

EXHIBIT “C”

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Sorbic acid-induced erythema and edema

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Sorbic acid concentrations as low as 0.1% produced transient erythema with edema and flare after open or closed application to human skin. Multiple areas of the body were tested. Reactions were most intense on the face but also could be produced on the back, forearm, and deltoid areas. Sorbic acid-induced erythema, edema, and flare were not associated with mast cell degranulation. Pretreatment of skin with topical steroids to induce vasoconstriction resulted in a diminished response to sorbic acid. Aspirin blocked the erythematous component, suggesting that prostaglandins are important mediators. Systemic steroids, antihistamines, and hydroxyzine failed to influence sorbic acid-induced erythema and edema. The anti-inflammatory effect of topical steroids was not affected by sorbic acid-induced erythema. (*J AM ACAD DERMATOL* **14**:234-241, 1986.)

Sorbic acid is a frequently used preservative in cosmetic and pharmaceutical creams. Previous observations that sorbic acid can induce erythema, edema, and mild stinging, which can be partially

blocked by antihistamines, have led to the concept that this agent can be responsible for "nonimmunologic urticaria."¹⁻³ Fryklof³ reported erythema and edema in nearly 50% of a panel of twenty subjects who had creams and ointments containing sorbic acid applied to their cheeks. Clemmensen and Hjorth² reported perioral contact urticaria in eighteen of twenty playful children who applied a salad dressing to their faces during an unsupervised lunch period. In further studies they demonstrated a concentration-dependent er-

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ythema to closed patch tests applied to the forearms of ninety-one volunteers, with a 20% reaction rate to 0.1% concentration, a 62% reaction rate to 1% concentration, and a 65% reaction rate to 5% concentration. Pretreatment with antihistamines produced a partial but significant reduction in erythema. Lahti¹ reported edema and/or erythema to closed and open patch tests in which 2.5% sorbic acid was applied to the upper portion of the back of fifty subjects with an atopic background and fifty control volunteers. The reaction rate ranged from 14% to 49%, with open patch tests showing a greater degree of positive reaction than closed tests, although this difference was not statistically significant.

These previous observations suggest (1) that reactions to topically applied sorbic acid consisting of erythema and edema may be common, (2) that differences in the prevalence and intensity of reaction may occur at different body sites, and (3) that the concentration of sorbic acid is an important factor. Although sorbic acid-induced erythema and edema are now viewed as examples of "non-immunologic urticaria," data are insufficient to incriminate mast cell degranulation and the release of histamine as the mechanisms of this reaction. Furthermore, the clinically relevant question of whether the management of inflammatory disorders with corticosteroid preparations that contain sorbic acid as a preservative is compromised by this type of erythema and edema reaction has not been answered.

In this study, we investigated the effect, on different body regions, of various concentrations of sorbic acid used as an ingredient in steroid preparations and other vehicles. We also attempted to determine whether this reaction could adversely effect the anti-inflammatory effect of corticosteroid creams. In addition, we employed electron microscopic study as well as various pharmacologic manipulations in an attempt to determine possible mechanisms for sorbic acid-induced erythema and edema.

MATERIALS AND METHODS

Effect of sorbic acid concentration and body site. Sorbic acid, 0.1 ml of 1%, 0.5%, and 0.1%, in 2-isopropanol and water 1:1 was pipetted into a 1-cm

nonwoven cotton cloth (Webril, Curity) within a recessed aluminum chamber that was fixed to the skin with Scanepor tape for 20 minutes. Ten minutes after removal, skin reactions were graded on a scale of 0 to 4:

- 0 = No reaction
- +1 = Patchy erythema
- +2 = Confluent erythema
- +3 = Erythema and edema
- +4 = Erythema, edema, and flare

The deltoid muscle, the volar aspect of the forearm, and the upper portion of the back were tested in fifteen to seventeen subjects; 1%, 0.5%, 0.1%, and 0.05% concentrations of sorbic acid in ethanol and water were tested on the cheeks and forehead in fifteen of these subjects by applying 10 μ l on an 8-mm area outlined by stopcock grease, after which the site was covered with a plastic disc and tape. Twenty minutes later the dressing was removed and reactions were graded as described above.

In an additional seventeen subjects, 0.1% sorbic acid in ethanol and water, 1% hydrocortisone cream containing 0.1% sorbic acid as a preservative (Hytone), and a 1% hydrocortisone cream containing 0.1% potassium sorbate as a preservative (Fugera) were applied with a cotton applicator to a 1.5-cm² area on the forehead and cheek without occlusion. Each subject was tested for each agent in successive weeks. Twenty minutes later the creams were wiped off the face, and the sites were graded with the scale presented earlier in this section.

Effect of repeated applications of sorbic acid. Four subjects who demonstrated intense (+3 to +4) reactions to 5% sorbic acid in hydrophilic ointment, 0.1% sorbic acid in isopropanol and water (1:1), and 1% hydrocortisone cream containing 0.1% sorbic acid had these agents applied daily to the forehead and cheeks. Each application consisted of 0.1 ml delivered by tuberculin syringe to a 1.5-cm² area of the forehead and cheek. Reactions were graded 20 minutes after application.

Effect of pretreatment of skin with corticosteroid cream. In eight subjects, 0.1 ml of betamethasone valerate was applied to a 20-mm area of the volar aspect of the forearm and covered with an occlusive dressing for 6 hours. All eight subjects demonstrated vasoconstriction. Two hours after removal of the dressing (vasoconstriction unchanged), 0.1 ml of 1%, 0.5%, and 0.1% sorbic acid in isopropanol and water 1:1 was applied to sites of vasoconstriction for 20 minutes under an occlusive dressing. Ten minutes after removal of the sorbic acid, sites were graded for erythema and edema.

Table I. Effect of concentration of sorbic acid and body site

Reaction intensity	Concentration			
	1%	0.5%	0.1%	0.05%
Back, upper portion				
+4	13/17*	8/17	2/17	—
+3	4/17	5/17	1/17	—
+2	0/17	3/17	8/17	—
+1	0/17	1/17	6/17	—
0				
Forearm, volar aspect				
+4	6/15	5/15	0/15	—
+3	6/15	5/15	1/15	—
+2	3/15	2/15	3/15	—
+1		2/15	10/15	—
0		1/15	1/15	—
Deltoid muscle				
+4	1/17	1/17	1/17	—
+3	11/17	10/17	4/17	—
+2	4/17	4/17	7/17	—
+1	1/17	2/17	5/17	—
Cheeks				
+4	3/15	2/15	—	—
+3	10/15	8/15	7/15	4/15
+2	—	—	3/15	3/15
+1	2/15	4/15	4/15	7/15
0	—	1/15	1/15	1/15
Forehead				
+4	3/15	—	—	0
+3	9/15	8/15	4/15	5/15
+2	1/15	1/15	2/15	1/15
+1	2/15	5/15	8/15	7/15
0	—	1/15	1/15	2/15

*Positive reactions/number tested.

On the opposite forearm of each subject, the same concentrations of sorbic acid were applied without pretreatment with betamethasone valerate.

Effect of systemic steroids, antihistamines, and nonsteroidal anti-inflammatory agents. Five subjects who demonstrated +3 or +4 reaction to an open application of 5% sorbic acid in hydrophilic ointment to the cheek and antecubital fossa were tested 1 and 4 hours after a single dose of 900 mg of aspirin, 20 mg of prednisone, 25 mg of chlorpheniramine, and 25 mg of hydroxyzine. Each subject was tested with each of these drugs on successive weeks.

Effect of sorbic acid in 1% hydrocortisone in treatment of dermatitic skin. In the following two ways, we tested whether 1% hydrocortisone cream preserved with 0.1% sorbic acid might interfere with the anti-inflammatory effect of hydrocortisone:

1. Ten patients with bilateral moderately inflammatory atopic dermatitis of equal intensity were treated twice daily with 1% Hytone cream (contains sorbic acid) on one forearm and 1% Synacort (no sorbic acid) on the other arm for 2 weeks. Creams were applied daily by a technician, and patients were evaluated, without the examiner's knowledge of treatment application, for signs of erythema, excoriation, and lichenification.

2. A panel of five volunteers had three sites on the volar aspect of the forearm treated with 3% sodium lauryl sulfate under an occlusion dressing for 24 hours. One site was treated twice daily with Hytone cream, another with Synacort, and the third with the vehicle of Hytone cream.

Effect of pretreatment with intradermal lidocaine. On the volar aspect of the forearm of highly reactive individuals, 0.2 ml of 2% lidocaine (Xylo-

Table II. Effect of sorbic acid and potassium sorbate in topical steroid preparations

Reaction intensity	0.1% sorbic acid in ethanol/water	1% hydrocortisone with 0.1% sorbic acid	1% hydrocortisone with 0.1% potassium sorbate
Cheeks			
+4	3/17*	0/17	1/17
+3	12/17	4/17	4/17
+2	2/17	2/17	1/17
+1	—	5/17	5/17
0	—	6/17	6/17
Forehead			
+4	3/17	0/17	0/17
+3	10/17	1/17	0/17
+2	3/17	2/17	2/17
+1	1/17	7/17	5/17
0	0/17	7/17	10/17

*Positive reactions/total number tested.

caine) was injected intradermally at three sites in a circular pattern, with intervals of 1.5 cm between each injection. Fifteen minutes later, 10 μ l of 1.5% and 1% sorbic acid in 2-isopropanol and water was pipetted onto an 8-mm area contained by stopcock grease in the area surrounded by the injections. Test materials were then covered with a plastic disc for 20 minutes and graded.

Effect of capsaicin. The flare component of the wheal-and-flare reaction caused by histamine can be obliterated by pretreating skin with capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), the active agent in hot peppers.⁴ A 0.1% solution of capsaicin, 0.3 ml, was applied on a nonwoven cotton cloth (Webril, Curity) and occluded under a 20-mm Duhring chamber fixed to the skin with Scanpore tape. Four applications were made every 2 hours to two sites on the volar aspect of each forearm. The same procedure was repeated once on the following day. By the second day, there was no erythema or pain associated with the application of 0.1% capsaicin. One hour after removal of the occlusive dressing on the second day, one site on each arm was tested with an intradermal injection of 0.002 ml of a 1:10,000 solution of histamine to verify the loss of the flare component of the wheal-and-flare reaction. The other three sites on each arm were tested with topical application of 0.1 ml of a 1.0% solution of sorbic acid applied under a 10-mm Duhring chamber. Control sites consisted of areas of skin that were not exposed to capsaicin and that were tested with 0.1 ml of 1.0% sorbic acid.

Histologic studies. Three-milliliter punch biopsies were obtained from sites showing erythema, edema, and flare in response to 1%, 0.5%, and 0.1% sorbic acid on the upper portion of the back. Specimens were

processed for light microscopy with hematoxylin and eosin stain and Giemsa stain for mast cells. Each specimen was bisected and embedded in plastic for 1- μ m sections and electron microscopy.

RESULTS

Sorbic acid concentration and body site. At all body sites there was a high prevalence of either erythema or edema, with the dose response evident by the intensity of the reaction (Table I; Figs. 1 and 2). A +3 to +4 reaction was present in 100% of the sites on the upper portion of the back treated with 1%, in comparison with 76% of the sites showing a +3 to +4 reaction to 0.5% and 17.6% to 0.1%. On the volar aspect of the forearm, 80% showed a +3 to +4 reaction to 1% sorbic acid, 66% had a +3 to +4 reaction to 0.5%, and 6.6% demonstrated a +3 or +4 reaction with 0.1%. On the deltoid the +3 to +4 reaction rate was 70% for 1%, 65% for 0.5%, and 29.3% for 0.1%. On the face a +3 to +4 reaction developed in 86% on the cheeks and in 80% on the forehead with 1% sorbic acid; 66% on the cheeks and 53% on the forehead demonstrated a +3 or +4 to 0.05%, whereas 46.6% and 26.6% reacted with that intensity on the cheeks and forehead to 0.1%, and only 26.6% and 33.3% reacted with an intensity of +3 to +4 on the cheeks and forehead to 0.05%. On the face there was a significantly higher +3 to +4 reaction rate to 0.1% sorbic acid than was found on other body sites (chi square, $p < 0.05$). No significant differences in either the

Table III. Pretreatment of skin with betamethasone valerate

Subject No.	0.1% sorbic acid		0.5% sorbic acid		1% sorbic acid	
	Treated*	Not treated†	Treated	Not treated	Treated	Not treated
1	0	+1	+1	+3	+2	+3
2	0	+2	0	+3	+3	+3
3	—	+1	0	+1	+1	+1
4	+1	+2	+2	+3	+2	+3
5	0	+3	+2	+2	+4	+4
6	0	+1	+1	+2	+1	+2
7	0	+2	+1	+2	+2	+2
8	0	+2	+2	+2	+2	+2

*Site treated with 0.1% betamethasone valerate.

†Control, untreated site.

Table IV. Effect of systemic antihistamines, aspirin, and prednisone

Pretreatment reaction	Chlorpheniramine*		Hydroxyzine†		Aspirin‡		Prednisone§	
	1 hr	4 hr	1 hr	4 hr	1 hr	4 hr	1 hr	4 hr
Checks								
+3	+2	+3	+3	+3	Edema with blanching		+3	+2
+3	+2	+2	+3	+3	Edema with blanching		+3	+3
+3	+3	+3	+3	+4	Edema with blanching		+3	+3
+3	+3	+2	+3	+3	Edema with blanching		+3	+3
+4	+4	+4	+4	+4	Edema with blanching		+4	+4
Antecubital fossae								
+3	+2	+3	+3	+3	Edema with blanching		+3	+1
+3	+2	+2	+2	+3	Edema with blanching		+1	+1
+3	+3	+3	+3	+3	Edema with blanching		+1	+1
+4	+4	+4	+4	+4	Edema with blanching		+4	+1

*25 mg chlorpheniramine.

†25 mg hydroxyzine.

‡900 mg.

§20 mg.

rate or intensity of the reaction rate were found for the higher concentrations.

Reaction to sorbic acid in topical steroid creams. The reaction rate to 0.1% sorbic acid in ethanol and water was high, with a +3 to +4 reaction demonstrated on the cheeks in 88% and on the forehead in 76%. The 1% hydrocortisone preparation containing 0.1% sorbic acid showed a 23.5% +3 reaction rate on the cheeks and a 5.8% +3 reaction rate on the forehead, but there were no +4 reactions at either site. The 1% hydrocortisone containing 0.1% potassium sorbate resulted in a 23.5% +3 and a 5.8% +4 reaction rate on the cheeks and no +3 or +4 reaction on the forehead. The intensity of the reaction rate was sig-

nificantly less in topical steroid preparations than was seen in the isopropanol-water vehicle (chi square, $p < 0.05$) (Table II).

Repeated application of sorbic acid. All four subjects demonstrated a daily +3 or +4 reaction to 0.1% and 5% sorbic acid in hydrophilic ointment. The sites treated with 1% hydrocortisone with 0.1% sorbic acid had diminished reactions by day 3 in two of the four subjects (+1 reactions), and by day 5, all four subjects showed only a +1 reaction to the hydrocortisone preparation. A similar diminution in the intensity of erythema was seen in subjects treated daily with 0.1% sorbic acid in ethanol and water but not in those treated with 5% sorbic acid in hydrophilic ointment.

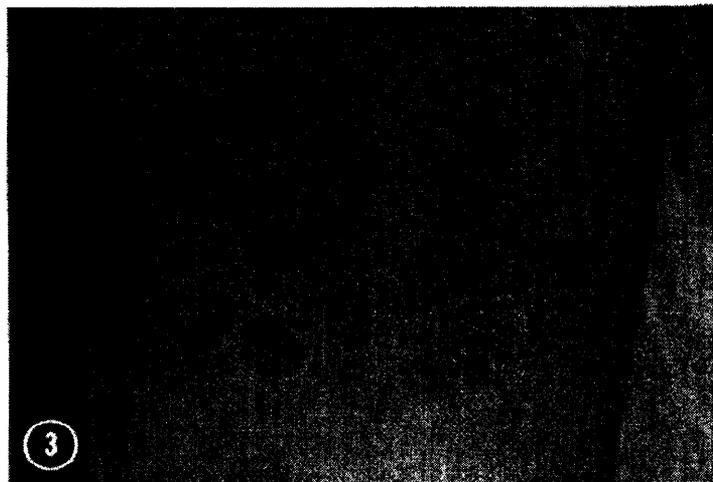
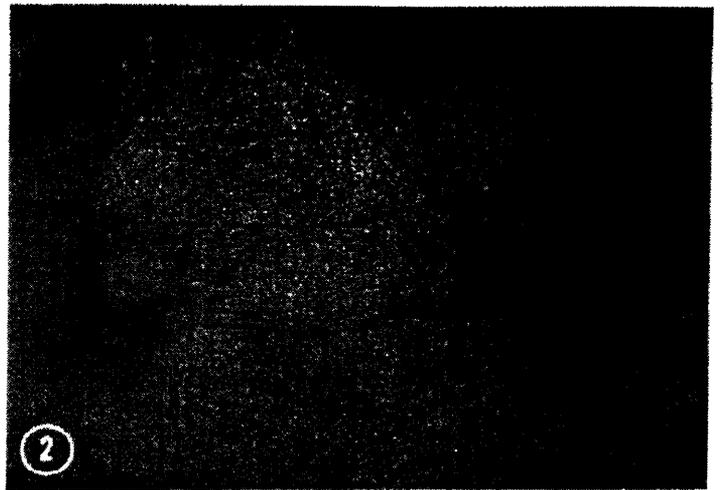
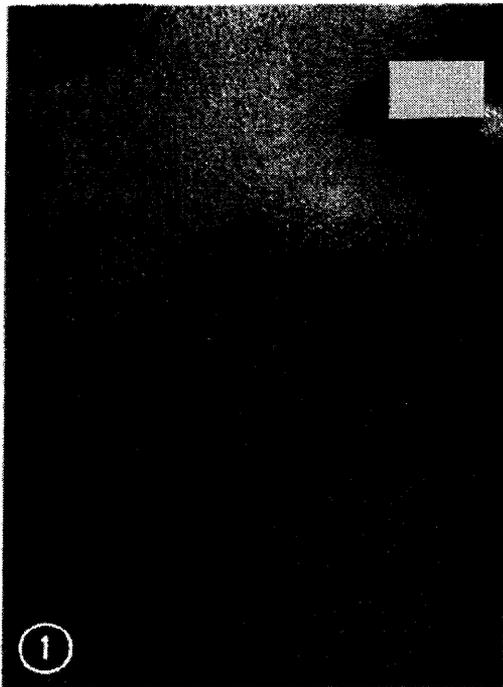


Fig. 1. Erythema with slight edema following 20 minutes of a closed patch test with 0.1% sorbic acid in a patient with rosacea.

Fig. 2. Erythema with pronounced edema and flare after 20 minutes of a closed patch test with 0.1% sorbic acid.

Fig. 3. Erythema and edema without a flare at sites injected with lidocaine (*right*). Control sites (*left*) show erythema, edema, and flare.

Pretreatment of skin with betamethasone valerate. After pretreatment with betamethasone valerate, only one subject showed a +1 reaction to 0.1% sorbic acid, whereas control sites showed reactions in all subjects (Table III). There was a

similar but less pronounced trend for suppression of reactions to 0.5% sorbic acid and far less diminution of reaction to 1% sorbic acid (Table III).

Effect of aspirin, prednisone, and antihistamine. Systemic steroid in the form of 20 mg of

Table V. Effect of intradermal lidocaine on sorbic acid reaction

Subject No.	Lidocaine		Control	
	1% sorbic acid	1.5% sorbic acid	1% sorbic acid	1.5% sorbic acid
1	+2	+2	+4	+4
2	+2	+2	+4	+4
3	+1	0	+2	+2
4	+3	+3	+4	+4

prednisone, 25 mg of chlorpheniramine, and 25 mg of hydroxyzine had little or no effect (Table IV). Each subject tested with 900 mg of aspirin showed a striking reduction in erythema, with the presence of edema still present as a blanched edema on the face. There was less of a reduction in erythema on the antecubital fossae, and edema was also still present.

Effect of sorbic acid in 1% hydrocortisone in treatment of dermatitic skin. Moderately inflamed atopic dermatitis showed improvement with a decrease in erythema, lichenification, and excoriations, along with subjective improvement of less pruritus after 2 weeks of therapy, but no subject completely cleared. No difference in signs or symptoms was seen between the two hydrocortisone preparations.

In the experimentally induced inflammation, sites treated with the two hydrocortisone preparations completely resolved in 5 days, whereas sites treated with the vehicle improved but had not completely cleared.

Effect of intradermal lidocaine. Intradermal injection of lidocaine blocked the flare and diminished the edema but did not influence erythema (Fig. 3; Table V).

Effect of capsaicin. After the flare component of the wheal-and-flare reaction was obliterated by repeated application of capsaicin, sorbic acid application no longer induced a flare, and there was less edema.

Histologic studies. No evidence of mast cell degranulation was found in sites with erythema, edema, and flare. Only an occasional cell with partial degranulation was observed.

DISCUSSION

In this study, we have demonstrated that sorbic acid will commonly induce transient localized er-

ythema with edema and flare. These reactions were dose dependent with respect to intensity, but all concentrations tested, including 0.1%, the concentration usually employed as a preservative, induced at least erythema. The face was the site of the most intense reaction at the 0.1% concentration. However, the upper portion of the back was the site where the highest percentage of intense reactions (+3, +4) occurred. These regional differences could reflect differences in penetration of sorbic acid at various regions of the body, including the dense neurovascular structures of facial skin.

Since sorbic acid is found in several topical steroid preparations, we were particularly interested in the effects that sorbic acid might have on the anti-inflammatory effects of corticosteroids and whether the vasoconstrictor and other effects of these agents could mute sorbic acid-induced reactions. We found that hydrocortisone containing 0.1% sorbic acid resulted in less intense erythema and edema than that containing 0.1% sorbic acid in an ethanol-and-water vehicle. This difference could reflect either a suppression effect of hydrocortisone in sorbic acid-induced erythema or differences in the bioavailability of sorbic acid in different vehicles. Pretreatment with a moderately potent steroid such as betamethasone valerate significantly suppressed sorbic acid erythema, suggesting that the vasoconstriction or other effects of steroids can suppress this reaction. More importantly, we could not find any adverse aspects of the anti-inflammatory effects of 1% hydrocortisone with 0.1% sorbic acid as a preservative in either atopic dermatitis or experimentally induced dermatitis.

The quality of sorbic acid reactions varies from erythema alone to erythema with edema and flare. The mechanism of this reaction does not seem to

involve mast cell degranulation, since we were unable to find evidence of anything more than an occasional partially degranulated mast cell. The ability of aspirin to substantially interfere with the erythema argues for prostaglandins as possible mediators. The finding that aspirin blocked the erythematous component but did not influence the edema suggests that other mediators may be involved. We were unable to block sorbic acid-induced erythema and edema with systemic antihistamines, hydroxyzine, or corticosteroids. It is possible that higher doses of these agents may have affected this reaction. Our failure to block sorbic acid-induced erythema and edema with antihistamines differs from the results of Clemmensen and Hjorth,² who found a partial suppression. They used a topically applied antihistamine, which may account for the difference in results.

These studies suggest that sorbic acid penetrates skin and induces prostaglandin formation, which causes vasodilatation. The fact that lidocaine and capsaicin block the flare component suggests that this aspect is similar to the flare seen with histamine in which antidromic neural transmission is followed by release of substance P, which causes further vasodilatation.⁵ Substance P release also can result in minor mast cell discharge,⁶ which would account for our observation of occasional partial degranulating mast cells.

The results of this study and those of other investigators¹⁻³ indicate that sorbic acid at concentrations used to preserve pharmaceutical and cosmetic preparations can induce erythema and edema in a high percentage of individuals. The possibility of sorbic acid-induced erythema should be considered in patients who describe erythema following topical applications of steroids or after the use of cosmetics. This reaction may occur more frequently or more dramatically in patients with rosacea who have vasomotor lability and who flush excessively (Fig. 1).

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ABSTRACTS

Monthly intravenous cyclophosphamide in the treatment of severe systemic lupus erythematosus

Sessoms SL, Kovarsky J: *Clin Exp Rheumatol* 2:247-251, 1984

Attempting to achieve reductions in the steroid requirement for the selected patients, these physicians explore intermittent use of a nitrogen mustard drug. They report significant toxicity in some patients, but some useful results.

P. C. Anderson, M.D.

A new nail dysplasia syndrome with onychonychia and absence and/or hypoplasia of distal phalanges

Cooks RG, Hertz M, Katznelson MB, et al: *Clin Genet* 27:85-91, 1985

This is a familial (autosomal dominant) nail dystrophy with hypoplasias and aplasias of fingers and other bony anomalies.

This general group of limb dysplasias has been described before, but never with enough clarity or detail.

P. C. Anderson, M.D.

Phenylalanine and UVA light for the treatment of vitiligo

Cormane RH, Siddiqui AH, Westerhof W, et al: *Arch Dermatol Res* 277:126-130, 1985

Needing further skeptical attention is this claim that phenylalanine, 3 to 4 gm orally each day with ultraviolet A (UVA) therapy, can correct vitiligo. Termed Phe-UVA, the new process comes from the University of Amsterdam and Dr. Cormane.

P. C. Anderson, M.D.