathogenesis of keloids is the concept that there is enhanced growth factor activity. A key explanation behind the alterations in growth factor activity in keloids is the relative hypoxia found in keloid tissue. The hypoxic microenvironment present in the early stages of wound healing triggers the release of angiogenic growth factors, inducing endothelial proliferation, delaying wound healing, and increasing collagen production. Some evidence also suggests that keloids are, to a degree, angiogenic lesions. Histologically, keloids show increased blood vessel density compared with normal dermis or normal scars. In fact, many of the treatments for keloids such as pulsed dye laser, interferon, and imiquimod are believed to target keloid development by inhibiting angiogenesis.

In vitro and in vivo studies have demonstrated a significantly higher angiogenic activity of keloid fibroblasts compared with normal fibroblasts, and vascular endothelial growth factor (VEGF) levels have been demonstrated to correlate with this activity. Hypoxic stress, an acute condition of the early wound, has been characterized as a powerful inducer of VEGF expression in vitro and in healing skin wounds. Recent works have demonstrated an accumulation of hypoxia-inducible factor 1α protein in freshly biopsied keloid tissue, thus providing first evidence that a local state of hypoxia exists in keloids. Hypoxia-inducible factor 1α contributes to keloid formation by activating transcription of VEGF. Reports have also demonstrated a strong association between elevated tissue expression of VEGF and vascular malformations. Nitric oxide is another molecule implicated in both the regulation of vascular endothelial cell proliferation by increasing VEGF expression and in the genesis of keloids.

This is the first case report, to our knowledge, of massive keloid overgrowth corresponding to the distribution of an underlying vascular malformation. This interesting case highlights the idea that in a susceptible patient, common, underlying elements including growth factors, hypoxia, and nitric oxide may play a role in the development of both vascular malformations and keloids. The most common causes of keloid formation are mechanical. Although the clinical time line does not suggest it, this patient’s keloid could have resulted from surgical treatment of his vascular formation, or, theoretically, from bleb formation, causing follicular occlusion and keloid formation. Although one would suspect keloid formation associated with a vascular malformation to be more common if the pathogenic mechanisms and etiologies were overlapping, as we theorize, it is nonetheless an interesting and valid idea. Because this is an isolated case, more research needs to be done in this area to truly link the pathogeneses of these two conditions.

REFERENCES


Psoriasis Triggered By Mefloquine

Joseph L. Pace, MD, FRCPEdin, FRCPLond

A 46-year-old Caucasian man living on the central Mediterranean island of Gozo (Malta) was started on mefloquine 250 mg once weekly before a trip to lower Egypt. He took his medication 1 week before starting his holiday and was advised to continue it for 4 weeks after returning. He did not take any other medication and enjoyed the holiday, which he initially intended to repeat in the near future. His medical history revealed a number of episodes of psoriasis for which he sought dermatologic advice. He had been given systemic therapy on at least one occasion, but the condition had been fairly quiescent for some time and he had not needed to consult a dermatologist for more than 4 years. Soon after the third tablet of mefloquine and effectively just after his return home to Gozo, the patient noticed that the psoriasis was “creeping back.” He noted progressive deterioration in his skin problem but nevertheless finished the recommended course of therapy considering that “being sure about not developing malaria was far more important than a touch of psoriasis.” The psoriasis worsened to the extent that he had taken off work for 2 weeks from his job as a self-employed carpenter at the time of referral. On examination, clearly there was a significant flare up of his psoriasis with severe involvement of the hands (Figure 1) and feet and less so over the rest of his body. He had been off work and matters were steadily getting worse in spite of topical treatment with a combination of calcipotriol-betamethasone ointment. Oral methotrexate 15 mg once weekly was commenced together with topical therapy with good results (Figure 2).
Psoriasis Triggered By Mefloquine

While cutaneous side effects of mefloquine have been greatly overshadowed by the neuropsychiatric problems related to this drug, it is important to remember that they can occur. It appears that in addition to cutaneous vasculitis,\(^{17}\) mefloquine may also, although rarely, cause an exacerbation of psoriasis. It nevertheless remains a choice in psoriatic patients who cannot avoid going to an area where malaria is endemic, but the possibility of a flare up needs to be kept in mind. Additionally, the very frequent psychological side effect encountered with this drug may constitute a potential further aggravating factor.

CONCLUSIONS

While cutaneous side effects of mefloquine have been greatly overshadowed by the neuropsychiatric problems related to this treatment, it is important to remember that they can occur. It appears that in addition to cutaneous vasculitis, mefloquine may also, although rarely, cause an exacerbation of psoriasis. It nevertheless remains a choice in psoriatic patients who cannot avoid going to an area where malaria is endemic, but the possibility of a flare up needs to be kept in mind. Additionally, the very frequent psychological side effect encountered with this drug may constitute a potential further aggravating factor.

REFERENCES

A 55-year-old high school science teacher with diabetes presented with severe pain and swelling of his left hand. He reported receiving a “shock” 2 days earlier while cleaning out his classroom’s aquarium with a bare left hand. Thinking it was a “short” in the electrical connections to the aquarium’s pump, he disconnected the electrical cord and continued to clean behind the pump mechanism. After a few more such shocks he put on a glove and retrieved 10 foot-long worms. Antibiotics were started. It took more than 2 weeks for the hand to return to its normal size. On presentation to our office, the patient’s left hand was moderately swollen, with blistering and purpura seen on his distal fingers. He reported pain, itching, and numbness in the hand, which was getting worse. No systemic symptoms were reported. The patient was a non–insulin-dependent diabetic who was also taking warfarin for a carotid vascular problem. He brought to our office a bucket with coiled aquatic worms at the bottom (Figure 1). When extended, they measured about 1 foot and their morphology could be better seen (Figure 2). No spicules could be seen in the patient’s hand on magnification, but taping was performed to remove any possible residual spicules. The patient was given oral antibiotics, a Medrol dose pack, oral antihistamines, and topical corticosteroids. Within 1 day of starting treatment his symptoms and hand swelling began to abate, by 1 week his hand skin peeled, and by 2 weeks the swelling and skin appearance was almost back to normal. Bacterial cultures of the hand’s wounds showed no growth.
The two most effective ways to remove the bristles are to use forceps or tape. The forceps method is usually too difficult because the very small bristles can be deeply embedded in the skin. One usually applies adhesive tape to the skin and a quick removal of the tape can pull out the bristles. To relieve pain, one can place the affected area in a hot water bath (110°F–115°F) with dilute vinegar or ammonia. Other topical remedies include meat tenderizer and 40% to 70% isopropyl alcohol. The pruritic and local urticarial component may be treated with cooling creams or lotions, topical corticosteroids, and antihistamines.9

CONCLUSIONS

We report a case of a middle-aged diabetic teacher who was stung repeatedly by a tropical sea worm, the bristle worm, when cleaning out the classroom's salt water aquarium. His hand significantly swelled and blistered, and, after treatment was initiated a few days post-envenomation, his recovery took approximately 2 weeks.

Sea worms of the family Amphinomidae can have chitinous bristles around their bodies. When touched, they raise their bristles in defense as the bodies of the worms contract. This presents to any enemy a continuous bristled surface. The bristles detach easily and can penetrate the skin in a similar fashion to cactus spines. They can be as difficult to remove as cactus spines as well.8,9 The worms found in our case had all the traditional markings of *Hermodice carunculata* Kinsberg, the most common bristle worm of the Gulf of Mexico. It most likely entered the school aquarium in porous rock bought at a local store.

Our case study highlights the increasingly more common occurrence of aquatic skin injuries and the need to be vigilant even with our own aquariums. Our patient had a relatively uneventful recovery but he had other medical problems that could have led to serious complications.

REFERENCES

5. Phillips C, Brady WH. *Sea Pests, Poisonous or Harmful Sea Life of Florida and the West Indies.* University Miami Press; Miami, FL. 1953:247.
CASE STUDY

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

Baris Malbora, MD;1 Engin Senel, MD;2 Zekai Avci, MD;1 Namik Ozbek, MD1

An 18-month-old boy was consulted to a pediatric clinic with a 5-month history of purpuric macules and nodules on the scalp. He had a history of trauma (falling down from a chair) to the scalp about 6 months before the consultation. He had been brought to an emergency department after the trauma. Cranial computed tomography revealed a small crack on the temporal bone. Purpuric macules and nodules of the scalp had been noticed on the control 1 month later. Results of total blood tests had been within normal limits. Dermatologic examination disclosed multiple purpuric infiltration cutaneous nodules and purpuric macules with diameters of 0.5 to 1.5 cm on his scalp (Figure 1). No petechiae or ecchymoses were seen. Cervical lymphadenopathy was detected during physical examination. There was no hepatosplenomegaly. A punch biopsy was obtained from one of the infiltrated nodules and was sent for histopathologic examination. Histopathologic examination revealed diffuse dermal and subcutaneous edema, erythrocyte extravasation and infiltration by monomorphic cells with large hyperchromatic nuclei, and high mitotic activity (Figure 2). Histopathologic staining was positive for leukocyte common antigen and CD68 in these cells. Results of complete blood count of the patient were as follows: hemoglobin: 8.44 g/dL; white blood cell count: 29.2 × 10⁹/L; and platelet count 55.6 × 10⁹/L. Bone marrow aspirate results showed 68.4% blast cells and a biopsy specimen confirmed the diagnosis of acute myeloid leukemia, with flow cytometry findings positive for acute monoblastic leukemia (AML) French-American-British (FAB)-M5 phenotype. We initiated induction chemotherapy for AML (AML-M5) according to the AML Berlin–Frankfurt–Munster 2004 protocol.1 Complete resolution of the leukemia cutis lesions was attained with chemotherapy at the end of the first month of treatment.

Cutaneous involvement can be the presenting sign of hematologic malignancies in children. Leukemia cutis is the infiltration of neoplastic leukocytes into the skin with clinically identifiable cutaneous lesions, and it is associated with poor prognosis of leukemia.

The incidence of AML is 4.8 to 6.6 per million in children younger than 15 years.2 There is no male or female preponderance. The incidence of leukemia cutis appears to be relatively higher in children than in adults. Skin involvement in leukemia has been observed in 25% to 30% of patients. Most of these patients have myelogenous leukemia. The pathogenesis of the migration of leukemic cells to the skin is not clear.

Skin lesions of leukemia cutis include specific lesions resulting from the infiltration of the skin by the leukemic cells and nonspecific lesions such as erythema, ecchymoses, or reactive dermatosis (eg, Sweet syndrome–like lesions and urticaria). The specific lesions of leukemia cutis are often asymptomatic and mostly seen in the nodular morphology.3 Blueberry muffin is a term referred to the appearance of the specific nodular lesions in addition to purpuric lesions. Although skin involvement may be the presenting feature of leukemia in a patient, as in our case, leukemia cutis is often a late involvement of leukemia and is associated with poorer prognosis. Investigators described 9 children with skin lesions as a presenting sign of leukemia and reported that these patients had unfavorable prognostic factors such as hepatosplenomegaly, early onset, and high leukocyte count.4 In a review of the medical literature on AML from 1965 to 2001, it was reported that the overall survival rate was 6% at 2 years in patients with leukemia cutis and 30% in those without leukemia cutis.5

The differential diagnosis of leukemia cutis in infancy includes metastatic neuroblastoma, urticaria pigmentosa, and Langerhans cell histiocytosis. Histopathologic findings of leukemia cutis show different patterns of infiltration of leukemic cells depending on the subtype of leukemia. The most common pattern has been reported to be diffuse infiltration, which may separate collagen bundles.7 A bandlike or compact nodular infiltration pattern may also be seen in acute myeloid leukemia with the large cells. Immunophenotyping of the infiltration with specific markers is required for subtyping. Acute myeloid leukemia cells...
stain with lysozyme but not with chloracetate esterase. M4 and M5 types of acute myeloid leukemia express CD15, CD43, and CD45; CD68 is also expressed in the M4 and the M5 types.7

Treatment of childhood acute myeloid leukemia consists of remission induction chemotherapy followed by post-remission chemotherapy with or without bone marrow transplant; however, aggressive chemotherapy and bone marrow transplant have been known to add increased risk of morbidity and mortality. A few cases with spontaneous regression have been reported in the literature.8

Physicians should be aware of the clinical features of leukemia cutis because occurrence of the skin lesions may be the presenting sign of leukemia and a skin biopsy may help in early diagnosis of the hematologic malignancy.

REFERENCES

For the esthetician, a most encyclopedic text. This book is so chock full of facts that its usefulness will not only be for its intended audience of estheticians and physician extenders but also for dermatologists and cosmetic chemists.

The textbook begins aptly with a chapter concerned with defining the roles of the licensed esthetician—“a person who is professionally interested in the health and beauty of…the skin”—the nurse and medical assistant, the physician assistant, nurse practitioner, and most of all, the physician, all of whom may be involved in the medical spa.

Major sections include basic physiology of the skin, reflecting the senior author’s excellent training at the University of California at San Francisco. This means good discussions of the skin barrier and contact dermatitis. There are additional snippets about commonly encountered skin diseases that could be useful for patient handouts about various diagnoses.

Additional sections are devoted to cosmeceuticals and “putting it into practice.”

In the chapter on botanical ingredients, there is straightforward information, as reflected by Table I and Table II.

The book seems carefully researched* and is well executed.

—Lawrence Charles Parish, MD, MD (Hon), Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

*I checked some of the details and found the authors were correct in stating that dental education can be three or four years. The University of the Pacific has the three-year curriculum.
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BRIEF SUMMARY

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

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

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

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

Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

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

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

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

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (two times daily) for which Locoid Lipocream is indicated are different from the subject population (mild to moderate atopic dermatitis) and the dosing regimen (three times daily) in this HPA axis study. The disease severity was higher in the HPA axis study, which may have contributed to the high percentage of subjects who were seen at doses ≥0.6 mg/kg/day (0.2X MTHD). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses ≥0.6 mg/kg/day (0.2X MTHD).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of Locoid Lipocream. Hydrocortisone butyrate revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y/TK+ mouse lymphoma assay) and one in vivo genotoxicity test (mouse micronucleus assay).

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

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

PATIENT COUNSELING INFORMATION
Patients using Locoid Lipocream should receive the following information and instructions:
Apply a thin layer to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin areas, as diapers or plastic pants may constitute occlusive dressings.
Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings.
Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician.
If no improvement is seen within 2 weeks, contact your physician.
Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.

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

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

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The power of an ointment with the elegance of a cream

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

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

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

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