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 animals[3] 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 B_4 (LTB_4) in the pathogenesis of acne has recently been described; administration of a novel LTB_4 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 LTB_4 inhibition, are well known.[1] Arachidonic acid, the major dietary omega-6 fatty acid, is a precursor to the manufacture of LTB_4,[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 nonwesternized 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)

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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 proinflammatory eicosanoids. This hypothesis is certainly reasonable given recent evidence showing that an LTB_4 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 populations[2] 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 al[5] 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 al[5] 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 report[11] 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)

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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 obtained 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 Pharmaceticals, 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]

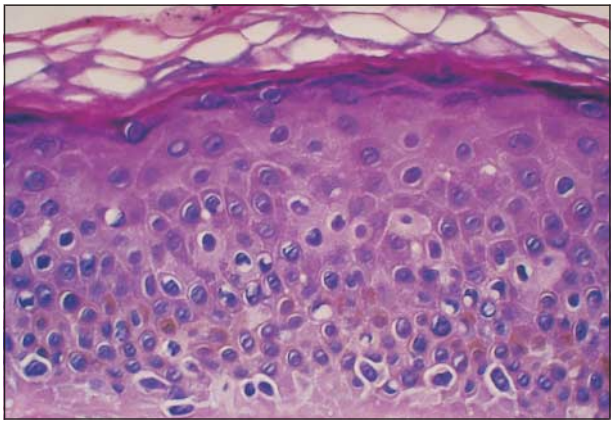

Figure 1. Characteristic lentiginous pattern of severely atypical melanocytes in lentigo maligna before 5% imiquimod therapy.

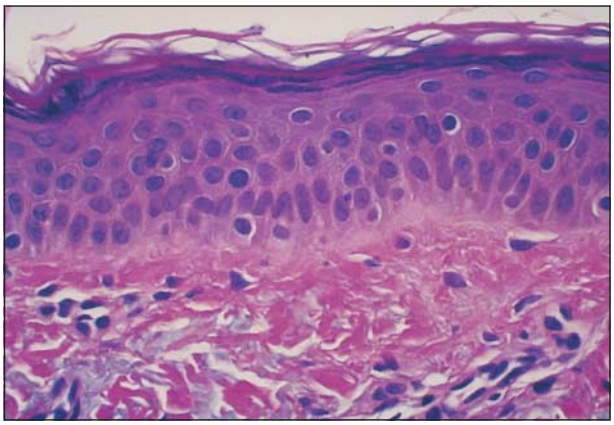

Figure 2. Residual normal-appearing melanocytes, with no evidence of lentigo maligna, after 3 months of 5% imiquimod therapy.