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CORRECTION OF THE CUTANEOUS MANIFESTATIONS OF ESSENTIAL FATTY ACID DEFICIENCY IN MAN BY APPLICATION OF SUNFLOWER-SEED OIL TO THE SKIN

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In three patients, previously shown to be essential fatty acid deficient as a result of chronic malabsorption, by virtue of their characteristically abnormal serum lipids, we have further identified cutaneous manifestations of the syndrome, including abnormally low levels of linoleic acid and the presence of 5,8,11-eicosatrienoic acid in their epidermal lecithin, and, in two patients, a scaly dermatitis.

After cutaneous application of sunflower-seed oil, which is rich in linoleic acid, to their right forearms for 2 weeks, the level of linoleic acid in their epidermal lecithin was markedly increased, the rate of transepidermal water loss was significantly lowered, and the scaly lesions disappeared. No such changes were seen in their left forearms after cutaneous application of olive oil, rich in oleic acid. Control patients who were not malabsorbers and were not deficient in essential fatty acids showed none of these changes after cutaneous application of sunflower-seed oil.

The condition of essential fatty acid (EFA) deficiency was first described in 1929 by Burr and Burr [1] for rats maintained on diets lacking in essential fatty acids, and was characterized by low weight gain and skin abnormalities. Since that time many reports have appeared which fully characterize this condition (for reviews, see Alfin-Slater and Aftergood [2], Holman [3]. EFA deficiency is also known in humans: Holt et al [4] and Hansen et al [5] maintained infants on low fat diets and similarly observed low weight gains and dermatologic disturbances (areas of raw eczema or dry leathery desquamation). In certain disease states, EFA deficiency has been reported: in infants suffering from chylous ascites and maintained on low fat diets [6] and, later, Warwick et al [7] described accompanying skin lesions.

More recently EFA deficiency has been shown to occur in patients suffering from fat malabsorption as a result of massive intestinal resection and maintained by intravenous feeding. Varco et al [8], Collins et al [9], Caldwell et al [10], Paulsrud et al [11], and Shimoyama et al [12] have separately studied such cases and described abnormally low levels of linoleic acid and arachidonic acid in the serum, together with the presence of 5,8,11-eicosatrienoic acid (C20:3ω9), which is diagnostic for the EFA-deficiency syndrome [13]. In some of these instances skin abnormalities have been reported.

EFA deficiency experimentally produced in animals may be reversed by reintroducing essential fatty acids to their diet, when full return to normal weight gain and skin condition is observed. With humans, particularly as a result of small bowel resection, however, this approach may not be successful due to the patients' inability to absorb dietary fat. Collins et al [9] have shown that parenteral administration of linoleic acid (as an emulsion of soybean lecithin) partially restores the abnormal serum lipids, and recently one of us has described how intravenous infusion of Intralipid successfully treats the deficiency [14].

The cutaneous manifestations of EFA deficiency in rats have been reversed by the cutaneous application of linoleic acid in various forms [15,16] and this mode of treatment has been utilized in this paper for 3 patients exhibiting EFA deficiency as a result of chronic fat malabsorption. In particular, we have examined the effect of treatment with sunflower-seed oil (a source rich in linoleic acid triglyceride) upon some portions of the syndrome: cutaneous lipid levels, the rate of transepidermal water loss (TEWL), and the appearance of the skin. A recent publication describes the effect of this treatment regime upon serum fatty acids [17].

MATERIALS AND METHODS

Patients

Full details of the 3 EFA-deficient patients have been given elsewhere [12,17]. None had more than 36 inches of small intestine remaining after resection, and all were

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managed on low fat diets to control their diarrhea. What little fat their diets contained was rich in linoleic acid (polyene/saturate = 2.1). The only clinical evidence of EFA deficiency was a dry, scaly eczema, particularly upon the forearms in 2 of the patients (W.D. and A.P.).

Control patients (4 males, 3 females) ranging in age from 48 to 77 years (mean, 59 years) were chosen from patients at the Harpurbury Hospital, Radlett, Herts. These patients, who suffered from various mental diseases, were otherwise healthy and all ate a normal diet.

Cutaneous treatment with vegetable oils

About 250 mg of the oils were applied to the flexor surface of the forearms (sunflower-seed oil to the right arm and olive oil to the left arm) and then gently rubbed in over the entire forearm. This was repeated daily for the duration of the study. Sunflower-seed oil was obtained from Alfonal Ltd., Byfleet, Surrey, and olive oil from the Boots Co. Ltd., Nottingham. The fatty acid compositions of the oils are given in Table I.

Sampling of Skin Surface Lipids

Skin surface lipids were extracted by rubbing the areas with swabs soaked in ethanol:ether (1:1 v/v) immediately after each TEWL measurement. This procedure was derived from that of Nicolaides, Hwei, and Rice [18], who found that hexane alone removed nonpolar skin surface lipids. We found that by using the mixture of the more polar solvents ethanol and ether, a proportion of the epidermal phospholipids was also removed with the surface film. Strips of surgical gauze 9 × 1½ inches were tightly rolled into swabs, then repeatedly extracted in ether:ethanol (1:1, v/v) for 4 hr. Swabs were kept individually in tightly stoppered vials containing ether: ethanol until required. The forearm was rubbed several times with a solvent-soaked swab held with a pair of forceps. The swabs were kept at 5°C in individual vials containing the solvent until required for analysis.

Liquid Extraction and Analysis

The swabs were repeatedly extracted with ether: ethanol (1:1, v/v), the extracts combined, evaporated to dryness, and the lipids dissolved in diethyl ether prior to separation by thin-layer chromatography.

Phospholipids of skin lipids were separated by thin-layer chromatography in Silica Gel H (Merck A.G., Darmstadt) using the solvent system: chloroform: methanol:glacial acetic acid:water (85:15:10:3.6), by vol) and the bands visualized under ultraviolet light after spraying with 0.1% dichlorofluorescein in ethanol. Phosphatidyl choline was identified by comparison with a pure standard run on the same plate. The area of the plates containing this lipid was then scraped directly into a tube and transmethylated by refluxing for 90 min with methanol:benzene:conc sulphuric acid (150:75:7.5, by vol). The remaining bands (triglycerides, sterol esters, free fatty acids), including the neutral lipids running at the solvent front, were combined and also transmethylated. The methyl esters were analyzed on a Pye 104 dual-column chromatograph using 108-inch glass columns ⅛ inch i.d., containing 10% FFAP (free fatty acid phase) on 100–200 mesh Gas Chrom Q (Applied Science Labs. Inc., State College, Pennsylvania, USA). The relative proportions of each methyl ester were calculated from retention time and peak height data.

TABLE I. *Fatty acid composition of sunflower-seed oil and olive oil*

Fatty Acid		% Composition	
		Sunflower-seed oil	Olive oil
Palmitate	16:0	9.3	14.5
Palmitoleate	16:1	0.2	1.0
Stearate	18:0	3.7	3.7
Oleate	18:1	24.3	76.8
Linoleate	18:2	61.5	4.0
Linolenate	18:3	1.0	0.0

Measurement of Transepidermal Water Loss

Transepidermal water loss determinations were made on each patient before the application of oil and then at intervals during and at the end of the 2-week period. The measurements on each patient were performed under similar conditions throughout the treatments inasmuch as they were either taken at Hammersmith Hospital (A.P.), the patient's home (W.D.), or Harpurbury Hospital (B.W. and the controls).

The method of measuring transepidermal water loss in vivo utilized a Meeco Electrolytic Water Analyser Model W, Warrington, Pennsylvania, as described by Thiele and Schutter [19] and Spruit and Malten [20]. The readings were taken on the flexor forearm at a midpoint between the wrist and the elbow. In all cases the readings were made with the measuring cup at the skin temperature of 31°C ± 1°C and an ambient temperature of 18°C to 20°C. Ambient relative humidities were not recorded.

RESULTS

The Effect of Cutaneous Application of Sunflower-Seed Oil and Olive Oil upon the Cutaneous Lipids

The material removed by swabbing the skin surface with ether:ethanol (1:1 v/v) was a complex mixture of lipids. These were derived from sebaceous gland secretions (mainly squalene, free fatty acids, triglycerides, sterol esters, and wax esters [18]), lipids derived from the epidermis as by-products of the keratinization process, structural phospholipids actually extracted from underlying epidermal membranes by the action of the polar solvent mixture, and remnants of the cutaneously applied vegetable oils (triglycerides, and products of their hydrolysis on the skin surface). When the total fatty acids were examined by gas–liquid chromatography a very confusing picture was seen. In the case of samples from skin receiving sunflower-seed oil, linoleic acid predominated; for olive oil application, oleic acid predominated in the fatty acid compositions. Thus, to obtain more meaningful data, epidermal lecithin was separated from the mixtures by thin-layer chromatography and then studied by gas–liquid chromatography. Table II shows the resultant fatty acid patterns. In all 3 EFA-deficient patients prior to treatment with the oils, the epidermal lecithin contained less linoleic acid than the controls, but arachidonic acid (20:4) levels were similar in both deficient and control patients. The most striking feature, however, was the presence of 5,8,11-eicosatrienoic acid (20:3ω9) in the lecithin of the deficient

TABLE II. *Fatty acid composition (%) of epidermal lecithin before and after cutaneous application of vegetable oils*

Fatty acid	Before application of oil			
	WD	BW	AP	CON
16:0	31.0	36.7	26.8	19.2 ± 2.0
16:1	5.7	5.8	4.8	10.1 ± 4.2
18:0	13.2	10.6	10.0	9.6 ± 6.2
18:1	18.3	6.7	28.1	18.7 ± 5.1
18:2	1.1	4.7	5.8	12.4 ± 4.4
18:3	tr	tr	0.5	1.3 ± 0.6
20:2	tr	tr	0.7	8.0 ± 3.2
20:3ω9	4.7	4.9	2.3	0
20:3ω6	0	0	0	tr
20:4	tr	1.6	1.4	tr
Branched[a]	9.6	10.3	6.0	11.2 ± 3.9
Odd number[b]	3.4	3.0	3.1	2.0 ± 0.5
Others	13.0	15.7	10.5	7.5 ± 3.1

Fatty acid	Sunflower-seed oil on right forearm										
	4 days			8 days				15 days			
	WD	BW	AP CON	WD	BW	AP	CON	WD	BW	AP	CON
16:0	12.8	17.1	Not determined	13.2	15.4	14.7	20.2 ± 8.0	12.5	18.8	17.5	19.9 ± 3.6
16:1	1.6	7.3		2.1	1.9	2.0	3.9 ± 2.0	1.2	1.6	6.7	3.1 ± 1.9
18:0	7.2	8.2		8.1	8.7	7.4	11.4 ± 9.4	5.3	9.3	8.5	11.2 ± 2.1
18:1	30.1	17.5		23.1	24.0	32.7	12.7 ± 3.5	26.6	33.3	17.0	15.6 ± 4.8
18:2	29.5	12.6		19.9	17.3	6.2	6.6 ± 1.5	14.3	11.7	11.2	9.0 ± 2.8
18:3	tr	0		0	tr	tr	2.4 ± 1.4	tr	tr	0.7	1.5 ± 0.7
20:2	tr	tr		0	tr	tr	10.2 ± 4.5	tr	tr	tr	0
20:3ω9	2.9	5.4		2.0	2.9	5.4	0	4.0	3.6	8.9	0
20:3ω6	0	0		0	0	0	0.3 ± 0.1	0	0	0	0
20:4	tr	2.4		0.7	tr	2.1	4.8 ± 3.3	tr	2.1	1.9	3.5 ± 1.3
Branched[a]	4.4	9.0		18.7	17.8	9.4	16.4 ± 3.1	13.5	5.8	10.7	15.3 ± 4.9
Odd number[b]	1.2	3.3		1.8	tr	1.7	3.0 ± 2.0	3.3	1.5	3.5	1.7 ± 0.5
Others	10.3	17.2		10.4	12.0	18.4	8.1 ± 3.1	19.3	12.3	13.4	14.9 ± 3.9

Fatty acid	Olive oil on left forearm										
	4 days			8 days				15 days			
	WD	BW	AP CON	WD	BW	AP	CON	WD	BW	AP	CON
16:0	17.9	14.0	Not determined	22.9	20.2	12.3	19.3 ± 5.8	14.9	22.3	15.8	21.2 ± 7.2
16:1	3.1	3.3		8.0	3.3	1.8	3.7 ± 1.5	1.2	1.7	2.8	3.8 ± 3.2
18:0	7.7	7.4		8.2	8.4	5.3	12.7 ± 11.4	5.6	7.9	7.2	11.7 ± 1.8
18:1	24.6	35.1		24.4	25.9	47.5	17.4 ± 6.5	50.8	38.7	28.1	20.4 ± 8.9
18:2	5.7	5.0		2.1	2.8	9.7	6.6 ± 2.3	8.4	4.7	5.7	5.3 ± 1.3
18:3	tr	0.7		0	tr	0	2.0 ± 0.3	tr	tr	1.3	1.8 ± 0.2
20:2	tr	tr		tr	tr	tr	9.5 ± 2.1	tr	tr	tr	8.5 ± 3.9
20:3ω9	9.5	7.2		5.9	3.9	4.7	0	3.8	3.0	7.8	0
20:3ω6	0	0		0	0	1.3	0.2 ± 0.1	0	0	0	0
20:4	tr	1.5		tr	tr	2.8	4.8 ± 2.7	tr	1.1	2.0	2.0 ± 0.8
Branched[a]	18.0	15.6		18.8	23.7	7.4	13.7 ± 4.7	4.4	5.9	16.5	15.1 ± 5.5
Odd number[b]	2.3	2.9		2.1	0.8	1.4	3.2 ± 1.9	0.7	2.3	3.0	2.0 ± 2.0
Others	11.2	7.3		7.6	11.0	5.8	6.9 ± 2.9	10.2	12.4	9.8	8.5 ± 1.9

[a] Containing iso-branched C16:0, C18:0, and C20:0, and anteiso-branched C15:0 and C17:0

[b] Containing C15:0 and C17:0 acids

Control values before treatment with vegetable oils represent mean of left and right forearm lecithin (CON) tr = trace, less than 0.1% of total

patients only. This acid is diagnostic for EFA deficiency [13] and was completely absent from the controls. Although palmitoleic acid (16:1) is known to be elevated in EFA-deficient rats [3], this was not the case with these patients. The effect of treating the right forearm with sunflower-seed oil was to rapidly introduce (within 4 days) more linoleic acid into the epidermal lecithin: this trend continued for the duration of the study. Control patients did not show these increases, however. Despite the restoration of linoleate in the lecithin of these patients there was no reduction of 20:3ω9, indicating the much longer turnover of this fatty acid in epidermal lecithin.

In the left arms of the patients treated with olive oil, there were immediate and sustained increases in oleic acid esterified to epidermal lecithin, but here no changes in linoleate were seen.

These data show that when vegetable oils were applied to the skin of EFA-deficient patients there was penetration and incorporation of their constituent fatty acids, into structural lipid of the epidermis. As the oils were triglyceride forms of the fatty acids, it is clear that they were actually metabolized by the skin (hydrolytic cleavage followed by acylation of lecithin). This is of particular significance to the treatment of the EFA-deficiency syndrome in that the abnormally low levels of cutaneous linoleate may be rapidly restored by cutaneous application.

The Effect of Cutaneous Application of Sunflower-Seed Oil and Olive Oil on the Rate of Transepidermal Water Loss

The rate of transepidermal water loss was measured on the forearms of the EFA-deficient patients before and during application of vegetable oils. Control patients, who received vegetable oils for the same treatment period, were also studied. The results are shown for the left arms (receiving olive oil) in Figure 1*A* and for the right arms (receiving sunflower-seed oil) in Figure 1*B*. In these Figures the hatched area indicates the observed upper and lower limits of the rate of transepidermal water loss exhibited by the control patients, with the dotted line representing the mean value of 7 individual determinations. The rate of transepidermal water loss for the 3 EFA-deficient patients was not abnormally high prior to treatment, unlike EFA-deficient rats [21]. When olive oil was applied to their left forearms, no significant reductions in transepidermal water loss were seen; however, in the right forearms of all 3 deficient patients, the effect of treatment with sunflower-seed oil was to reduce the initial levels markedly, by more than 50% for A.P. and W.D. and by 33% for B.W. This finding supports a recent observation (unpublished data) that cutaneous application of sunflower-seed oil (but not olive oil) reduces to normal the hitherto very high rate of transepidermal water loss in EFA-deficient rats.

Appearance of the Skin in EFA-deficient Humans and the Effect of Cutaneously Applied Vegetable Oils

One characteristic of EFA deficiency in rodents is a scaly epidermis, first reported in rats by Burr and Burr [1]. Sinclair [22] referred to the skin condition as a "seborrheic dermatitis" in which epidermal phospholipids containing little EFA formed imperfect membranes resulting in a scaly skin and a permeable barrier, and Wiese [23] has illustrated the dry, scaly, facial skin of infants raised on milk diets low in linoleic acid. Of the 3 EFA-deficient patients described here, W.D. and A.P. had very dry, scaly, "parchment-like" skin on their extensor forearms and on the shins and calves of their legs. No other regions of the body were affected and the hair and nails were normal. No erythema was associated with the scaliness. The skin of patient B.W., however, appeared normal. Figure 2 shows the right forearm of patient A.P. prior to application of sunflower-seed oil. Both W.D. and A.P. responded to cutaneously applied essential fats and within a week the condition of the right arm, receiving sunflower-seed oil, had improved remarkably, whereas the left arm, receiving olive oil still showed scaliness (shown for A.P. in Fig. 3). Both patients commented that the skin on the right arm felt smoother than the left arm.

DISCUSSION

This paper describes the cutaneous manifestations of clinically defined essential fatty acid deficiency in humans, and how restoration of certain parameters to normal may be affected by cutaneous application of essential fatty acids. Hitherto, it has been reported that this syndrome in humans may be reversed by feeding orally [5] or by parenteral alimentation [9,10] with essential fatty acids, although with EFA-deficient rats, restoration by cutaneous application is documented [15,16].

The 3 patients studied were originally designated EFA-deficient by virtue of the low level of linoleic acid and the presence of 5,8,11-eicosatrienoic acid in serum lecithin [12,17]. Basnayake and Sinclair [21] described the abnormal cutaneous fatty acid levels in EFA-deficient rats which were all rapidly corrected after feeding linoleic acid. Here, although the hitherto low levels of linoleic acid in epidermal lecithin were raised following cutaneous application of sunflower-seed oil, that of arachidonic acid, a metabolic product of linoleic acid, was not altered. Indeed, we found the level of arachidonic acid to range from a trace to about 5% of the total fatty acids in the epidermal lecithin of both deficient and normal patients (Table II). This level is less than that reported by Vroman, Nemecek, and Hsia [24] for total human epidermal phospholipid (9%). The presence of 5,8,11-eicosatrienoic acid, which is diagnostic for the deficiency syndrome [13], and never seen in

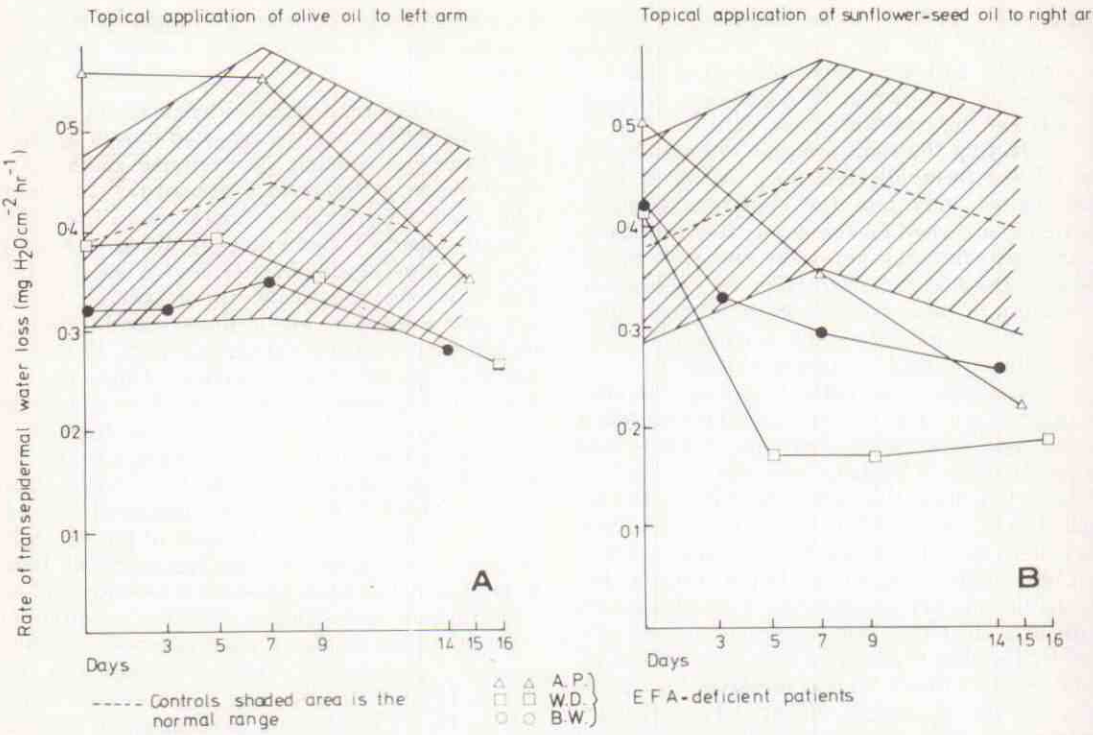


FIG. 1. Effect of topical application upon the transepidermal water loss (TEWL) of human forearm in normal and essential fatty acid (EFA)-deficient patients.

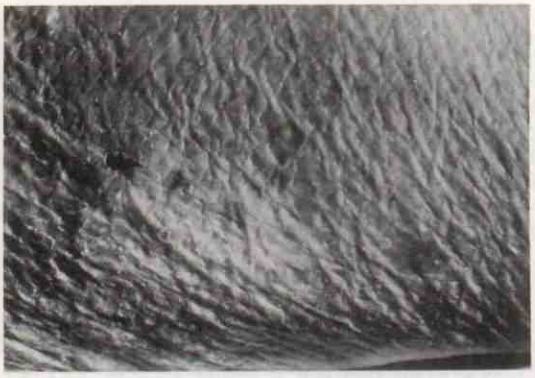


FIG. 2. Essential fatty acid (EFA)-deficient human skin (A.P.).

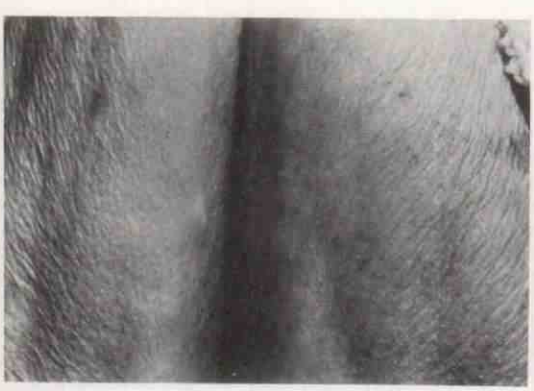
normals, was not altered by cutaneous application of sunflower-seed oil. Basnayake and Sinclair [21] showed abnormal levels of trienoic acids in the skin of EFA-deficient rats to be lowered following feeding of linoleic acid. We have shown elsewhere [17] that the serum lecithin of these 3 patients exhibited marked changes in the levels of linoleic acid, 5,8,11-eicosatrienoic acid, and arachidonic acid following cutaneous treatment with sunflower-seed oil, which were much greater in magnitude than those seen in epidermal lecithin at the site of application (Table II). In the skin of the left arms, which received olive oil, there were no obvious changes in these fatty acids in the epidermal lecithin. This suggested that although the serum lecithin had been corrected by cutaneous application of sunflower-seed oil for 2 weeks, similar changes had not yet been made in skin distal to the treatment site. Our studies on EFA-deficient rats (unpublished data) show that during onset of deficiency the skin becomes depleted of essential fatty acids before the serum, whereas during recovery after feeding essential fat the serum is restored to normal long before the skin. The patients received cutaneously about 2 to 3 mg per kg linoleic acid daily, which is only about 10% of the level generally thought to be the adult human daily requirement. Thus, only by administering much more linoleic acid cutaneously could we have corrected lipid levels in the skin distal to the site of application.

In all 3 deficient patients prior to cutaneous application of sunflower-seed oil, the rates of transepidermal water loss were no different from the values of the control patients, being in the range 0.3 to 0.6 mg H_2O cm^{-2} hr^{-1} (Fig. 1). This is within the range of values quoted by others (reviewed by Idson [25]), although one should not generalize as the value of this parameter is dependent upon conditions of ambient temperature, humidity and air flow, and body site. Spruit and Malten [20], using similar instrumentation, reported the level of transepidermal water loss on the forearms of normal humans to be of the order of 0.5 mg H_2O cm^{-2} hr^{-1}, although we have found the mean value for the flexor forearm, computed from determinations on about 100 adults during recent

years in our laboratory, to be about 0.35 mg H_2O cm^{-2} hr^{-1} (unpublished data). The skin of the EFA-deficient rat is more permeable to water [21] and so our finding that TEWL was not abnormally high in the 3 deficient patients is unclear. Basnayake and Sinclair [21] showed that during onset of EFA deficiency in the rat, altered skin fatty acid levels were observed after only 5 weeks on the deficient diet, whereas TEWL did not begin to rise until after 8 weeks. Thus, one may have animals showing chemical signs of deficiency without abnormal barrier function. The same may apply to the deficient patients.

Cutaneous application of sunflower-seed oil to the deficient patients lowered the rate of TEWL at the site of application below the normal values of the controls. This was not seen with olive oil application to the left arm of the patients, nor with the controls treated with either oil. Table II shows that with the deficient patients only, and then only at the site of application of sunflower-seed oil, was there specific enrichment of the epidermal lecithin with linoleic acid. Thus, one may suggest that epidermal barrier function and cutaneous essential fatty acid levels are related. This is illustrated in Figure 4, where total epidermal lecithin essential fatty acids (i.e., linoleic plus arachidonic acid) are plotted against rate of TEWL, and the points follow a line of regression. Our results would suggest that when there is a greater than normal level of essential fatty acid in epidermal lecithin, there is a more impervious than normal cutaneous barrier, but this could not be substantiated with the controls. A recent paper by Jelencko et al [26] emphasises the importance of linoleic acid in skin—in experimentally burned skin there was an observed reduction in TEWL 12 hr after cutaneous application of ethyl linoleate.

Two of the EFA-deficient patients studied exhibited a mild degree of scaliness on their arms and legs, but this did not appear to be as severe as that illustrated by Wiese [23] for infants raised on milk diets low in linoleic acid. Presumably, deficiency in dietary linoleic acid would be more deleterious to rapidly growing infants than to mature adults.



Sunflower-seed oil Olive oil

FIG. 3. Essential fatty acid (EFA)-deficient human skin following cutaneous application of oils.

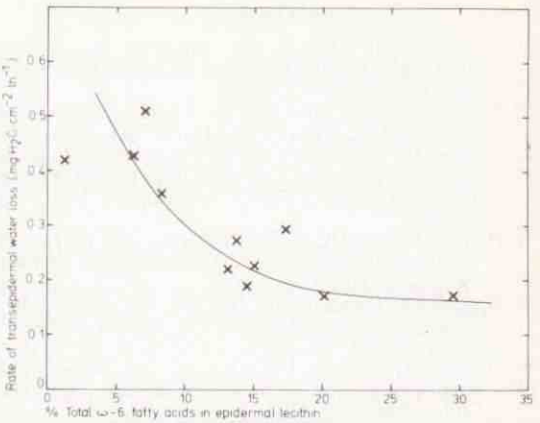


FIG. 4. Relationship of linoleic acid in epidermal lecithin and rate of transepidermal water loss in humans.

Wiese [23] also described microscopic changes occurring in the epidermis of EFA-deficient humans which resembled in some ways those seen in EFA-deficient rats [27] and mice [28], namely, a dense and compacted stratum corneum, hyperplasia, and acanthosis, and often parakeratosis. We obtained a suction blister biopsy from the flexor surface of the forearm of patient A.P. but this showed the epidermis to be normal, and this would confirm that the degree of EFA deficiency of the 3 patients was probably not so extreme as described in infants by Wiese.

From a study of serum fatty acid levels, the EFA-deficiency syndrome as a result of fat malabsorption following intestinal resection [14] was ascribed to these patients, and in this paper we have described some attendant cutaneous abnormalities which are characteristic of the deficiency in animals. In a similar fashion to the correction of EFA deficiency in rats by cutaneous application of oils containing linoleic acid [15], we have shown that the cutaneous route is an important means of introducing essential fatty acids into the body when intestinal absorption is not possible. Also, the applied oil is metabolized by the skin and linoleic acid is incorporated into structural lipid.

Recently, Ziboh and Hsia [29] have suggested a link between EFA deficiency, keratinization, and cutaneously applied prostaglandins, by their demonstration that the scaly skin lesions in deficient rats were cleared by the application of PGE_2. As linoleic acid, by means of its conversion to arachidonic acid (sic) is a precursor of PGE_2 one may postulate that cutaneous application of linoleate in EFA deficiency provides suitable substrate for prostaglandin synthesis. It is known that in the EFA-deficient rat, prostaglandin synthesis is prevented by lack of substrate and not lack of the enzyme [30]. For this to be confirmed as the mechanism by which cutaneously applied linoleic acid exerts its beneficial actions upon skin chemistry and physiology, however, further research will be required.

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