

COMMENTS AND OPINIONS

Fill the Mind—and Exercise It, Too!

I read with pleasure Dr Rycroft's¹ essay titled "Going to See Jack" in the "The Art and the Calling" section of the November 2002 issue of the ARCHIVES. His paean to Samuel Johnson and to the unique turn of mind of that polyglot is a poignant reminder of our own intellectual obligations to our art and to our calling. In seeking to capture the distinctive mentality of Johnson in his own words, Rycroft quotes him as writing that after a "hard journey in the Scottish highlands . . . I should have been sorry to have missed any of the inconveniences, to have had more light, or less rain, for their cooperation crowded the scene, and filled the mind." Rycroft then continued, in his own words, as follows: "Filled the mind—that surely is the key to our professional well-being."

After having perused the rest of the issue, I am prompted to suggest that as important as it is that the mind be filled, it is just as essential that the mind be exercised effectively by dint of logical, critical, incisive thought. And that brings me to 3 statements made in different articles in the same issue that not only are clichés but also, in my opinion, contain ideas that should be passé: (1) "Actinic keratoses (AKs) are precancerous epidermal lesions found most frequently on areas of the skin exposed to the sun."² (2) "Basal cell carcinoma (BCC) is the most common skin cancer in whites, with a steadily increasing incidence."³ (3) "The annual incidence of malignant melanoma per 100 000 individuals almost tripled among American men, from 6.7 in 1973 to 19.3 in 1997, and more than doubled among American women, from 5.9 to 13.8 for the same period."⁴

I believe that all evidence leads to the conclusions that actinic keratoses are *not* precancerous lesions but superficial squamous cell carcinomas,⁵ that squamous cell carcinoma (of which actinic keratosis is 1 type), *not* basal cell carcinoma, is the most common cancer of the skin,⁶ and that there is *no* epidemic of melanoma.⁷

In sum, as wonderful as it is to fill the mind, it is equally as marvelous to use it in a critical manner.

A. Bernard Ackerman, MD
Ackerman Academy of Dermatopathology
145 E 32nd St, 10th Floor
New York, NY 10016
(e-mail: abernard@ameripath.com)

The author has no relevant financial interest in this article.

1. Rycroft RJG. Going to see Jack. *Arch Dermatol*. 2002;138:1435-1436.
2. Stockfleth E, Meyer T, Benninghoff B, et al. A randomized, double-blind, vehicle-

3. Heckmann M, Zogelmeier F, Konz B. Frequency of facial basal cell carcinoma does not correlate with site-specific UV exposure. *Arch Dermatol*. 2002;138:1494-1497.
4. Al Mahroos M, Yaar M, Phillips TJ, Bhawan J, Gilchrist BA. Effect of sunscreen application on UV-induced thymine dimers. *Arch Dermatol*. 2002;138:1480-1485.
5. Heaphy MR Jr, Ackerman AB. The nature of solar keratosis: a critical review in historical perspective. *J Am Acad Dermatol*. 2000;43:138-150.
6. Brand D, Ackerman AB. Squamous cell carcinoma, not basal cell carcinoma, is the most common cancer in humans. *J Am Acad Dermatol*. 2000;42:523-526.
7. Swica Y, Koehler A, Ackerman AB. Lies, damn lies, and statistics: why there is no epidemic of melanoma. *Dermatopathol Pract Concept*. 2001;7:347-354.

The Unwelcome Return of the Acne Diet

Commenting on the subject of remarriage, Samuel Johnson (1709-1784) called it a triumph of hope over experience. His wisdom might well apply to dermatology's renewed interest in a possible diet-acne connection as proposed in the article "Acne Vulgaris: A Disease of Western Civilization."¹

This observation presents an unbalanced comparison of processed snack foods with primitive dietary staples, implying that all westerners consume higher glycemic loads than do natives of nonindustrialized countries. In fact, contrasted with the high meat and dairy content of the US diet, primitive diets often derive a greater share of total calories from starchy foods like boiled rice, corn products, potatoes, and refined flour. Thus, American teens not inclined toward sweets and soft drinks probably consume relatively low glycemic loads yet still are acne prone.²

The authors' theories are speculative at best. Their suggestion that diet-induced hyperinsulinemia and elevated levels of free insulinlike growth factor 1 cause acne via overproduction of ovarian and testicular hormones is unlikely for several reasons. First, acne prevalence among premenarchal girls is correlated with adrenal rather than ovarian androgens, and further, hormone levels are normal in most patients with acne.³ Also, there is a distinct demographic divide between populations with acne vulgaris, principally a teenage disorder, and those showing insulin resistance, mainly overweight adults. Finally, acne was ubiquitous in American adolescents 3 decades ago,² prior to the proliferation of soda and candy machines in secondary schools, when the teen obesity rate was only one third of today's 14%.

The suggestion that diet-related reduction of insulinlike growth factor binding protein 3 causes acne by interfering with retinoid metabolism might be intriguing, except that vitamin A deficiency severe enough to cause follicular hyperkeratosis is associated with sebaceous atrophy, not acne.⁴

In an isolated subculture, attributing disease protection to a single variable like dietary glycemic index is

an oversimplification. An indigenous group has a common genetic ancestry, the strongest determinant of familial disorders like acne. In addition, such societies share environmental conditions other than nutrition, including climate, sun exposure, work, stress, physical activity, and local microbes.

In their thoughtful editorial comments, Drs Thiboutot and Strauss³ point out that the authors failed to test the western diet for acnegenicity in the native groups. In addition, acne efficacy of the primitive diet in westerners was not shown.

Whereas low-glycemic diets are appropriate for patients with polycystic ovary syndrome and insulin resistance, data are nonexistent that diet causes or cures acne.

Susan Bershad, MD
28 S Mountain Ave
Montclair, NJ 07042
(e-mail: skinhealer@aol.com)

1. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. *Arch Dermatol*. 2002;138:1584-1590.
2. Roberts J. *Skin Conditions of Youths 12-17 Years, United States*. Washington, DC: US Dept of Health, Education and Welfare; 1976. Data from Vital and Health Statistics, Series 11, National Health Survey No. 157; publication (HRA) 76-1639.
3. Lucky AW, Biro FM, Huster GA, et al. Acne vulgaris in premenarchal girls: an early sign of puberty associated with rising levels of dehydroepiandrosterone. *Arch Dermatol*. 1994;130:308-314.
4. Elder DE, Johnson BL, Jaworsky C, Elenitsas R. *Lever's Histopathology of the Skin*. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1997.
5. Thiboutot DM, Strauss JS. Diet and acne revisited [editorial]. *Arch Dermatol*. 2002;138:1591-1592.

Diet and Acne Redux

The science of nutrition has produced dramatic findings over the past few decades. Of particular note is the expansion of knowledge about essential fatty acids during the 1980s. Also, profound changes in the concept of daily nutritional requirements find the United States replacing "recommended daily allowances" with "dietary reference intakes." This reflects the consideration of optimal nutrient levels rather than minimum daily requirements. The vitamin paradigm changed forever when neural tube defects declined radically with folic acid supplementation.¹ No longer do we think only of preventing nutritional deficiency diseases. Now we are learning to provide optimal nutrient intake for optimal function.

Cardiologists have embraced this concept and now prescribe vitamin B₁₂, vitamin B₆, and folate to bring down elevated homocysteine levels in patients at risk for stroke and myocardial infarction.² Although causality has not been proved, study findings are highly suggestive, and supplementation carries few risks. The American Heart Association also acknowledges the benefit of daily fish oil supplementation for some patients.³ However, few physicians in other fields seem to take advantage of recent discoveries in nutrition and apply them clinically.

Dermatology has been particularly tied to older nutrition dogma with regard to acne and diet. The article

by Cordain et al⁴ in a recent issue of ARCHIVES should serve to awaken us to the relevance of nutrition to skin disease and stir us to review the dogma. The major textbooks of dermatology tend to view diet as irrelevant to the treatment of acne. The primary references to which the texts refer are both more than 30 years old.^{5,6}

In 1971, Anderson⁵ observed 27 college students on a "typical high-carbohydrate dorm diet." The students believed that specific foods caused inflammatory flares within 3 days of ingestion. They received the culprit foods on a daily basis and returned daily for facial mapping of lesions. None flared. While the uniformity of response was impressive, the study had a few glaring flaws. The sample size was fairly limited. The study was neither controlled nor blinded. The article was not peer reviewed by dermatologists (published in the *American Family Physician*). Most importantly, given the effects of chronically elevated insulin posited by Cordain et al,⁴ the baseline diet may have obscured the findings.

In 1969, Fulton et al⁶ explored the effect of chocolate on acne by using "pseudo-chocolate" bars made with 28% partially hydrogenated vegetable oil as the control. With our 2002 lens, we can see that the high proportion of *trans* fats in the control bar limits the usefulness of the study. *Trans* fats compete with essential fatty acids in the production of prostaglandins and appear to significantly contribute to inflammation.⁷

In the nutrition literature, evidence supporting dietary effects on health continues to mount, and dermatology is no exception. Many of our patients' skin conditions are affected by what they eat. It may be time for us to open our minds and our nutrition textbooks.

Valori Treloar, MD, CNS
37 Hillside Rd
Newton, MA 02461
(e-mail: trescon@rcn.com)

1. Botto LD, Moore CA, Khoury MJ, Erickson JD. Medical progress: neural-tube defects. *N Engl J Med*. 1999;341:1509-1519.
2. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ*. 2002;325:1202.
3. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284-2299.
4. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. *Arch Dermatol*. 2002;138:1584-1590.
5. Anderson PC. Foods as the cause of acne. *Am Fam Physician*. 1971;3:102-103.
6. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA*. 1969;210:2071-2074.
7. Calder PC. Dietary modification of inflammation with lipids. *Proc Nutr Soc*. 2002;61:345-358.

Omega-3 Fatty Acids and Acne

I read with great interest the recent article by Cordain et al.¹ This group makes a strong argument for the involvement of diet-induced hyperinsulinemia in the pathogenesis of acne vulgaris. In addition to the glycemic load of the typical western refined-food diet, it is also important to note that the western diet typically includes a much lower intake of omega-3 fatty acids, an

excess of proinflammatory omega-6 and *trans* fatty acids, and a reduced intake of dietary antioxidant vitamins. The current ratio of omega-6 to omega-3 fatty acids in the western diet reaches 20:1, while through evolution and in a traditional hunter-gatherer diet it is closer to 1:1.² Fish, wild game, and wild plants have much higher levels of omega-3 fatty acids than do refined western foods.

In addition to being higher in omega-3 fatty acids, the diets consumed by the Kitavans and Aché may also include increased quantities of plant-derived antioxidant vitamins, minerals, and phytochemicals that support antioxidant pathways. Research shows that omega-3 fatty acids can increase insulinlike growth factor binding protein 3 in animals³ and decrease insulinlike growth factor 1 in healthy humans.⁴ Therefore, in support of the ideas of Cordain et al,¹ a diet high in omega-3 fatty acids may also be involved in the prevention of the hyperkeratinization of sebaceous follicles. In addition, the involvement of proinflammatory leukotriene B₄ (LTB₄) in the pathogenesis of acne has recently been described; administration of a novel LTB₄ blocker led to a 70% reduction in inflammatory acne lesions, improvements that correlated with a reduction in proinflammatory lipid levels.⁵ The anti-inflammatory properties of omega-3 fatty acids, including LTB₄ inhibition, are well known.¹ Arachidonic acid, the major dietary omega-6 fatty acid, is a precursor to the manufacture of LTB₄,⁵ indicating that dietary choices may play a role in inflammatory acne lesions. It is possible that dietary omega-3 fatty acids could have a synergistic effect on any potential benefit of adhering to a diet with a low glycemic load.

Clearly, further research is required. In particular, a more detailed dietary analysis of the Kitavans and Aché may help determine if additional relevant differences occur between the western diet and that consumed by non-westernized populations.

Alan C. Logan, ND, FRSH
CFS-FM Integrative Care Centre of Toronto
3600 Ellesmere Rd, Unit 4
Toronto, Ontario, Canada M1C 4Y8
(e-mail: aclnd@cfs-fm.org)

1. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. *Arch Dermatol*. 2002;138:1584-1590.
2. Simopoulos AP. Evolutionary aspects of diet and essential fatty acids. *World Rev Nutr Diet*. 2001;88:18-27.
3. Li Y, Seifert MF, Ney DM, et al. Dietary conjugated linoleic acids alter serum IGF-1 and IGF binding protein concentrations and reduce bone formation in rats fed (n-6) or (n-3) fatty acids. *J Bone Miner Res*. 1999;14:1153-1162.
4. Bhatena SJ, Berlin E, Judd JT, et al. Effects of omega 3 fatty acids and vitamin E on hormones involved in carbohydrate and lipid metabolism in men. *Am J Clin Nutr*. 1991;54:684-688.
5. Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? *Dermatology*. 2001;203:277-279.

In reply

In his letter, Dr Logan proposes that a lower dietary omega-6-omega-3 ratio in the Kitavan and Aché people may play a synergistic role along with a lower glycemic load in preventing the development of acne via reductions of proin-

flammatory eicosanoids. This hypothesis is certainly reasonable given recent evidence showing that an LTB₄ blocker led to a 70% reduction in inflammatory acne lesions after 3 months.¹ We have previously reported that the Kitavans indeed maintain a significantly lower dietary omega-6-omega-3 ratio than do western populations² and that a lower dietary omega-6-omega-3 ratio is characteristic of virtually all hunter-gatherer diets.³ Another feature that distinguishes Kitavan and Aché diets from western diets is the absence of milk, which exhibits a low glycemic index but paradoxically is highly insulinotropic.⁴ As with high-glycemic-load carbohydrates, dietary interventions will be required to assess the effectiveness of any nutritional treatment on the development of acne.

In her letter, Dr Treloar implies that "the emperor wears no clothes" by pointing out to the dermatology community that the nearly universal assumption that diet and acne are unrelated is based largely on 2 marginal and poorly designed studies that are now over 30 years old.^{5,6} Her conclusion is not unique; a previous report summarized, "There are few, if any, well-controlled studies on the effects of various dietary factors in acne."⁷ Although the single article by Fulton et al⁵ has been often cited as the definitive work dissociating diet and acne, serious design flaws in the study were identified more than 25 years ago showing that the fat and sugar content of the placebo bar did not differ significantly from chocolate.⁸ If high-glycemic-load carbohydrates represent the environmental trigger for the development of acne in genetically susceptible individuals, then the double-blind study by Fulton et al⁵ would not have been able to detect a treatment effect because the glycemic load of the placebo and treatment were nearly identical.

Many early 20th-century anecdotal observations by dermatologists and physicians have linked sugars and refined cereals to acne.^{9,10} Unfortunately, at the time, these observations lacked objectivity because the mechanistic understanding of the endocrine and cytokine basis underlying the development of acne was in its infancy and because well-controlled dietary interventions were rarely or never performed. Regrettably, we still cannot confirm or deny these early observations because well-controlled dietary interventions have yet to be conducted. In the 21st century, we now have the tools and knowledge to adequately test the diet-acne hypothesis—be it high-glycemic-load carbohydrates, insulinotropic dairy products, *trans* fatty acids, a high dietary omega-6-omega-3 ratio, or all of the above.

In science, when observable facts are inconsistent with prevailing theory, the facts are not necessarily thrown out or ignored. Frequently, new facts make prevailing theory untenable. Our report¹¹ demonstrates that an inconsistency may exist between the observable facts (the total absence of acne in nonwesternized populations) and the prevailing theory (that diet and acne are unrelated). This information should not be viewed as an "unwelcome return of the acne diet," but rather should provide a theoretical construct for critically reexamining the diet-acne hypothesis. As Dr Treloar has pointed out, the current foundation for rejecting the diet-acne hypothesis is virtually nonexistent and relies almost entirely on two 30-year-old, poorly controlled studies. No amount of discussion in "letters to the editor" will ultimately resolve this issue. The currency of science is good data generated from well-controlled experi-

ments. Until this information becomes available, it is premature to either reject or accept the diet-acne hypothesis.

Loren Cordain, PhD
Department of Health and Exercise Science
Colorado State University
Fort Collins, CO 80523
(e-mail: cordain@cahs.colostate.edu)

1. Zouboulis CC, Nestoris S, Adler YD, et al. Treatment of inflammatory acne with an oral 5-lipoxygenase inhibitor. *J Invest Dermatol.* 2001;117:547.
2. Lindeberg S, Nilsson-Ehle P, Vessby B. Lipoprotein composition and serum cholesterol ester fatty acids in nonwesternized Melanesians. *Lipids.* 1996; 31:153-158.
3. Cordain L, Eaton SB, Brand Miller J, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. *Eur J Clin Nutr.* 2002;56(suppl 1):S42-S52.
4. Ostman EM, Liljeberg Elmstahl HG, Bjorck IM. Inconsistency between glycaemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr.* 2001;74:96-100.
5. Fulton JE, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA.* 1969;210:2071-2074.
6. Anderson PC. Foods as the cause of acne. *Am Fam Physician.* 1971;3:102-103.
7. Michaelsson G. Diet and acne. *Nutr Rev.* 1981;39:104-106.
8. Mackie BS, Mackie LE. Chocolate and acne. *Australas J Dermatol.* 1974;15: 103-109.
9. Barber HW. Diseases of the skin: acne vulgaris. In: Poulton EP, ed. *Taylor's Practice of Medicine.* 15th ed. London, England: JA Churchill Ltd; 1936:860-861.
10. Urbach E, LeWinn EB. Diseases of sebaceous and sudoriferous glands: acne vulgaris. In: Urbach E, LeWinn EB, eds. *Skin Diseases Nutrition and Metabolism.* New York, NY: Grune & Stratton; 1946:483-521.
11. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. *Arch Dermatol.* 2002;138:1584-1590.

VIGNETTES

Histologic Resolution of Melanoma In Situ (Lentigo Maligna) With 5% Imiquimod Cream



Lentigo maligna (LM) is an in situ melanoma that occurs on the face and other sun-exposed areas. It may histologically extend beyond the clinical borders of the lesion; therefore, obtaining clear surgical margins is difficult.

Report of a Case. A 55-year-old woman presented with an irregular, brown-to-tan, poorly differentiated, 2.3 × 1.9-cm patch on her right cheek that was accentuated by Wood lamp examination. The hyperpigmented area had been treated 2 years earlier with carbon dioxide laser ablation without biopsy confirmation, but the lesion had recurred and appeared to be darker and larger. A biopsy specimen showed LM (**Figure 1**). After a thorough discussion of treatment options, including surgical excision, cryotherapy, and radiation therapy, the patient opted for a nonsurgical approach. The discussion to use 5% imiquimod cream, off-label, included a detailed explanation of the risks, potential failure, and departure from the current standard of care. After the patient applied 5% imiquimod cream once or twice a day for 3 months, multiple punch biopsy specimens ob-

tained from the tumor site showed no residual LM (**Figure 2**). Clinical examination and Wood lamp examination of the area also showed fading of pigmentation and no extension of the lesion.

Comment. Lentigo maligna is an in situ pattern of melanoma that occurs on sun-exposed areas, such as the face, forearms, and legs. Like other in situ melanomas, LM does not metastasize if it is completely excised. However, because the majority of LM occurs on the face, surgical excision can lead to significant disfigurement. Because LM is poorly defined clinically, excision margins are frequently involved, requiring multiple surgical procedures.

5% Imiquimod cream (Aldara; 3M Pharmaceuticals, St Paul, Minn) is a unique immunomodulator that is currently approved only for the treatment of genital warts. The medication actually modulates or up-regulates multiple cytokines to eradicate the human papillomavirus. Cytokines, such as interferon α , interleukin 12, and interferon γ , are increased in the skin at the application site, mimicking the normal host immune response to human papillomavirus eradication.¹ Injectable interferon alfa has also been shown to cause resolution of actinic keratoses, squamous cell carcinoma, postsurgical keloids, and superficial basal cell carcinoma.² Currently, systemic interferon alfa is used as adjuvant therapy for metastatic melanoma.³

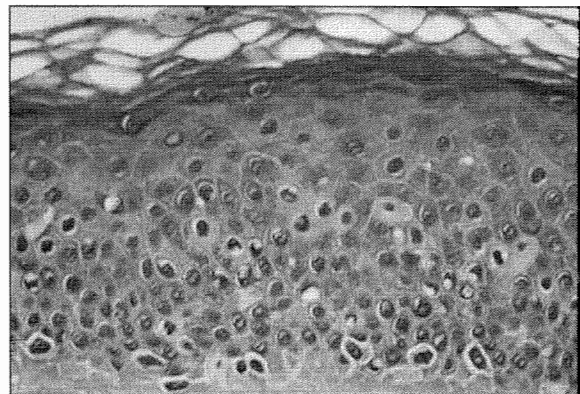


Figure 1. Characteristic lentiginous pattern of severely atypical melanocytes in lentigo maligna before 5% imiquimod therapy.

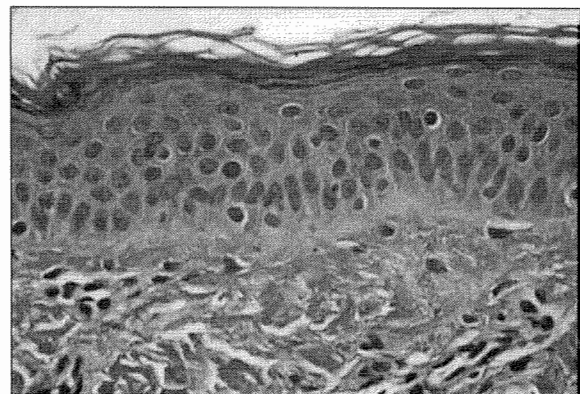


Figure 2. Residual normal-appearing melanocytes, with no evidence of lentigo maligna, after 3 months of 5% imiquimod therapy.