

COMMENTS AND OPINIONS

Ivermectin: A Few Caveats Are Warranted Before Initiating Therapy for Scabies

We read with interest the excellent article by Chouela et al¹ and the insightful editorial by del Giudice and Marty² concerning ivermectin therapy for scabies in a recent issue of the ARCHIVES. We would like to offer additional comments concerning dosage, the safety of ivermectin therapy with respect to neurotoxic effects, and concern for developing resistance.

Ivermectin Dosage. As alluded to by Chouela et al,¹ a single 200-mg/kg dose of ivermectin is not always successful in the treatment of scabies. In Toledo, Ohio, we have increased our dosage to 250 mg/kg,³ since we were achieving only 80% success rates with 200 mg/kg. A colleague is presently treating patients with 400 mg/kg. From veterinary literature, different animals require this higher dosage with ivermectin therapy.

In agreement with both authors, a second 200-mg/kg oral dose of ivermectin 1 week after initial treatment is a more reliable treatment option. This scheduling is identical to that for the treatment of head lice with this oral drug.^{4,5} Inasmuch as (1) scabietic mites feed by ingesting intracellular fluids within the epidermis, (2) their eggs hatch every 8 to 10 days, and (3) the serum half-life of ivermectin is 16 hours, one can assume that the second dose of ivermectin is needed to eradicate newly hatched scabietic nymphs.

Safety of Ivermectin. To assess potential adverse effects of this insecticide, a short discussion of its mechanism of action is required. Ivermectin works by binding selectively to specific receptors of neurotransmitters that function in the peripheral motor synapses of invertebrates, but these same neurotransmitters exist in brains of mammals. Specifically, ivermectin blocks chemical transmission across the nerve synapses that use glutamate-gated anion channels or γ -aminobutyric acid-gated chloride channels. They do not affect synapses gated by other transmitter substances, such as acetylcholine, norepinephrine, and serotonin. In humans (unlike invertebrates), γ -aminobutyric acid and glutamate do not affect peripheral motor function. This is the reason invertebrates are selectively paralyzed by the drug.

Nevertheless, these 2 neurotransmitters are found elsewhere in the central nervous system of mammals. γ -Aminobutyric acid is a neurotransmitter in the spinal

cord and brain, and glutamate is a neurotransmitter in many sensory pathways and in the cortex. Basically, ivermectin can only be toxic to mammals if the drug passes across the blood-brain barrier into the spinal cord, mid-brain, or cerebrum. Such a scenario could result from higher unbound plasma ivermectin concentration, a more permeable blood-brain barrier, suboptimal functioning of P-glycoproteins, or a specific blood-brain transport mechanism for ivermectin. The package insert only reassures us somewhat by stating that "ivermectin does not readily cross the blood-brain barrier in humans."

In short, ivermectin therapy should not be administered to children under 15 kg, and caution should be used when treating pregnant women or mothers who are breastfeeding. From veterinary literature, it has been substantiated that the blood-brain barrier may be deficient in young mammals. This allows ivermectin to enter the central nervous system, causing adverse effects, including depression, tremors, ataxia, coma, and breathing difficulties. Additionally, at very high dosages, treatment with ivermectin has caused embryotoxicity in animals.⁶ Although the drug has been used outside the United States by millions of people, including pregnant women and mothers who are breastfeeding, to treat onchocerciasis with no major sequelae,⁷⁻⁹ one should still be cautious until further studies are completed.

Ivermectin Therapy Resistance. As alluded to in the article by del Giudice and Marty,² resistance to ivermectin therapy has already been documented in horses, sheep, and goats after almost 20 years of extensive use.^{10,11} Two mechanisms of resistance are known. First, resistance can be achieved via alteration of P-glycoprotein, which is a membrane protein that actively transports ivermectin across cell membranes.¹² Second, alterations of the chloride channel receptor may decrease the organism's responsiveness to ivermectin therapy. Of note, no resistance has been reported in humans.

Craig N. Burkhart, BS
 Sylvania, Ohio
 Craig G. Burkhart, MSPH, MD
 Department of Medicine
 Medical College of Ohio
 5600 Monroe
 Suite 106B
 Sylvania, OH 43560

1. Chouela EN, Abeldano AM, Pellerano G, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol.* 1999;135:651-655.
2. del Giudice P, Marty P. Ivermectin: a new therapeutic weapon in dermatology? *Arch Dermatol.* 1999;135:705-706.
3. Burkhart CG, Burkhart CN. An epidemiologic and therapeutic reassessment of scabies. *Cutis.* In press.
4. Burkhart CG, Burkhart CN, Burkhart KM. An assessment of topical and oral,

prescription and over-the-counter treatments for head lice. *J Am Acad Med.* 1998;38:979-982.

- Meinking TL, Burkhart CG, Burkhart CN. Update on treatment of scabies and head lice. In: James WD, Cockrell DJ, Dzubow LM, Paller AS, Yancy KB, eds. *Advances of Dermatology.* St Louis, Mo: Mosby-Year Book Inc; 1999; 15:1-42.
- Poul JM. Effects of perinatal ivermectin exposure on behavioral development of rats. *Neurotoxicol Teratol.* 1988;10:267-272.
- Pacque M, Munoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet.* 1990;15:1486-1489.
- Doumbo O, Soula G, Kodio G, Perrenoud M. Ivermectin and pregnancy in mass treatment in Mali. *Bull Soc Pathol Exot.* 1992;85:247-251.
- Chippaux JP, Gardon-Wendel N, Gardon J, Ernould JC. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg.* 1993;87:318-319.
- Waller PJ, Echevarria F, Eddi C, Maciel S, Nari A, Hansen JW. The prevalence of anthelmintic resistance in nematode parasites of sheep in southern Latin America: general overview. *Vet Parasitol.* 1996;62:181-187.
- LeJambre LF, Gill JH, Lenane JJ, Lacey E. Characterization of an ivermectin resistant strain of Australian *Haemonchus contortus*. *Int J Parasitol.* 1995;25: 691-698.
- Xu M, Molento M, Blackhall W, Ribeiro P, Beech R, Prichard R. Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog. *Mol Biochem Parasitol.* 1998;91:327-335.

Ivermectin for Scabies

I applaud the efforts of Chouela et al¹ in confirming the efficacy and safety of ivermectin for treating human scabies. Scabies can be difficult to diagnose and the regulations of the Clinical Laboratory Improvement Amendments of 1998² have severely hampered the dermatologist from making bedside diagnoses in nursing home patients. The sequelae of missed diagnoses of scabies in nursing home patients in the memory loss unit, where I consult, recently resulted in costs of \$15 000 for cleaning and medications. Easily administered and safe oral treatments are welcome for the persistent and potentially serious problem of scabies and the subsequent costs. I agree with Chouela et al¹ that further studies are necessary to confirm the long-term safety and efficacy of ivermectin for the treatment of scabies, especially among immunosuppressed and pediatric patients.

Topical preparations containing permethrin and lindane, while effective and safe, lack the ideal characteristics for treating scabies in an institutional setting, such as a nursing home, for several reasons. First, even the best nursing homes are frequently understaffed, and current therapies greatly strain the limited nursing time. Second, applying creams to the entire body of a patient is difficult in nursing home populations because patients are frequently confused, hostile, and combative. For example, the phenomenon of sundowning experienced by patients with dementia makes the usual overnight topical application of these products a hazardous experience. Third, nursing home patients frequently have conditions, such as contractures, spasticity, and rigidity, that make applying topical products to the entire body a taxing, if not impossible, task. Finally, as pointed out in the editorial by del Giudice,³ treatment-related dermatitis can be difficult to distinguish from persistent scabies.

Based on current data, ivermectin appears to be the best available, first-line treatment for cases of scabies in adult nursing homes and institutions. The manufacturer (Merck, West Point, Pa) should work toward the availability of the use of the drug as oral treatment for

patients with scabies. In addition, the US Food and Drug Administration should work with pharmacological manufacturers to facilitate the approval of ivermectin and other potential antiparasitic oral medications to fill this definite need.

Jeffrey S. Altman, MD
Altman Dermatology Associates
121 S Wilke Rd, Suite 404
Arlington Heights, IL 60005

- Chouela EN, Abeldaño AM, Pellerano G, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol.* 1999;135:651-655.
- Clinical Laboratory Improvement Amendments of 1998 (CLIA). Pub L No. 100-578, 42 USC 201 (1998).
- del Giudice P. Ivermectin: a new therapeutic weapon in dermatology. *Arch Dermatol.* 1999;135:705-706.

IgE Level and the Validation of the Diagnostic Criteria for Atopic Dermatitis

One is perplexed that neither the article titled "Validation of the Diagnostic Criteria for Atopic Dermatitis" by Firooz et al¹ nor the accompanying editorial titled "Diagnostic Criteria for Atopic Dermatitis: Where Do We Go From Here?" by Williams² address an elevated IgE level as a diagnostic criterion for atopic dermatitis. To quote John Hanifin, MD, an internationally renowned expert on atopic dermatitis, "Numerous studies have established the fact that serum IgE levels are elevated in most patients with atopic dermatitis, and that the degree of elevation tends to parallel the extent and severity of the disease in most instances."³ All criteria mentioned are observer-dependent; therefore, at least to some extent, dependent on individual interpretation, and thus potentially subjective. An accurately performed test for an elevated IgE level has a sensitivity for atopic dermatitis of approximately 80%, considerably higher than the 69% of the criteria stated and, in theory, should have a specificity of at least 96% of that criteria.⁴

David A. Fisher, MD
University of California Medical Schools
at San Francisco and Davis
3701 Lone Tree Way
Suite 6
Antioch, CA 94509

- Firooz A, Davoudi SM, Farahmand AN, Majzedah R, Nasiri Kashani M, Dowlati Y. Validation of the diagnostic criteria for atopic dermatitis. *Arch Dermatol.* 1999;135:514-516.
- Williams HC. Diagnostic criteria for atopic dermatitis: where do we go from here? *Arch Dermatol.* 1999;135:583-586.
- Hanifin JM. Atopic dermatitis. *J Am Acad Dermatol.* 1982;6:1-13.
- Stone SP, Muller SA, Gleich GJ. IgE levels in atopic dermatitis. *Arch Dermatol.* 1973;108:806-811.

In reply

We thank Dr Fisher for his comment on our article.¹ A raised serum IgE level is one of several diagnostic criteria for atopic dermatitis proposed by Dr Hanifin.² Although it is a useful diagnostic tool in some instances, it is an invasive and somewhat expensive test that is not available everywhere. So it

is not commonly used in routine clinical practice, especially for children who constitute most of the patients with atopic dermatitis. On the other hand, it cannot be used in large-scale, population-based studies at all. The limitations of this criterion as well as limitations of other of Hanifin's criteria³ prompted Williams et al⁴⁻⁶ to develop a new set of criteria for clinical diagnosis of atopic dermatitis that were validated in our study.¹

Alireza Firooz, MD
Yahya Dowlati, MD, DPharm
Center for Research and Training
in Skin Diseases and Leprosy
Tehran University of Medical Sciences
79 Taleghani Ave
Tehran 14166, Iran

1. Firooz A, Davoudi SM, Farahmand AN, Majdzedah R, Nasiri Kashani M, Dowlati Y. Validation of the diagnostic criteria for atopic dermatitis. *Arch Dermatol.* 1999;135:514-516.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl.* 1980;92:44-47.
3. Schultz-Larsen F. The epidemiology of atopic dermatitis. *Monogr Allergy.* 1993; 31:9-28.
4. Williams HC, Burney PGJ, Hay RJ, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis, I: derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol.* 1994;131:383-396.
5. Williams HC, Burney PGJ, Strachan D, Hay RJ. The U.K. Working Party's diagnostic criteria for atopic dermatitis, II: observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol.* 1994;131:397-405.
6. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The U.K. Working Party's diagnostic criteria for atopic dermatitis, III: independent hospital validation. *Br J Dermatol.* 1994;131:406-416.

Diagnostic Criteria for Atopic Dermatitis: Consider the Context

I am writing in response to the May 1999 article¹ and editorial² in the ARCHIVES about diagnostic criteria for atopic dermatitis (AD). Having been one of the first proponents of diagnostic criteria for AD, I feel a need to make some clarifying comments before we are completely lost in muddy waters. Seeking some assurance that different groups were studying the same disease, Dr Lobitz and I first laid out diagnostic guidelines for AD in a 1977 article.³ The more well-known criteria evolved further during an active discussion at the First International Symposium on Atopic Dermatitis in 1979.⁴ These criteria were too complex for population-based screening, and Williams et al⁵ performed a service by deriving a minimum set of discriminators for epidemiologic use. The editorial by Williams² is a good analysis of a problem that Firooz et al¹ have uncovered. Until there is a precise laboratory marker, we are dependent on obviously imprecise clinical criteria. We must constantly remember that these criteria are imprecise; no amount of mathematical, statistical manipulation or validation will make them precise, and we should not be disheartened if a study does not validate them.

The editorial is incorrect in suggesting that the latest version of criteria⁶ is the acceptable one for research studies. That abbreviated list of criteria, along with a similar list for childhood AD,⁷ was to simplify diagnosis in the clinical practice setting. I would not consider either of these to be satisfactory for a research study, although

it might have helped in the study of Firooz et al¹ if M.N.K. had followed such indicators for diagnosing AD. I have to agree with Williams et al⁵ that the diagnosis of AD in a non-itchy patient with no history of flexural eczema raises concerns about the criterion standard.

Clearly, the article by Firooz et al¹ requires us to re-examine major AD criteria in the wider context of racial, cultural, and climatic factors, along with different word meanings. As an example, even among English speakers, the term *flexural* has been reinterpreted and expanded from our description—limited to antecubital and popliteals—to now include neck and facial areas.⁵ We all must guard against working in cultural isolation, and I am glad that both of these reports have reminded us to proceed cautiously and communicate widely.

Jon M. Hanifin, MD
Department of Dermatology, MC L 468
Oregon Health Sciences University
3181 SW Sam Jackson Rd
Portland, OR 97201-3098
(e-mail: hanifinj@ohsu.edu)

1. Firooz A, Davoudi SM, Farahmand AN, Majdzedah R, Kashani MN, Dowlati Y. Validation of the diagnostic criteria for atopic dermatitis. *Arch Dermatol.* 1999;135:514-516.
2. Williams HC. Diagnostic criteria for atopic dermatitis: where do we go from here? [editorial]. *Arch Dermatol.* 1999;135:583-586.
3. Hanifin JM, Lobitz WC. Newer concepts of atopic dermatitis. *Arch Dermatol.* 1977;113:663-670.
4. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92:44-47.
5. Williams HC, Burney PGJ, Hay RJ, et al. The UK working party's diagnostic criteria for atopic dermatitis, I: derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol.* 1994;131:383-396.
6. Hanifin JM. Atopic dermatitis. In: Moschella SL, Hurley HJ, eds. *Dermatology.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1992:441-464.
7. Hanifin JM. Atopic dermatitis in infants and children: pediatric dermatology. *Pediatr Clin North Am.* 1991;38:763-789.

VIGNETTES

Melanoma Arising in Burn Scars: Report of 3 Observations and a Literature Review

Malignant melanoma (MM) arising in burn scars is rarer than the classic form, with only about 22 cases reported in the literature.¹ We report 3 new cases and the results of a literature review focusing on the promoting factors of this particular malignant transformation.

Observations. Three female patients, aged 57, 65, and 75 years, respectively, consulted us for tumoral lesions (2 thoracic and 1 abdominal) arising in scars from burns incurred 47, 59, and 70 years previously (**Figure 1**). The histologic diagnosis for the 2 younger patients was MM of nodular type 2 (**Figure 2**) and for the oldest patient, superficial spreading melanoma. After only surgical treatment, 2 patients remained alive and without disease after 45 and 54 months of follow-up, respectively; 1 died of metastatic disease 11 months after diagnosis.



Figure 1. Nodular pigmented lesion in a thoracic cheloid scar with mammary hypoplasia.



Figure 2. Malignant melanocytic proliferation infiltrating a densely fibrous cicatricial dermis (hematoxylin-eosin stain, original magnification $\times 100$).

Comment. Malignant transformation of burn scars is an exceptional event, occurring in only 2% of cases but leading to carcinomatous lesions in most of these cases.^{1,2} Malignant melanoma occurrence is exceptional, and since the first case cited by Giblin et al² in 1965, there have been only 22 cases in the literature, only 4 of which have been mentioned here.^{1,3,4,5} In our institution, of the 2134 skin cancers diagnosed over a 21-year period (1975-1995), 50 occurred in burn scars, 47 were spinocellular carcinomas, and 3 were malignant melanomas. The frequency of scar melanoma (3/142 [2.1%]) is similar to that of scar carcinomas (47/1992 [2.36%]). From our literature review, we found the mean age at MM occurrence to be 51.6 years (65.6 years for our patients), with male predominance (but all of our patients were women). Mean age at the time the burn was incurred was younger than

10 years (more than 50% in the literature) in all of our patients.

The mean latency period between the burn and MM diagnosis was 58 years for our 3 patients but 37.5 years in the literature. Malignant melanoma reported in the literature occurred mostly in the limbs (lower, 39%; upper, 33%), the most frequent burn site, but in our cases all the lesions occurred in the thoracoabdominal area. The mean size of the MMs was approximately 20 mm but with high variability (3-110 mm), which may be explained by the delay in diagnosis or by the lesion being located in an old, pigmented, polychromatic area. The lesion was frequently nodular and ulcerated with a high Clark level and a depth greater than 1.5 mm.

The cause of this secondary MM remains unclear, and many hypotheses have been proposed. Malignant melanoma in burn scars frequently occurs in covered areas protected from sunlight, which suggests that malignant transformations arise from the frequent trauma and/or ulcerations in the limbs and articular zones of the thin and fragile burned skin due to the hypovascularization induced by the dense cicatricial fibrosis.^{1,5} Repeated and constant irritation of cicatricial areas leads to multiple skin reparations and eventually promotes malignant transformation.¹ Toxin liberation by cicatricial cells after autoheterolysis has been suggested.¹ Another hypothesis is that hypovascularization and lymphatic vessel depletion transform the burned area in an immunodeficient and immunologically isolated zone by the fibrotic scar.² Cellular proliferation then occurs outside the control of the immunocompetent system. In the literature, we found 7 cases of spinocellular carcinoma associated with the MM.¹ This association is another argument for the inducer role of burns in the occurrence of malignancy. The rarity of MM compared with other carcinomas may be explained by the rarity of melanocytes in burned skin.

The treatment of secondary MM is surgical, if possible, as for classic melanoma. We used this approach for 2 of our 3 patients and achieved a safe surgical resection; both patients are alive without disease 45 and 54 months, respectively, after surgery. Skin grafts are not protective against malignant transformation, as we saw for 4 of the 18 grafted cases reported in the literature. The natural history of secondary MM is quite different from that of classic melanoma, with a frequent regional evolution probably due to the limiting role of the fibrotic barrier that blocks tumor spread.

Jerbi Ghazi, MD
 Institut Salah Azaiz
 Boulevard du 9 Avril, Bab Saadoun
 Tunis, Tunisia
 (e-mail: hamouda.boussen@rns.tn)
 Boussen Hamouda, MD
 Gamoudi Amor, MD
 Ennaifer-Jerbi Emna, MD
 Karboul Samira, MD
 Ben Osman Amel, MD
 Rahal Khaled, MD
 Tunis

1. Alconchel MD, Olivares C, Alvarez R. Squamous cell carcinoma, malignant melanoma and malignant fibrous histiocytoma arising in burn scars. *Br J Dermatol.* 1997;137:793-798.
2. Giblin T, Pickrell K, Pitts W, Armstrong D. Malignant degeneration in burn scars: Marjolin's ulcer. *Ann Surg.* 1965;162:291-297.
3. Delaunay MM, Courouge Dorcier D, Castede JC. Mélanome malin sur cicatrice de brûlure. *Ann Dermatol Venerol.* 1991;118:129-130.
4. Fleming MD, Hunt JL, Purdue GF, Sanstad J. Marjolin's ulcer: a review and reevaluation of a difficult problem. *J Burn Care Rehabil.* 1990;11:460-469.
5. Akiyama M, Inamoto N, Nakamura K. Malignant melanoma and squamous cell carcinoma forming one tumour on a burn scar. *Dermatology.* 1997;194:157-161.

Melanoma Incidence by Body Site: Effects of Birth-Cohort Adjustment

Traditionally, melanoma age curves by histologic type vary; coding of histologic site has not been consistent. However, histologic sites tend to correspond to the body site of the melanoma. Superficial spreading melanoma, common on the upper back or the female leg, occurs in the fourth and fifth decades of life.^{1,2} Nodular melanoma, common on the trunk, is usually reported in the fifth or sixth decade of life.^{1,2} Lentigo maligna melanoma occurs most often on the head and is most commonly diagnosed in the seventh decade of life.^{1,2} Superficial spreading melanoma accounts for about 70% of melanomas, whereas nodular and lentigo maligna melanomas account for 10% to 15% and 5% of melanomas, respectively.² Overall, melanomas of the trunk, arms, and legs are generally superficial spreading melanomas and some nodular melanomas, while melanomas of the head are lentigo maligna melanomas. In an attempt to understand how types of melanoma vary with age, the crude and birth-cohort adjusted melanoma incidence rates were examined by body site.

Methods. Incident cases of invasive malignant melanoma among white patients aged 20 to 84 years were obtained from the Surveillance, Epidemiology, and End Results program, Bethesda, Md, for the years 1973 through 1994.³ Cases ascertained from autopsies only or death certificates only were excluded, leaving 43 806 incident cases. Incidence curves by age were computed, adjusted for birth-cohort effects by including 5-year birth-cohort categories (1895-1899 to 1960-1964) in the regression model separately by sex and body site.⁴ The rate ratios for each age group were multiplied by the observed incidence rates for the 30- to 34-year-old reference group.

Results. The crude and birth-cohort adjusted age-specific rates of melanoma of the head and trunk are shown in **Figure 1** and **Figure 2**. The crude rates for melanoma of the head (Figure 1) increase with increasing age. For melanoma of the trunk (Figure 2), crude rates increase to ages 55 to 59 years, and then seem to level off. Similarly, for melanoma of the arm, crude rates increase to age 70 years, and then seem to level off. Among women, crude rates of melanoma of the leg increase until about ages 55 to 59 years before leveling off or decreasing. For men, melanoma of the leg continues to increase past age 80 years. The adjusted rates for persons aged 50 years and older are all higher than the crude rates. For each body site, the age-specific incidence rates steadily

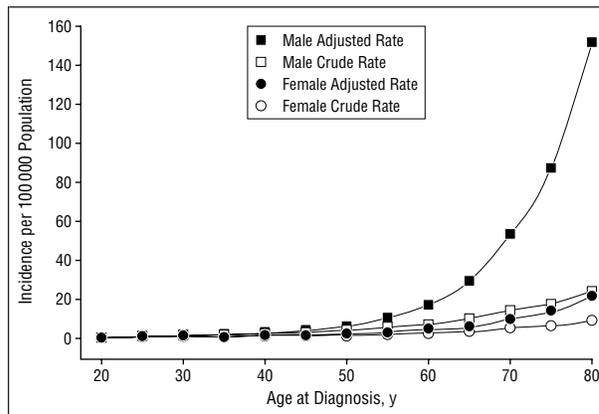


Figure 1. Crude and adjusted (for birth cohort) age-specific incidence (per 100 000 population) of melanoma of the head for men and women. Data are based on 1973 to 1994 Surveillance, Epidemiology, and End Results Program data adjusted for birth-cohort effects.

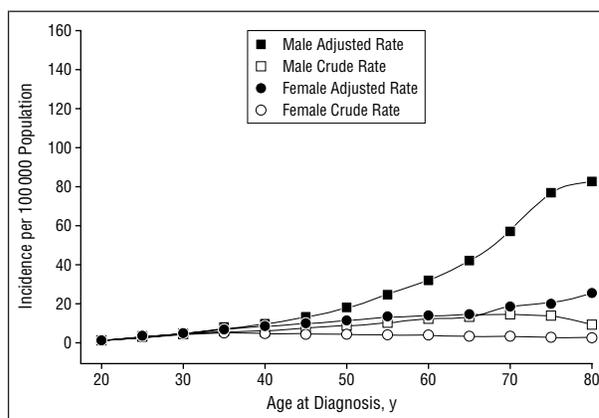


Figure 2. Crude and adjusted (for birth cohort) age-specific incidence (per 100 000 population) of melanoma of the trunk for men and women. Data are based on 1973 to 1994 Surveillance, Epidemiology, and End Results Program data adjusted for birth-cohort effects.

increase with age through ages 80 to 84 years after adjustment for birth-cohort effects. The slopes of the adjusted rates are steeper than the crude rates.

Comment. The birth-cohort adjusted rates sharply increase with age for melanoma of the head and trunk and do not level off in the older age groups as the crude and traditional reported rates have.^{1,2} This suggests sharp increases with age for superficial spreading melanoma and lentigo maligna melanoma. Because the birth years for individuals aged 30 to 34 years during data collection (1973-1994) range from 1939 to 1964, the rates can be interpreted as the estimated age-specific rates of melanoma as the Baby-Boomer generation (born 1946-1965) ages. These rates will continue to increase as earlier cohorts age.

Leslie K. Dennis, PhD, MS
 Department of Epidemiology
 College of Public Health
 2800 Steindler Bldg
 University of Iowa
 Iowa City, IA 52245

This research was supported in part by the Cleveland Foundation, grant 94C1533 94-0610, and the Department of Epi-

1. MacKie RM. Melanocytic naevi and malignant melanoma. In: *Textbook of Dermatology*. Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Vol 2. 6th ed. Oxford, England: Blackwell Science Ltd; 1998.
2. Barnhill RL, Mihm MC Jr, Fitzpatrick TB, Sober AJ. Neoplasms: malignant melanoma. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austin KF, eds. *Dermatology in General Medicine*. Vol 2. 4th ed. New, NY: McGraw Hill Inc; 1993.
3. *Surveillance, Epidemiology, and End Results (SEER) Program* [public use CD-ROM (1973-1994)], Bethesda, Md: National Cancer Institute; DCPC, Surveillance Program, Cancer Statistics Branch, May 1997.
4. Breslow NE, Day NE. The analysis of case-control studies. In: *Statistical Methods in Cancer Research*. Vol 1. Lyon, France: International Agency for Cancer Research; 1980.

Clinical Characteristics of 20 Italian Melanoma-Prone Families

The incidence and mortality rates of cutaneous malignant melanoma (CMM) are dramatically increasing worldwide,¹ particularly in Europe.² About 10% of CMM cases arise in a familial setting, where there are at least 2 CMM cases in first-degree relatives (melanoma-prone families).³ Most data on familial melanoma derive from countries where fair skin type predominates. Herein, we present clinical data on 20 melanoma-prone kindreds with mainly dark complexion.

Patients and Methods. Twenty melanoma-prone kindreds were identified at Bufalini Hospital, Cesena, Italy, with review board approval. Each subject signed an informed consent. Clinical examination and evaluation of skin, eye, and hair color of family members were performed by 1 dermatologist (D.C.). The most atypical (dysplastic) nevi were counted and photographed; the backs of the subjects were also photographed to allow a nevus count. To be defined as dysplastic, a nevus had to be 5 mm or larger in greatest dimension and predominantly flat and have at least 2 of the following criteria: variable pigmentation, indistinct borders, and irregular outline.⁴ Tumor slides and pathological reports were collected in all cases, and 70% of the diagnoses were histologically reviewed by an expert pathologist (W.H.C.).

Results. Fifteen families had 2 or 3 first-degree relatives with CMM; the rest had second- or third-degree relatives with CMM. A total of 135 subjects were examined. Most subjects, including those with CMM and those with dysplastic nevi (DN), had dark skin, hair, and eye color (**Table 1**). Melanoma was present in 46 subjects. The median age at first melanoma diagnosis was 46.5 years (range, 15-80 years), with a mean difference between older and younger generations of 29 years. Body site distribution of melanomas varied by sex, with the most frequent sites being the lower limbs in females (n = 15 [51%]) and the upper part of the trunk in males (n = 12 [63%]). Most melanomas were superficial spreading (78%); 18% were nodular. The relatively high number of nodular melanomas may reflect a late diagnosis of superficial spreading melanoma. The tumor thickness of nodular melanomas ranged from 2.8 to 10 mm, with greater thickness in males. Five subjects had multiple primary melanomas, with age at diagnosis ranging from 15 to 58 years;

Table 1. Family Members by Skin, Eye, and Hair Color and Disease Status*

	No. (%)		
	Unaffected	DN	CMM
Skin color			
Pale/fair	17 (28)	15 (44)	10 (43)
Medium dark	38 (62)	19 (56)	11 (48)
Very dark	6 (10)	0	2 (9)
Eye color			
Black/dark brown	30 (49)	12 (35)	10 (43)
Light brown	12 (20)	7 (21)	2 (10)
Light blue	12 (20)	9 (26)	10 (43)
Gray/green	7 (11)	6 (18)	1 (4)
Hair color			
Black/dark brown	40 (66)	18 (53)	14 (61)
Light brown	17 (28)	12 (35)	6 (26)
Blonde	2 (3)	2 (6)	3 (13)
Red	2 (3)	2 (6)	0

*Total number of subjects examined, 128. DN indicates dysplastic nevi; CMM, cutaneous malignant melanoma. Ten subjects had indeterminate DN status because of age and were excluded from the analysis.

Table 2. Unaffected Family Members and CMM Cases by Total No. of Nevi and DN*

DN	Total Nevi, No. (%)†		
	<10	10-30	>30
Unaffected Members			
0	22 (85)	13 (65)	2 (6)
≤5	2 (8)	1 (5)	7 (21)
>5	2 (8)	6 (30)	24 (73)
CMM Cases			
0	3 (60)	1 (50)	0
≤5	1 (20)	0	2 (17)
>5	1 (20)	1 (50)	10 (83)

*CMM indicates cutaneous malignant melanoma; DN, dysplastic nevi. Subjects for whom data were missing and subjects with indeterminate DN status because of age were excluded from the analysis.

†Nevi counted on the backs of the subjects.

tumor thickness ranged from 0.30 mm (Clark level II) to 0.70 mm (Clark level III).

Seventeen families had at least 1 member with DN. Absence of DN in members of 3 families suggests the possibility of multiple pathways of tumor progression for CMM and DN. The distribution of DN did not vary by sex, skin color, or skin type. The number of DN in family members was associated with their total number of nevi, irrespective of melanoma status (**Table 2**), as in the general Italian population.⁵ In a comparison between subjects with and without DN, about 57% subjects without melanoma and without DN had 10 or fewer nevi on their backs, compared with 70% of subjects without melanoma but with DN who had 30 or more nevi. An even stronger association was observed in melanoma cases, although it was based on small numbers: 75% of CMM cases without DN had 10 or fewer nevi, while 80% of cases with DN had 30 or more nevi. As expected,⁴ both total number of nevi and number of DN were higher in melanoma cases.

Several nonmelanoma tumors were reported in the families. Gastrointestinal tract cancers were the most frequent, with 11 cases among males and 4 cases among females. No pancreatic tumors were reported. Seven patients with melanoma also had nonmelanoma tumors, without a significant excess of a particular tumor type.

In conclusion, the clinical characteristics in these Italian families are generally similar to those seen in fair-skinned populations, except for a higher proportion of nodular melanomas. These families would benefit from enhanced screening procedures and public education programs, which would identify lesions at an early stage and reduce the number of melanomas and other tumors.

Maria Teresa Landi, MD, PhD
Genetic Epidemiology Branch
National Cancer Institute
National Institutes of Health
EPS 7114
6120 Executive Blvd
Bethesda, MD, 20892
Donato Calista, MD
Giorgio Landi, MD
Cesena, Italy
Ilaria Bernucci, MD
Pier Alberto Bertazzi, MD, MPH
Milan, Italy
Wallace H. Clark, Jr, MD
Boston, Mass
Alisa M. Goldstein PhD
Margaret A. Tucker, MD
Bethesda

Presented in part at the 89th Annual Meeting of the American Association for Cancer Research, New Orleans, La, March 29, 1998, and the 48th Annual Meeting of the American Society of Human Genetics, Denver, Colo, October 31, 1998.

We thank the families for their cooperation and Deborah Zametkin, RN, for her assistance in data management.

1. Perkin DM, Muir CS, Helan SL. *Cancer Incidence in Five Continents*. Vol 6. Lyon, France: International Agency for Research on Cancer; 1992:1033. IARC Scientific Publication 120.
2. Balzi D, Carli P, Geddes M. Malignant melanoma in Europe: changes in mortality rates (1970-90) in European community countries. *Cancer Causes Control*. 1996;8:85-92.
3. Greene MH, Fraumeni JF Jr. The hereditary variant of malignant melanoma. In: Clark WH Jr, Goldman LI, Mastrangelo MJ, eds. *Human Malignant Melanoma*. New York, NY: Grune & Stratton Inc; 1979:139-166.
4. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. *JAMA*. 1997;277:1439-1444
5. Carli P, Biggeri A, Nardini P, Salani B, Giannotti B. Epidemiology of atypical melanocytic naevi: an analytical study in a Mediterranean population. *Eur J Cancer Prev*. 1997;6:506-511.

Temporary Hair Loss Simulating Alopecia Areata After Endovascular Surgery of Cerebral Arteriovenous Malformations: A Report of 3 Cases

There is further evidence of possible adverse effects to the skin of prolonged fluoroscopic imaging procedures in a report of 4 cases of chronic radiodermatitis due to irradiation during coronary an-



Figure 1. Case 1. Large area of almost total alopecia in the temporoparietal region of the scalp.

giography.¹⁻² Intraoperative fluoroscopic imaging is also widely used during endovascular surgery of cerebral arteriovenous malformations. This is associated with a considerable risk of injury from irradiation, especially with prolonged or multiple procedures.³

We describe here 3 patients who developed temporary alopecia after fluoroscopic imaging-guided endovascular embolization or surgery for arteriovenous malformations of the brain. Owing to selective involvement of the temporo-occipital area along the scalp margins, all of these patients were initially diagnosed as having ophiasis.

Report of Cases. *Case 1.* A 30-year-old woman was referred to us for alopecia areata in January 1999, with the diagnosis of stress-induced ophiasis. Results of the clinical examination revealed a 13 × 4-cm oval patch of almost total hair loss on the left temporoparietal region (**Figure 1**).

The scalp was normal, and exclamation-mark hairs were not visible. Hair loss had suddenly appeared 2 weeks before our examination and had remained quite stable. Results of the pull test were normal both around the patch and in the contralateral scalp. There was no family history of alopecia areata. Findings of the medical history revealed that in December 1998, the patient had undergone fluoroscopically guided superselective embolization of a left temporo-occipital arteriovenous malformation. x-Ray radiation-induced temporary epilation was diagnosed. No treatment was prescribed. Results of clinical examination 1 month after our first examination revealed homogeneous hair regrowth, although the color of the regrowing hair was lighter than that of the surrounding hair.

Case 2. A 44-year-old woman presented in February 1996 with a 1-week history of a bald patch along the occipital margin. The patient's dermatologist had diagnosed alopecia areata and referred the patient to us for topical immunotherapy. Results of the pull test were abnormal both in the occipital and temporal scalp with extraction of 5 to 7 hairs. Microscopic examination of the hairs showed the presence of dystrophic hair roots. The medical history revealed that on January 1996, she had undergone superselective angiography for surgical removal of an arteriovenous malformation of the commu-



Figure 2. Case 3. Relapse of alopecia with ophiasis pattern after further neurosurgical procedure.

nicant anterior artery of the brain. Spontaneous regrowth occurred 6 weeks after examination.

Case 3. A 35-year-old woman was diagnosed for supraclinoid aneurysms of both internal carotid arteries in July 1998. In December 1998, she underwent surgical dissection of the right aneurysm with the endovascular balloon catheter technique under intraoperative angiography. In January 1999, she developed diffuse alopecia along the parietal and occipital hairline bilaterally. She was diagnosed as having ophiasis and treated with intraleisional steroid injections at another institution. She first consulted us in February 1999 when the alopecic area showed diffuse regrowth of 1-cm-long hair. On April 1, 1999, she underwent another neurosurgical procedure in which the same technique was used for dissection of the left supraclinoid aneurysm. She again experienced diffuse hair loss on the parietal and occipital scalp 2 weeks later. At this time results of the clinical examination revealed diffuse alopecia with an ophiasis pattern (**Figure 2**). Exclamation-mark hairs were not present. Results of the pull test from the surrounding scalp were abnormal, with extraction of numerous dystrophic hair roots. Hair regrowth started after 2 weeks without any treatment.

Comment. Temporary epilation is a well-known effect of irradiation that typically occurs after a single short-term exposure to 300 to 600 Gy of irradiation. Epilation is generally permanent after doses of about 700 Gy. Irradiation-induced epilation depends on the high susceptibility of anagen follicles to radiation. Loss of dystrophic hairs (anagen effluvium) due to acute damage to actively dividing matrix cells of anagen follicles is followed by telogen shedding due to premature catagen entry of follicles in late anagen subphases at the time of damage. Complete hair regrowth generally occurs 2 to 4 months after irradiation.⁴

Although irradiation-induced temporary epilation is well known to dermatologists because of the use of radiotherapy for the treatment of tinea capitis,⁵⁻⁶ the major dermatological and hair textbooks do not mention the occurrence of localized reversible alopecia after neuro-radiologically guided surgical procedures. In all of our patients, irradiation-induced epilation had been misdiagnosed as alopecia areata by a dermatologist, and one

patient had been unnecessarily treated with intraleisional steroid injections. The differential diagnosis of alopecia areata may be difficult because the bald patch is devoid of inflammatory signs, and hair loss is characterized by dystrophic hairs. The location of the bald patches along the scalp margins with an ophiasis pattern occurs because this scalp region receives the highest doses of radiation therapy during fluoroscopy.⁷ This, together with the lighter color of the regrowing hair, may also lead to a wrong diagnosis of alopecia areata. The history of neurosurgery was interpreted in our patients as a stressful event that triggered the onset of alopecia areata rather than a possible source of radiation exposure.

Neuroradiologists are aware of this common sequela of diagnostic and therapeutic imaging procedures, which often require prolonged exposure of patients to radiation.⁷ While there is only a single report of this adverse effect in the dermatological literature,⁸ dermatologists should keep in mind this transitory adverse effect of fluoroscopic imaging, since therapeutical applications of interventional neuroradiology are rapidly increasing.

Antonella Tosti, MD
 Department of Dermatology
 University of Bologna
 Via Massarenti, 1 I- 40138
 Bologna, Italy
 (e-mail tosti@almadns.unibo.it)
 Bianca Maria Piraccini, MD
 Giorgio Alagna, MD
 Bologna

1. Malkinson FD. Radiation injury following fluoroscopically guided procedures. *Arch Dermatol.* 1996;132:695-696.
2. Lichtenstein DA, Klapholz L, Vardy D, et al. Chronic radiodermatitis following cardiac catheterization. *Arch Dermatol.* 1996;132:663-667.
3. Kuwayama N, Takaku A, Endo S, Nishijima M, Kamei T. Radiation exposure in endovascular surgery of the head and neck. *Am J Neuroradiol.* 1994;15:1801-1808.
4. Van Scott EJ, Reinertson RP. Detection of radiation effects on hair roots of the human scalp. *J Invest Dermatol.* 1957;29:205-212.
5. Dawber RPR, Fenton DA. Cicatricial alopecia. In: Dawber R, ed. *Diseases of the Hair and Scalp*. 3rd ed. Oxford, England: Blackwell Publishers; 1997:390-391.
6. Grossman KL, Kvedar JC. Anagen hair loss. In: Olsen EA, ed. *Disorders of Hair Growth*. New York, NY: Mc Graw-Hill Book Co; 1994:225-226.
7. Huda W, Peters KR. Radiation-induced temporary epilation after a neuro-radiologically guided embolization procedure. *Radiology.* 1994;193:642-644.
8. Krasovec M, Trüeb RM. Temporäre Röntgenepilation nach Embolisation einer zerebralen Gefäßmüßbildung. *Hautarzt.* 1998;49:307-309.

The Spectrum of Cutaneous Eruptions in 22 Patients With Isolated Serological Evidence of Infection by Parvovirus B19

It is widely known that human parvovirus B19 (B19) can cause a number of dermatological¹⁻⁴ and systemic problems.⁵ Erythema infectiosum¹ and papular-purpuric "gloves and socks" syndrome² commonly occur in B19-infected patients as dermatological features. In the present study, we report the clinical features of 22 adult patients with IgM antibodies positive to B19. Eight cases revealed reticular erythema. Maculopapular eruptions similar to rubella occurred in 7 other cases. Pe-



Figure 1. Purpuric eruption on the breast and abdomen of a 34-year-old woman with IgM antibody to human parvovirus B19.



Figure 2. Purpuric eruption on the popliteal skin of a 27-year-old woman with IgM antibody to human parvovirus B19.

techia and purpura not limited to the gloves and socks lesions occurred in the remaining 7 cases.

Patients. We studied the clinical features of 22 adult patients (1 man and 21 women), aged from 16 to 70 years (mean [SD], 30.5 [12.4] years), with IgM antibodies positive to B19. All patients consulted our department between April and October 1998. IgM antibody titers to rubella and measles were tested in 18 patients and all were negative.

Results. General Condition. Nineteen of 22 patients had a temperature between 37.3°C and 39.0°C for 3 to 7 days. Skin eruptions appeared after defervescence in 11 cases, and 1 patient revealed eruption at the same time as the fever. The fever continued after the eruptions appeared in the remaining 7 cases. There were complaints of multiple arthralgias in 16 cases, general fatigue in 15 cases, edema of the lower extremities in 6 cases, and swelling of the fingers in 6 cases. Lymph node swelling of the neck and retroauricular area occurred in 7 and 8 cases, respectively. These symptoms disappeared within 2 weeks after the first consultation.

Skin Eruption. Reticular erythema occurred in 8 cases, which generally happens in erythema infectiosum. Maculopapular eruptions similar to rubella occurred in 7 cases. Petechiae and purpura occurred in 7 cases (**Figure 1** and **Figure 2**), but there was no case in which the lesions were limited to the hands and feet; rather, the lesions erupted on the lower extremities in 2 cases, the lower

and upper extremities in 2 cases, the trunk in only 1 case, and the trunk and all 4 extremities in 2 cases. There was no mucosal involvement such as ulcer or plaque.

Antibody Titers to B19. IgM and IgG antibody titers to B19 were determined by enzyme immunoassay. The mean (SD) IgM antibody titer in the 22 patients was 9.11 (2.87). IgG antibody titers were determined in 13 cases and all were positive for B19 (mean [SD], 5.39 [4.69]). IgM titers examined after 2 months in 8 cases were all negative.

Histological Findings. Histological findings of the skin specimens from 2 patients with purpura showed lymphocyte infiltrates around the capillaries in the upper and middle dermis and dilation of the lymph vessels in the upper dermis, but no vasculitis. Results of direct immunofluorescence studies showed negative staining with IgG, IgA, and C3.

Comment. The cutaneous manifestations in 22 patients with B19 IgM antibody can be classified into 3 types, each including nearly one third of our patients: (1) typical erythema infectiosum, (2) rubella-like maculopapular eruptions, and (3) purpuric eruptions. However, various eruptions such as erythema nodosum³ and polyarteritis nodosa⁴ other than these 3 types may appear in the viremic phase of B19.

Mariko Seishima, MD
 Department of Dermatology
 Ogaki Municipal Hospital
 Minaminokawa-cho 4-86,
 Ogaki City, 503-8502, Japan
 (e-mail: seimarik@gmail.cc.gifu-u.ac.jp)
 Hiroyuki Kanoh, MD, PhD
 Tomoko Izumi, MD
 Ogaki City

1. Anderson MJ, Jones SE, Fisher-Hoch SP, et al. Human parvovirus: the cause of erythema infectiosum (fifth disease)? [letter]. *Lancet*. 1983;1:1378.
2. Harms M, Feldmann R, Saurat J-H. Papular-purpuric "gloves and socks" syndrome. *J Am Acad Dermatol*. 1990;23:850-854.
3. Borreda D. Twenty-four cases of parvovirus B19 in children. *Ann Pediatr (Paris)*. 1992;39:543-549.
4. Finkel TH, Török TJ, Ferguson PJ, et al. Chronic parvovirus B19 infection and systemic necrotizing vasculitis: opportunistic infection or aetiological agent? *Lancet*. 1994;343:1255-1258.
5. Woolf AD, Campion GV, Chishick A, et al. Clinical manifestations of human parvovirus B19 in adults. *Arch Intern Med*. 1989;149:1153-1156.

Status of Residual Tumor in Patients With Squamous Cell Carcinoma Referred for Mohs Micrographic Surgery

We have often observed that patients with a histological diagnosis of skin cancer present for definitive treatment without clinical evidence of residual tumor. In the case of squamous cell carcinoma (SCC), there is a perceived need for more extensive treatment given the small, but real, possibility of metastasis. A second biopsy specimen can be obtained to assess the presence of residual tumor, but this approach was proved unreliable.¹ Based on tumor location, these patients are often referred for Mohs micro-

Summary of Squamous Cell Carcinoma Tumors Examined in 34 Patients Who Underwent Mohs Micrographic Surgery*

Patient No./ Age, y/Sex†	Tumor Site	Recurrent Squamous Cell Carcinoma	Scar Size, cm	Biopsy Margins		Histological Grade§	Nuclear Atypia	Inflammation	Pattern of Tumor Growth	Residual Tumor
				Base, %	Lateral‡					
1/81/M	Superior helix	No	0.9 × 0.6	50-75	1	1	Moderate	Mild	Pushing borders	No
2/79/M	Preauricular	No	1.0 × 0.8	50-75	1	3	Severe	Moderate	Single cells	No
3/77/F	Lower lip	No	2.0 × 1.0	50-75	2	2	Moderate	Moderate	Detached islands	No
4/72/M	Midcheek	Yes	0.9 × 0.5	25-50	1	1	Severe	Mild	Detached islands	+ First stage
5/56/M	Inferior antihelix	No	0.5 × 0.5	<25	1	1	Mild	Moderate	Pushing borders	No
6/44/M	Superior helix	No	0.6 × 0.4	<25	0	2	Moderate	Mild	Pushing borders	No
7/35/M	Nasal tip	No	0.6 × 0.5	<25	0	1	Mild	Moderate	Pushing borders	No
8/66/M	Midhelix	No	1.0 × 0.5	25-50	0	2	Severe	Marked	Pushing borders	No
9/82/M	Temple	No	1.0 × 0.5
10/76/M	Nasal sidewall	No	0.5 × 0.4
11/59/F	Temple	No	0.7 × 0.6	<25	0	1	Moderate	Marked	Pushing borders	No
12/58/F	Forehead	No	0.6 × 0.4	50-75	0	1	Mild	Moderate	Pushing borders	No
13/73/M	Lower lip	No	0.6 × 0.5	0	2	1	Moderate	Marked	Detached islands	No
14/70/M	Forehead	No	1.3 × 0.8
15/58/M	Forehead	No	1.0 × 1.0	<25	0	1	Moderate	Marked	Detached islands	No
16/78/M	Inferior helix	No	0.4 × 0.3	>75	2	2	Moderate	Marked	Detached islands	No
17/62/M	Ear concha	No	0.5 × 0.5	<25	1	1	Moderate	Moderate	Pushing borders	No
18/51/M	Midcheek	No	0.6 × 0.4	<25	0	1	Mild	Moderate	Pushing borders	No
19/43/F	Forehead	No	0.5 × 0.5	25-50	0	1	Moderate	Moderate	Pushing borders	No
20/74/M	Mandibular cheek	No	0.8 × 0.3	25-50	1	1	Mild	Marked	Detached islands	No
21/60/F	Nasal tip	No	0.5 × 0.4	>75	2	1	Mild	Mild	Pushing borders	No
22/81/M	Midcheek	No	0.9 × 0.5	<25	1	1	Mild	Marked	Pushing borders	No
23/62/M	Lateral cheek	No	0.5 × 0.5	>75	0	1	Moderate	Marked	Detached islands	No
24/58/M	Forehead	No	1.0 × 0.7	50-75	0	1	Mild	Mild	Detached islands	No
25/77/M	Nasal bridge	No	0.9 × 0.8
26/52/F	Dorsal foot	No	0.9 × 0.4	<25	0	2	Severe	Moderate	Pushing borders	No
27/49/M	Dorsal foot	No	0.8 × 0.6	25-50	0	2	Moderate	Mild	Detached islands	Yes
28/76/M	Nasal ala	No	0.3 × 0.3	25-50	0	2	Moderate	Mild	Detached islands	+ First stage
29/77/M	Cheek	No	0.7 × 0.5	>75	0	3	Moderate	Moderate	Pushing borders	No
30/73/M	Inferior helix	No	0.3 × 0.3	>75	1	1	Moderate	Mild	Pushing borders	No
31/54/M	Cheek	No	0.5 × 0.5	50-75	0	2	Moderate	Mild	Pushing borders	No
32/51/M	Cheek	No	0.5 × 0.5	50-75	0	3	Moderate	Mild	Detached islands	No
33/55/F	Nasal tip	No	0.5 × 0.4	>75	0	2	Moderate	Mild	Pushing borders	No
34/81/M	Cheek	No	0.6 × 0.6	>75	1	1	Moderate	Mild	Detached islands	No

*Shave biopsy specimens were obtained at initial examination of all lesions. The original slide of the biopsy specimen was examined for residual tumor in the margins. Ellipses indicate not applicable.

†In patients 9, 10, and 25, the tumors were reclassified as hypertrophic actinic keratosis. In patient 14, the tumor was reclassified as squamous cell carcinoma in situ.

‡The presence of residual tumor in the lateral margins was classified as 0, no residual tumor; 1, residual tumor in 1 margin; and 2, residual tumor in both margins. Squamous cell carcinoma in situ was considered residual tumor, but actinic keratosis was not.

§The histological grade was reported according to the Broders' classification system,³ in which 1 indicates well-differentiated and 4, poorly differentiated.

||Tumor was present at first Mohs stage (layer).

graphic surgery (MMS). Because MMS involves examination of the deep and lateral margins rather than cross-sectional evaluation of the entire biopsy specimen, the status of actual residual tumor at the time of surgery is often not known. We were surprised to find that among patients with SCC who presented for MMS with no clinical evidence of tumor, the vast majority showed no histological evidence of residual tumor on completely sectioned biopsy specimens.

Patients and Methods. During a 7-month period in 1997 and a 5-month period in 1998-1999, 1150 patients were referred for MMS; of these, 139 had a histological diagnosis of SCC. Patients were examined on the day of surgery (approximately 4-8 weeks following original biopsy specimen) and 34 of 139 patients without clinical evidence of tumor were studied. Patients with clinical evidence of re-

sidual tumor, such as nodulation, induration, ulceration, crusting, oozing, or tenderness, were excluded. The MMS procedure was performed in the usual manner,² with only the outermost margin from the initial stage examined by frozen section. Tissue specimen blocks were then fixed in formalin, bisected, and serially sectioned to assess the presence of residual tumor. In all cases scar tissue was seen, confirming that the excision included the original biopsy site. For each case, the histological slides from the original biopsy specimens were subsequently reviewed by a dermatopathologist (E.J.G.).

Results. The study group consisted of 34 patients with a histological diagnosis of SCC (**Table**). These patients were referred by 23 different physicians. On review of the original biopsy specimens, 4 were reclassified as SCC in situ (1) or hypertrophic actinic keratosis (3). Histological review

of the initial biopsy specimens demonstrated residual tumor in at least 1 positive margin in each of the remaining 30 tumors: 17 in the lateral margins and 29 in the deep margins. Only patient 4 had a recurrent SCC in the midcheek that had been treated by electrodesiccation and curettage. This patient and patient 28 were the only 2 patients who had residual tumors at the first Mohs stage. There was no residual tumor in the biopsy specimens of patient 27 at the first Mohs stage, but there was remaining SCC present within the tissue from the first Mohs stage.

None of the other patients were found to have residual tumor on examination of each entire surgical specimen. Thus, 27 (90%) of the 30 patients with SCC and histological margins with residual tumor in biopsy specimens had no residual tumor. Of the 30 patients, 21 (70%) of the tumors revealed moderate or severe nuclear atypia and in 13 (43%) there were infiltrating (islands or single cells) growth patterns. The histological grade using Broders' classification³ for the 30 tumors was grade 1 for 18 tumors, grade 2 for 9 tumors, and grade 3 for 3 tumors.

Comment. The patient with a diagnosis of SCC in whom the skin lesion appears to have resolved after biopsy presents a common therapeutic dilemma. We investigated the extent of residual SCC in a cohort of these patients. We found that, of 30 patients, only 3 (10%) had microscopic evidence of residual tumor. Although it is well established for basal cell carcinomas⁴⁻⁸ that some incompletely removed primary tumors do not clinically recur within 5 years, the same is generally not accepted for SCCs. While SCCs that are large, recurrent, or display aggressive growth require definitive excision,⁷ these results suggest that there is a subset of SCC that may not require significant therapy after adequate biopsy of the tumor.

Our study did not determine the form of hemostasis performed at the time of the original tumor biopsy. Although it would be important in future studies to determine if the method of hemostasis removed additional tumor, the conclusions from our study do not depend on the type of hemostasis but on the clinical appearance of the biopsy site at the time of surgery.

Many physicians are understandably uncomfortable merely observing a patient with SCC for fear of possible recurrence or metastasis if there is residual microscopic tumor. Our findings suggest that such concern may be excessive in certain circumstances. Observation may be appropriate for some primary SCCs that appear clinically to have resolved 1 to 2 months after biopsy of the tumor. A study of a larger group is needed, however, and close follow-up of such patients is important.

Thomas W. McGovern, MD
Douglas Grossman, MD, PhD
David Fitzgerald, MB, ChB, MRCP
Earl J. Glusac, MD
New Haven
David Leffell, MD
Department of Dermatology
Yale University School of Medicine
PO Box 208059
New Haven, CT 06520-8059

Dr Fitzgerald is now with the Department of Dermatology, Hope Hospital, Manchester, England.

A portion of these data was presented at the Annual Meeting of the American College of Mohs Micrographic Surgery and Cutaneous Oncology in Miami, Fla, May 18, 1999.

1. Torres A, Seeburger J, Robison D, Glogau R. The reliability of a second biopsy for determining residual tumor. *J Am Acad Dermatol.* 1992;27:70-73.
2. Swanson NA. Mohs surgery: technique, indications, applications, and the future. *Arch Dermatol.* 1983;119:761-773.
3. Broders AC. Squamous-cell epithelioma of the skin. *Ann Surg.* 1921;73:141-160.
4. Sarma DP, Griffing CC, Weillbaecher TG. Observations on the inadequately excised basal cell carcinomas. *J Surg Oncol.* 1984;25:79-80.
5. Richmond JD, Davie RM. The significance of incomplete excision in patients with basal cell carcinoma. *Br J Plast Surg.* 1987;40:63-70.
6. Gooding CA, White G, Yatsuhashi M. Significance of marginal extension in excised basal-cell carcinoma. *N Engl J Med.* 1965;273:923-924.
7. Bielely HC, Kirsner RS, Reyes BA, Garland LD. The use of Mohs micrographic surgery for determination of residual tumor in incompletely excised basal cell carcinoma. *J Am Acad Dermatol.* 1992;26:754-756.
8. Pascal RR, Hobby LC, Lattes R, Crikelair GF. Prognosis of "incompletely excised" versus "completely excised" basal cell carcinoma. *Plast Reconstr Surg.* 1968;41:328-332.

Analysis of the TP53 Gene in Normal Skin and Hair Follicle Samples From Sun-Exposed and Non-Sun-Exposed Sites on Normal and Albino Individuals Living in Southeast Brazil

Nonmelanoma skin cancers (NMSCs) are the most common malignant neoplasms in white populations. Epidemiological studies have revealed a positive correlation between the incidence of NMSCs and UV exposure, as well as an inverse relationship with the degree of skin pigmentation.¹ The early role of sunlight in cutaneous carcinogenesis is supported by the finding of UV-induced mutations in the *TP53* tumor suppressor gene in precancerous lesions and in chronically sun-exposed epidermis. *TP53* mutations may accumulate in normal skin, with a frequency that directly reflects an individual's skin type and sun exposure and serves as an initial step that starts the cells on a path toward cancer.² *TP53*-mutated clones have been detected in normal interfollicular epidermis as well as in hair follicles, which are the locations of the presumed stem cells in skin and appear to be the source of tumors in experimental animals.³

We were interested in examining samples of normal epidermis from sun-exposed and non-sun-exposed sites on subjects living in southeast Brazil, an area with high levels of sun exposure, since no studies on the prevalence of *TP53* mutations have been performed in Brazilian populations. To this end, we screened mutations in exons 5 through 9 of the *TP53* gene by polymerase chain reaction-single-strand conformation polymorphism analysis⁴ in 41 samples of normal skin and 16 hair follicles (37 sun-exposed sites and 20 non-sun-exposed sites) from 53 healthy subjects and 3 albino individuals (51 women and 5 men).

No samples of normal skin from sun-exposed or non-sun-exposed sites showed a *TP53* gene alteration. Our analysis of hair follicle samples, including those from the albino individuals, also demonstrated no alteration. The results were particularly unexpected in albino indi-

viduals, because they lack melanin protection and present a considerable increase in skin cancer risk. However, these individuals protected their skin with clothing or sunscreens, which possibly influenced the interpretation of our results. Our findings could also be the result of the relatively low mean age (mean age, 46.7 years; age range, 13-86 years) of our subjects, since *TP53* mutations are frequently observed in normal skin samples from older persons. Also, most of our patients (96.4%) made no mention of outdoor work, and *TP53* alterations may be related to a continuous and cumulative sun exposure, although Ouhitit et al⁵ demonstrated no statistically significant association between *TP53* mutation frequency and age or total lifetime sun exposure.

Our results suggest that *TP53* mutations are not obligatorily frequent in chronically sun-exposed skin samples, but may be related to age, DNA-repair capacity, or immune response, or even to differences in skin type that are related to the ethnic composition of the populations and the degree of protection. However, we cannot rule out the possibility that small mutated clones and normal cells were mixed in the samples, since p53 immunoreaction and microdissection of mutated clones were not performed. Our findings show that it is possible to investigate *TP53* DNA mutations in epidermal cells using hair follicles. Because of their accessibility and the possibility of ethically excising consecutive samples without surgical intervention, hair follicles may offer potentially important insights into the earliest stages of human skin cancer.

Érika Cristina Pavarino-Bertelli, PhD
 Flávia Cristina Carvalho Rodrigues, BS
 Antônio Roberto Bozola, MD
 São José do Rio Preto
 Eloiza Helena Tajara, PhD
 Department of Biology
 Instituto de Biociências, Letras e Ciências
 Exatas—Universidade Estadual Paulista
 CP 136
 15054-000, São José do Rio Preto, SP, Brazil

1. Strom SS, Yamamura Y. Epidemiology of nonmelanoma skin cancer. *Clin Plast Surg*. 1997;24:627-636.
2. Kraemer KH. Sunlight and skin cancer: another link revealed. *Proc Natl Acad Sci U S A*. 1997;94:11-14.
3. Jonason AS, Kunala S, Price GJ, et al. Frequent clones of p53-mutated keratinocytes in normal human skin. *Proc Natl Acad Sci U S A*. 1996;93:1425-1429.
4. Bassam BJ, Caetano-Anollés G. Silver staining of DNA in polyacrylamide gels. *Appl Biochem Biotechnol*. 1993;42:181-188.
5. Ouhitit A, Nakazawa H, Armstrong BK, et al. UV-radiation-specific p53 mutation frequency in normal skin as a predictor of risk of basal cell carcinoma. *J Natl Cancer Inst*. 1998;90:523-531.

Treatment of Subcutaneous Sarcoidosis With Allopurinol

We report the case of a 30-year-old patient with subcutaneous sarcoidosis who refused standard treatment with corticosteroids and received allopurinol instead, resulting in a poor therapeutic response.

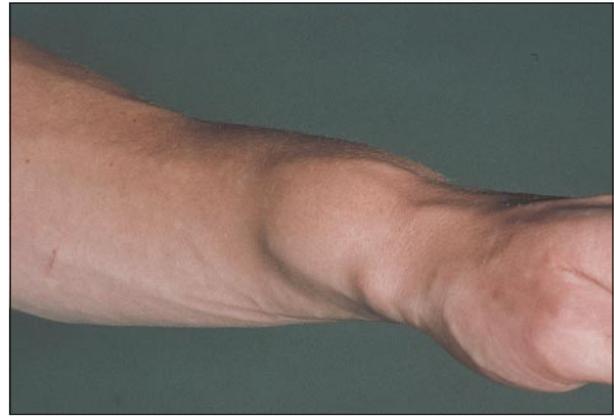


Figure 1. Osseous manifestation of sarcoidosis on the distal aspect of the right radius.

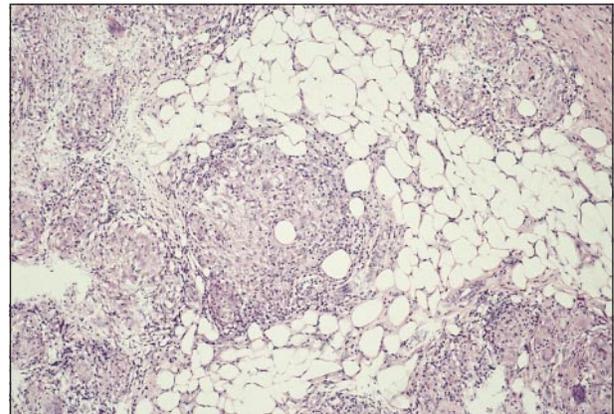


Figure 2. Epithelioid granulomas in the subcutaneous tissue (hematoxylin-eosin, original magnification $\times 100$).

Report of a Case. A 30-year-old man presented to our clinic with a massively superinfected, 6.5 \times 3.2-cm, nodular ulceration on his right thigh; a firm, painful swelling around his distal right radius (**Figure 1**) and several painless, plum-sized lumps and enlarged, freely mobile lymph nodes in his groin and axillae. The skin overlying all these nodules was immobile and bluish. Pronounced finger-clubbing was present. Radiographic imaging revealed enlarged bilateral mediastinal lymph nodes and a 60 \times 15-mm soft-tissue tumor of his right radius with cortical thickening. Histological findings revealed a normal epidermis and papillary dermis (**Figure 2**). The lower aspects of the reticular dermis and subcutaneous fat tissue contained epithelioid granulomas with slight necrosis and a sparse rim of lymphoid cells (“naked” tubercles). The diagnosis of a subcutaneous sarcoidosis was made; the most important differential diagnoses, the diagnoses of deep mycoses, tuberculosis, and immunological disorders, were excluded. The angiotensin-converting enzyme (ACE) level was elevated at 46 U/L (normal range, 8-21 U/L). Treatment with allopurinol was initiated at 200 mg/day. It was later increased to a maximum of 600 mg/day and was well tolerated. An initial regression of both mediastinal and cutaneous nodular lesions was observed. However, follow-up examinations revealed progression of the disease after 6

months of treatment and increased angiotensin-converting enzyme values. Allopurinol was therefore replaced by prednisolone (Decortin H) 100 milligrams/day for 5 days and then tapered over 5 months as disease symptoms lessened.

Comment. This is the first report of a subcutaneous sarcoidosis occurring with an osseous manifestation treated with allopurinol. Subcutaneous sarcoidosis is rare, and only about 30 cases have been reported thus far in the literature.¹ The skin covering the nodules is frequently bluish and tends to ulcerate after trauma. Skeletal lesions as a manifestation of systemic sarcoidosis are infrequent and occur as a lesion even less frequently with subcutaneous sarcoidosis. These lesions typically involve the small bones of the hands and feet and are associated with a 4-fold increase in disease mortality. The early detection of bony lesions in patients with chronic skin lesions is therefore extremely important.² Spontaneous remissions occur in up to 90 % of patients.³ Corticosteroids are the treatment of choice for sarcoidosis, particularly if critical organs like the heart or brain are involved, and/or if disfiguring skin lesions or functionally impairing osseous lesions are present. If corticosteroids are contraindicated or inefficient,

methotrexate may be considered as an alternative treatment.⁴

Allopurinol does not seem to be of real benefit to patients with subcutaneous sarcoidosis even though positive responses to allopurinol^{5,6} are reported in the literature (these responses may be spontaneous remissions and might have occurred without treatment.)

1. James DG, Neville E, Siltzbach LE. A worldwide review of sarcoidosis. *Ann N Y Acad Sci.* 1976;278:321-334.
2. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. *Q J Med.* 1983;52:525-533.
3. Brechtel B, Haas N, Henz BM, Kolde G. Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol.* 1996;135:307-309.
4. Rosof, BM. Allopurinol for sarcoid? *New Engl J Med.* 1976;294:447.
5. Lower EE, Baugham RD. The use of low dose methotrexate in refractory sarcoidosis. *Am J Med Sci.* 1990;299:153-157.

Susanne Voelter-Mahlknecht, MD
Anja Benez, MD
Silke Metzger, MD
Gerhard Fierlbeck, MD
Department of Dermatology
University of Tuebingen
Liebermeisterstr 25
D-72076 Tuebingen
Germany

the symptoms in patients presenting with follicular histological findings were more likely to show a complete response. Furthermore, the reason for the persistence of some of the injected nodules might be found in the high expression of the apoptosis inhibitor bcl-2, which is rarely observed in primary cutaneous B-cell lymphomas.¹⁶⁻¹⁹ Staging, however, did not reveal extracutaneous manifestations. Another reason for the limitation in the disappearance of the lesions could be the insufficient infiltration with macrophages and other effector cells that are able to clear the site of antibody-bound B cells. Nevertheless, especially patient 1 was satisfied with the clinical result.

We conclude that intralesional rituximab might be an effective and feasible treatment alternative to systemic intravenous therapy with the anti-CD20 monoclonal antibody. If other treatment options are exhausted or not applicable, the intratumoral injection of rituximab may be a promising treatment approach that deserves further investigation in controlled clinical trials.

Accepted for publication September 9, 1999.

Reprints: Günter Burg, MD, University Hospital Zürich, Dermatologische Klinik, Gloriastrasse 31, 8091 Zürich, Switzerland.

REFERENCES

1. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood*. 1997;90:354-371.
2. Bürg G, Schmid MH, Kung E, Dommann S, Dummer R. Semimalignant ("pseudolymphomatous") cutaneous B-cell lymphomas. *Dermatol Clin*. 1994;12:399-407.
3. Joly P, Charlotte F, Leibowitch M, et al. Cutaneous lymphomas other than mycosis fungoides: follow-up study of 52 patients. *J Clin Oncol*. 1991;9:1994-2001.
4. Dummer R. Cutaneous lymphomas [in German]. *Hautarzt*. 1998;48(suppl 1):S49-S55.
5. Ralfkiaer E. Immunohistological markers for the diagnosis of cutaneous lymphomas. *Semin Diagn Pathol*. 1991;8:62-72.
6. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today*. 1994;15:450-454.
7. Link BK, Grossbard ML, Fisher RI, et al. Phase II pilot study of the safety and efficacy of rituximab in combination with CHOP chemotherapy in patients with previously untreated intermediate- or high-grade NHL. In: Program and abstracts of the 34th Annual Meeting of the American Society of Clinical Oncology; May 16-19, 1998; Los Angeles, Calif. Abstract 7.
8. Davis T, Maloney D, White CA, et al. Combination immunotherapy of low grade or follicular (LG/F) non-Hodgkin's lymphoma (NHL) with rituximab and alpha interferon: interim analysis. In: Program and abstracts of the 34th Annual Meeting of the American Society of Clinical Oncology; May 16-19, 1998; Los Angeles, Calif. Abstract 39.
9. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*. 1997;90:2188-2195.
10. Böni R, Böni RA, Steinert H, et al. Staging of metastatic melanoma by whole-body positron emission tomography using 2-fluorine-18-fluoro-2-deoxy-D-glucose. *Br J Dermatol*. 1995;132:556-562.
11. Kempf W, Dummer R, Hess M, Fritz T, Wüthrich B, Bürg G. Intralesional cisplatin for the treatment of cutaneous B-cell lymphoma. *Arch Dermatol*. 1998;134:1343-1345.
12. Maloney DG, Smith B, Appelbaum FR. The anti-tumor effect of monoclonal anti-CD20 antibody (mAb) therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma (NHL) cell lines [abstract]. *Blood*. 1996;88(suppl 1):637a.
13. Shan D, Ledbetter JA, Press OW. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. *Blood*. 1998;91:1644-1652.
14. Zackheim HS, Epstein EJ, Crain W. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol*. 1990;22:802-810.
15. Maloney DG, Grillo-López AJ, Bodkin DJ, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin Oncol*. 1997;15:3266-3274.
16. Geelen FA, Vermeer MH, Meijer CJ, et al. bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. *J Clin Oncol*. 1998;16:2080-2085.
17. Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B-cell lymphoma: a unique type of low-grade lymphoma: clinicopathologic and immunologic study of 83 cases. *Cancer*. 1991;67:2311-2326.
18. Chimenti S, Cerroni L, Zenahlik P, Peris K, Kerl H. The role of MT2 and anti-bcl-2 protein antibodies in the differentiation of benign from malignant cutaneous infiltrates of B-lymphocytes with germinal center formation. *J Cutan Pathol*. 1996;23:319-322.
19. Cerroni L, Volkenandt M, Rieger E, Soyer P, Kerl H. bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas. *J Invest Dermatol*. 1994;102:231-235.

Correction

Error in Dosage. In the correspondence titled "Ivermectin: A Few Caveats Are Warranted Before Initiating Therapy for Scabies," published in the December issue of the ARCHIVES (1999;135:1549-1550), all dosage units are in milligrams per kilogram and should have been micrograms per kilogram. Therefore, the following corrections should be made: "200 mg/kg" should be "200 µg/kg," "250 mg/kg" should be "250 µg/kg," and "400 mg/kg" should be "400 µg/kg."