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Psoriasis and Vitamin A

Plasma Transport and Skin Content of Retinol, Dehydroretinol and Carotenoids in Adult Patients Versus Healthy Controls

O. Rollman and A. Vahlquist

Department of Dermatology, University Hospital, S-751 85 Uppsala, Sweden

Summary. The vitamin-A status of 107 patients with psoriasis and 37 healthy controls was investigated. The mean serum level of retinol-binding protein (RBP) was normal in the 79 patients with chronic plaque psoriasis covering 25% or less of the skin surface. In the 28 patients with more extensive plaque lesions or pustular/erythrodermic psoriasis, the mean serum RBP level was significantly lower than in the controls ($P < 0.05$). The cutaneous concentrations of retinol (vitamin A_1), dehydroretinol (vitamin A_2) and carotenoids were measured in extracts of saponified shave-biopsy specimens of uninvolved and involved skin from 33 patients with plaque psoriasis. Their retinol values did not differ significantly from those found in control skin (mean, 252 ng/g), whereas the carotenoid levels in both uninvolved and involved skin were 25%–50% lower. In contrast, the dehydroretinol concentration was higher in the patients' involved skin (mean, 237 ng/g) than in their uninvolved skin (94 ng/g) and healthy control skin (70 ng/g; $P < 0.01$). Although the origin of increased dehydroretinol levels in involved psoriatic skin is unknown, similar increments were observed in control epidermis in which proliferation had been induced by tape stripping. In 7 patients treated with oral etretinate (aromatic retinoid) for 2–3 weeks, the median retinol and dehydroretinol levels in involved skin increased by 107% and 212%, respectively; the vitamin-A concentrations in uninvolved skin did not change significantly. Oral treatment with β-carotene/canthaxanthin raised the median carotenoid levels in uninvolved and involved skin by 170% and 610%, respectively, without significantly affecting the vitamin-A composition.

Offprint requests to: Dr. A. Vahlquist (address see above)

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Introduction

The favourable results of treating psoriasis with oral synthetic retinoids have led us to focus our attention on the vitamin-A status in this hyperproliferative skin disease. A further reason for this interest is that an unusual natural retinoid, dehydroretinol (vitamin A_2), has recently been identified in psoriatic skin [25]. This retinoid, which is also present in small amounts in normal skin, appears to be an epidermal metabolite of retinol (H. Törmä and A. Vahlquist, submitted for publication). Certain carotenoids may also be converted to dehydroretinol [2].

Retinoids are important regulators of epithelial differentiation and proliferation. In experimental animals, both an excess and a deficiency of retinoids have been found to result in epidermal hyperproliferation [5, 9]. Furthermore, in a recent series of experiments on cultivated keratinocytes, it has been established that the phenotypic expression of keratins is modified by vitamin A [4, 6]. Interestingly, the keratin pattern in psoriatic skin lesions is, in some cases, almost indistinguishable from that of normal keratinocytes cultured in a surplus of vitamin A [6, 35]. Since the available data do not support the concept of a structural gene defect being a cause of the abnormal keratin synthesis found in psoriasis [13], alternative explanations, such as the occurrence of abnormal concentrations of gene regulators (e.g. vitamin A), are worth exploring.

Measurements of both natural and synthetic retinoids can be obtained from high-pressure liquid

chromatography (HPLC) analysis of saponified skin extracts [26]; this has revealed several examples of abnormal concentrations of retinol and dehydroretinol [19, 21, 30, 32]. These abnormalities appear to be the result either of aberrant transport of retinol to the skin or of localized alteration in the vitamin-A metabolism. In contrast, the total concentration of carotenoids, some of which are vitamin-A precursors, has not been found to be abnormal in any previously investigated skin disease [21, 32].

Recent studies have emphasized the role played by serum retinol-binding protein (RBP) in the transport and delivery of vitamin A to the skin [24]. In the present study, we examined vitamin-A transport in psoriasis patients and investigated vitamin-A and carotenoid concentrations in uninvolved and involved skin as compared to normal skin. In addition, we studied the effects of oral treatment with etretinate and carotenoids on variables related to vitamin A in psoriatic skin.

Materials and Methods

Patients and Controls

Three groups of patients were investigated:

1. Serum RBP determinations were performed on 107 patients, 97 of which had chronic plaque psoriasis with limited (less than 10%), moderate (10%–25%) or extensive (30%–70%) involvement of the body surface. The other 10 patients had unstable psoriasis with acral pustulosis (4 patients), generalized pustular eruption (3 patients) or erythrodermia (3 patients). One patient with acral pustulosis had active inflammatory joint disease and was receiving systemic methotrexate and corticosteroid therapy. No patient was being treated with oral vitamin A or synthetic retinoids. Topical treatment included emollients, dithranol and corticosteroids. Three patients had received UV therapy. None of the women were using oral contraceptives.

2. The levels of vitamin A and carotenoids in the skin and serum of 33 patients (11 women, 22 men) with chronic plaque psoriasis were studied. Their age ranged from 20 to 75 years (mean, 48 years) and the length of time since the onset of psoriasis ranged between 1 and 50 years (mean, 17 years). None of the patients had received UV therapy for at least 2 months before the study. All topical applications, except for emollients, were withdrawn 2 weeks or more prior to the investigation.

3. Fifteen of the patients in group 2 (7 women, 8 men) were studied before and after 2–3 weeks of treatment with either Tigason (etretinate; 50 mg daily) or Phenoro (β-carotene/canthaxanthin; 50/75 mg daily).

The control group consisted of 37 apparently healthy subjects (mainly medical students and hospital employees), 22 of whom have previously been reported [31].

Informed consent was obtained from all participants, and the study was approved by the Ethical Committee of Uppsala University.

Serum and Skin Sampling

A blood sample (taken with the subject fasting) and a skin biopsy were taken on the same occasion under normal indoor illumination. The serum was collected under reduced light and stored at −20°C until analysed. Superficial shave biopsies ('epidermis') were obtained using a razor blade, as described elsewhere [31]. Histological examination of a few shave biopsies showed that dermis accounted for 20% or less of the sample volume. One biopsy was taken from clinically normal skin on the shoulder or buttock. In the patients, a second shave biopsy was similarly obtained from the periphery of a long-standing, moderately thick and slightly scaling plaque on the back or thigh. The samples were immediately snap-frozen on dry ice in a dark vessel and stored for 1–5 months at −70°C until required.

In 2 healthy male subjects, an area (5 × 15 cm) on the buttock was stripped [17] by 15 consecutive applications of adhesive tape (Athletic tape, Johnson and Johnson). Serial skin biopsies were collected at intervals thereafter.

Serum Analysis

RBP was assayed by radial immunodiffusion, and retinol was assayed by fluorimetry, as previously described [29]. Total carotenoids were measured by spectrophotometry [16] as follows: 0.25 ml serum, 0.25 ml spectrophotographic ethanol (Svensk Sprit, Stockholm) and 0.5 ml hexane (Rathburn Chemicals, Walkerburn, Scotland) were mixed in a glass tube (3 ml). The tubes were vigorously shaken (Voss Instruments, Maldon, England) for 1 min and centrifuged at 1,300 *g* for 2 min. The upper layer was transferred to a microcuvette, and the absorbance value at 450 nm was determined using a Hitachi (Tokyo) model-101 spectrophotometer. The concentration of carotenoids was calculated using an extinction coefficient ($E^{1\%}_{1\,cm}$) of 2,500, assuming that the coefficients for various carotenoids were similar [7]. All serum analyses were performed in duplicate.

Skin Analysis

The skin samples (15–30 mg) were hydrolysed in the presence of internal retinoid standards and subsequently extracted with hexane, as previously described [26]. The concentration of carotenoids was measured by spectrophotometry [31], using the same extinction coefficient as that employed for serum analysis. The levels of retinoids were determined by reverse-phase HPLC, using an aromatic retinol analogue (Ro 12-0586) as the internal standard for the measurement of retinol and dehydroretinol [26], and all-*trans* retinoic acid for the measurement of etretinate [20]. The protein content of the hydrolysed and neutralized sample was assayed by the biuret technique as outlined previously [31].

Statistics

Computerized statistical evaluation was performed by general linear models [22] and correlation analysis. Both sex and age variables were included in the models. The significance levels were assessed at the 1% and 5% levels by Duncan's multiple-range test. The Wilcoxon signed rank test [3] was used for evaluating changes following treatment.

Results

Serum Retinol-Binding Protein

The mean RBP concentrations found in the subgroups of the 107 patients with psoriasis of different types and in the 37 healthy controls are given in Table 1.

Table 1. Serum concentrations (mean ± SD) of retinol-binding protein (RBP) in 107 psoriasis patients and in healthy controls

Diagnosis	Number of subjects	Age (years)	Years since onset of psoriasis	RBP (μg/ml)
Chronic plaque psoriasis				
Limited	44 (26)[a]	41 (22–75)[b]	15 (1–53)[b]	49.4 ± 8.8
Moderate	35 (23)	41 (16–74)	20 (3–54)	48.9 ± 10.2
Extensive	18 (12)	46 (20–73)	23 (1–50)	38.3 ± 5.5*
Pustular or erythrodermic psoriasis[c]	10 (8)	49 (25–77)	21 (2–35)	36.4 ± 11.6*
Healthy controls	37 (16)	38 (21–75)	–	45.7 ± 9.8

* $P < 0.05$ (statistical significance of difference versus healthy controls)
[a] Number of males in parenthesis
[b] Mean and range
[c] The mean RBP values for various categories of patients were: acral pustulosis ($n = 4$), 38.6 μg/ml; generalized pustulosis ($n = 3$), 34.5 μg/ml; erythrodermia ($n = 3$), 34.8 μg/ml

Table 2. Epidermal concentrations (mean ± SD) of retinol, dehydroretinol and carotenoids in 33 psoriasis patients and 37 healthy controls

	Retinol	Dehydroretinol	Carotenoids
	ng/g wet tissue (ng/mg protein)		
Chronic plaque psoriasis			
Uninvolved skin	223 ± 94 (1.56 ± 0.77)	94 ± 51 (0.56 ± 0.25)	1536 ± 1118* (9.08 ± 5.04)
Involved skin[a]	245 ± 120 (1.27 ± 0.76)	237 ± 180** (1.10 ± 0.58)	1474 ± 648** (6.84 ± 2.48)
Healthy controls	252 ± 104 (1.60 ± 0.44)	70 ± 54 (0.39 ± 0.22)	2078 ± 864 (13.5 ± 6.00)

* $P < 0.05$; ** $P < 0.01$ (statistical significance of difference versus healthy controls calculated for wet-weight values) [a] Values from 23 patients

Patients with limited or moderate psoriasis of the plaque type had RBP values that were similar to those of the controls. In subjects with extensive plaque psoriasis and in those with pustular psoriasis or erythrodermia, the mean values were significantly lower than those in the controls. Sex and age had no significant influence on the RBP values in patients and controls.

Skin Concentrations of Retinol, Dehydroretinol and Carotenoids

Thirty-three patients with chronic plaque psoriasis were investigated. The epidermal concentrations of retinol, dehydroretinol and carotenoids found in uninvolved and involved skin are shown in Table 2. The mean retinol values of this group did not differ significantly from the control values. In contrast, the dehydroretinol concentration was markedly elevated in the involved – but not in the uninvolved – psoriatic skin. The carotenoid values in both types of psoriatic skin were lower than those found in healthy control skin. Sex, age and the site of biopsy (shoulder or buttock) did not contribute significantly to the variability of any of the parameters. The statistical outcome was independent of whether wet-weight or protein-related values were used, but the latter values were generally more precise.

Correlations Between Serum and Skin Vitamin-A Variables

The concentrations (ng/mg protein) of retinol and carotenoids in uninvolved skin were related to the serum concentrations of RBP, retinol and carotenoids. As shown in the scatter diagramms of Fig. 1a–c, serum RBP (but not serum retinol) was significantly correlated with epidermal retinol both in patients ($P < 0.05$) and in healthy controls ($P < 0.005$); the range of values was similar in both groups. The carotenoid levels, on the other hand, showed better correlation in the patients ($P = 0.005$) than in the controls ($P > 0.05$), and the range of values differed markedly between the two groups. For example, the mean serum carotenoid level in the patients (50 μg/dl) was significantly lower than that of the controls (108 μg/dl; $P < 0.01$), thus corroborating the reduced epidermal carotenoid levels in the patients.

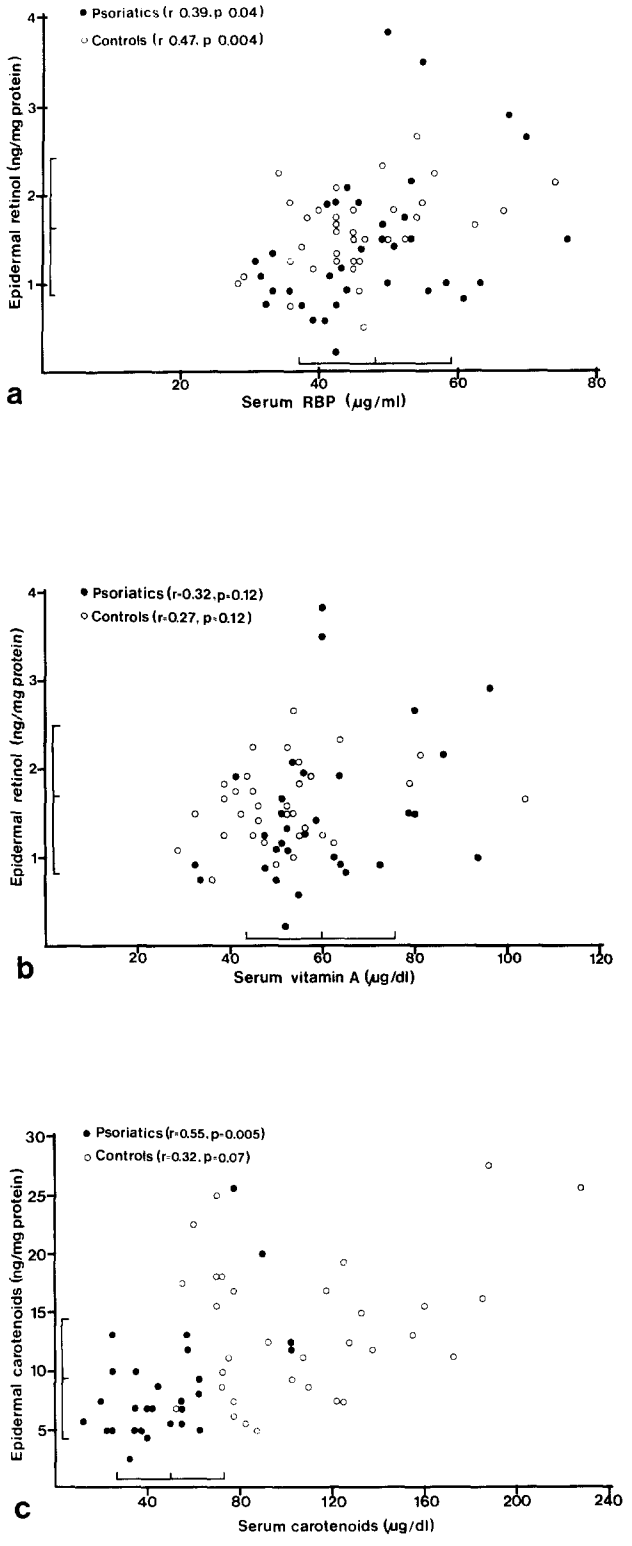

Fig. 1a–c. Scatter plot of vitamin-A and carotenoid variables in the skin and serum of patients with chronic plaque psoriasis (●) and healthy controls (○). **a** Epidermal retinol versus serum RBP; **b** epidermal retinol versus serum retinol; **c** epidermal carotenoids versus serum carotenoids. Pearson's correlation coefficients are given for both groups of subjects. *Bars*, means ± SD for psoriasis patients

Skin Concentrations in Relation to Extension of Plaque Psoriasis

Table 3 shows the epidermal concentrations (ng/mg protein) of retinol, dehydroretinol and carotenoids according to the extent of psoriasis involvement. The mean retinol value was somewhat decreased ($P < 0.05$) in the uninvolved skin of patients with extensive disease, but was otherwise similar to that found in the controls. There was no consistent difference between the retinol concentrations in uninvolved and involved skin of the three groups of patients. The mean dehydroretinol level was markedly increased ($P < 0.01$) in all types of involved skin. The patients' carotenoid levels were usually lower in involved skin as compared to uninvolved skin, but the values were not overtly related to the extent of the disease.

The disproportion between the two retinoids in the uninvolved and involved skin of the different groups of patients is further illustrated in Fig. 2, which shows the ratio of dehydroretinol to retinol. This variable, which is independent of the weight and protein content of the sample, was increased ($P < 0.01$) in involved psoriatic skin, although without any obvious relationship to the extent of the lesions. The ratio was also increased ($P < 0.05$) in the uninvolved skin of patients with extensive disease.

Effects of Tape Stripping of Control Skin

The possibility that high dehydroretinol concentrations are related to epidermal hyperproliferation was investigated under experimental conditions. Serial shave biopsies were obtained from 2 healthy subjects before and 0, 24, 48 and 72 h after tape stripping of glabrous skin. Histological examinations verified that the stratum corneum was removed in toto by the strippings, and that acanthosis and parakeratosis developed after 24–48 h, in accordance with previous findings [17]. As shown in Fig. 3, the dehydroretinol concentration began to increase within 24 h of stripping, reaching a maximum of 60% above the original level at 48 h. The concentrations of retinol and carotenoids remained at about the original level throughout the period of observation (data not shown).

Effects of Oral Retinoid and Carotenoid Treatment

Fifteen patients were treated with either etretinate or β-carotene/canthaxanthin in order to see whether these compounds corrected the abnormal concentrations of endogenous retinoids and carotenoids in psoriatic skin. Table 4 shows the situation after 2–3 weeks of treatment, when the clinical response to both

Table 3. Epidermal concentrations (mean ± SD) of retinol, dehydroretinol and carotenoids in relation to the extent of chronic plaque psoriasis

Area of involvement	Number of patients	Uninvolved skin (ng/mg protein)			Number of patients	Involved skin (ng/mg protein)		
		Retinol	Dehydro-retinol	Carotenoids		Retinol	Dehydro-retinol	Carotenoids
Limited	10	1.75±0.90	0.47±0.14	8.30±2.94*	6	1.00±0.65	0.95±0.18**	7.23±2.67*
Moderate	13	1.75±0.82	0.59±0.22*	10.8 ±6.36	9	1.43±0.92	1.21±0.53**	7.48±2.62*
Extensive	10	1.12±0.34*	0.58±0.33	7.97±5.63*	8	1.37±0.71	1.12±0.83**	5.15±1.46**

* $P < 0.05$; ** $P < 0.01$ (statistical significance of differences versus healthy control values; see Table 2)

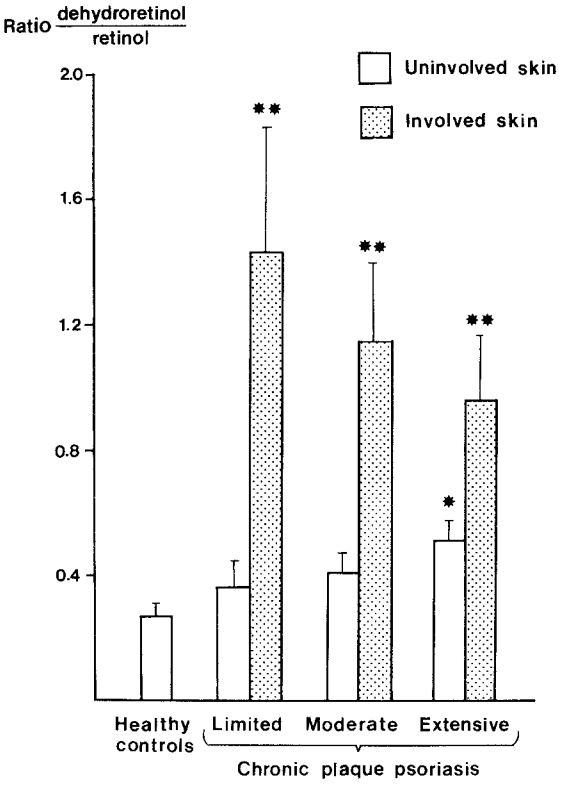

Fig. 2. The ratio (mean + SEM) of dehydroretinol to retinol in the skin of patients with chronic plaque psoriasis. Statistical significance of difference versus controls: * $P < 0.05$; ** $P < 0.01$

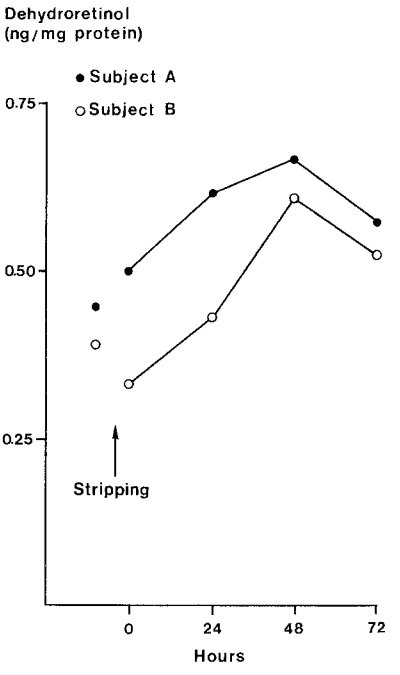

Fig. 3. The effect of tape stripping on the epidermal concentrations of dehydroretinol in 2 healthy subjects

forms of therapy was still not apparent. In patients treated with etretinate, the drug concentration was similar in uninvolved and involved skin, yet the effects of the drug on endogenous retinoids were markedly different in the two skin areas. Thus, significant, although individually very variable (10% – 400%), increases in both retinol and dehydroretinol levels were noted in involved skin, whereas in uninvolved skin, there was only a slight decrease in the retinol level and virtually no change at all in the dehydroretinol concentration. The carotenoid levels in the skin remained constant during etretinate treatment (data not given).

During treatment with β-carotene/canthaxanthin, the epidermal carotenoid levels increased by 150% – 850%. The drug-related median concentration of carotenoids (treatment value minus pretreatment value) in involved skin was 3.7 times higher than in uninvolved skin ($P < 0.05$). Despite the high carotenoid levels attained in epidermis during treatment, no significant changes in the levels of retinol and dehydroretinol were noted in either type of skin.

Table 4. Median drug concentrations and percentage change in vitamin-A levels in epidermis of patients receiving short-term treatment with etretinate (Tigason) or carotenoids (Phenoro)

Treatment[a]	Type of skin	Number of samples	Drug[b] (ng/mg protein)	Retinol	Dehydroretinol
				(% change vs pretreatment value)	
Tigason	Uninvolved	9	0.80 (0.40– 1.83)	– 18	– 3
	Involved	7	1.07 (0.54– 2.10)	+107**	+212**
Phenoro	Uninvolved	6	17.5 (9.3 –22.0)	+ 7	– 4
	Involved	6	64.4 (33.1 –95.0)	– 29	0

** $P < 0.01$ (statistical significance of differences versus pretreatment value)

[a] For details, see Methods

[b] The range of epidermal values is given in parenthesis. The drug-related carotenoid concentration was calculated as the treatment value minus the pretreatment value. The difference between carotenoid levels in uninvolved and involved skin was statistically significant ($P < 0.05$). The median serum concentrations of Tigason and Phenoro were 21 and 580 μg/dl, respectively

Discussion

Judged by the concentrations of retinol and RBP, the plasma transport of vitamin A was normal in patients with a limited to moderate extension of chronic plaque psoriasis. This is in agreement with the finding of normal concentrations of vitamin A [8, 12, 15] and RBP [1] in patients with psoriasis of unspecified severity, and excludes the possibility of a genetic defect in RBP synthesis in this disease. Although decreased serum RBP levels were found in patients with widespread plaque psoriasis or pustular/erythrodermic psoriasis, this probably reflected increased inflammatory activity and is not a specific feature of the disease. Similarly reduced values have been reported in, for example, severe acne [14] and some other major inflammatory diseases [23, 28].

Normal serum RBP and retinol levels virtually preclude insufficient transport of vitamin A to the tissues, but do not rule out the possibility of defective uptake of the vitamin by the cells. Indeed, indirect evidence for the altered expression of RBP receptors on psoriatic keratinocytes has been presented [18]. Since such an alteration could result in abnormal vitamin-A concentrations in the epidermis, quantitative measurements of retinol in skin biopsies was performed. The methodological aspects of the assay have been discussed elsewhere [21]. Our results showed essentially normal retinol levels in the uninvolved skin of patients with chronic plaque psoriasis; other types of psoriasis were not investigated in this respect. The concentrations of retinol in the skin and of RBP in serum were significantly correlated (Fig. 1 a), thus explaining the somewhat reduced mean level of retinol in the uninvolved skin of patients with extensive plaque lesions. The retinol concentrations in involved skin were also essentially normal, although in should be emphasized that wet-weight and protein-related values are not always appropriate when diseased and normal skin are compared. (Differences in sample histology and the protein-to-wet-weight ratio may affect the vitamin-A concentration.) However, when considered together, the results argue strongly against defective delivery of retinol to the skin in plaque psoriasis.

The most notable finding of our study was the increased levels of dehydroretinol in psoriatic lesions irrespective of the severity of the disease. A similar, but less pronounced, increase in dehydroretinol was seen in the uninvolved skin of patients with moderate to extensive psoriasis (Table 3) and in tape-stripped control skin (Fig. 3). Although recent data indicate that dehydroretinol is an epidermal metabolite of retinol (H. Törmä and A. Vahlquist, submitted for publication), it is not known whether elevated levels are due to increased formation or inhibited metabolism of this compound. Notwithstanding its obscure origin, the increased dehydroretinol content seems to be related to the epidermal hyperproliferation occurring to a varying extent in involved psoriatic skin [33], tape-stripped control skin [17] and uninvolved psoriatic skin [34]. Similar increases in skin dehydroretinol levels have been found in other hyperproliferative skin disorders [19, 21]. Although this may be an epiphenomenon (perhaps secondary to skin inflammation), the early increase in dehydroretinol after tape stripping suggests otherwise. The possibility that the abnormal keratin pattern in psoriatic lesions – reminiscent of that in vitamin-A-stimulated cultured keratinocytes [6, 35] – is, in some way, connected with this increased dehydroretinol level remains to be investigated.

The patients' carotenoid levels were lower than normal in both serum and skin. The significance of this finding is uncertain, since carotenoid levels in serum are known to very markedly, depending both on the intake of carotene-rich vegetables and on the

efficacy of intestinal absorption. In a previous study, Lee et al. [11] identified carotenoid pigments in the epidermis of healthy volunteers supplemented with β-carotene. We found that treatment with large doses of β-carotene/canthaxanthin raised the carotenoid concentration in psoriatic skin far beyond the normal range, without significantly affecting the levels of retinol and dehydroretinol (Table 4). The reason why lesional skin had a higher concentration of the administered carotenoids is unclear.

Despite a lack of clinical improvement within the short period of observation, treatment with the aromatic retinoid etretinate markedly elevated the vitamin-A concentrations in involved skin (Table 4). Etretinate, which is structurally related to the physiologically occurring all-*trans* retinoic acid, cannot be converted into vitamin A and does not interfere with the serum levels of this vitamin [10]. It appears, therefore, that the drug either enhances the cellular uptake of retinol or, which is more likely, inhibits the local vitamin-A metabolism via feed-back mechanisms. The pronounced rise in dehydroretinol levels enhanced the pre-existing abnormality of the vitamin-A composition in lesional skin. In a preliminary study of a few patients with various disorders of keratinization, treatment with etretinate (resulting in partial healing of the lesions) had the opposite effect, i.e. dehydroretinol decreased relative to retinol [27]. In the present study, the effects of etretinate therapy on the vitamin-A composition of uninvolved psoriatic skin were slight, but the change in the ratio of dehydroretinol to retinol was consistent with that found previously [20].

From the present data, we conclude that:

1. The plasma transport of vitamin A is usually normal in plaque psoriasis.

2. The epidermal concentrations of retinol, which are correlated to the serum levels of RBP, are mostly normal in both uninvolved and lesional psoriatic skin.

3. Psoriatic lesions and tape-stripped control skin contain increased amounts of dehydroretinol, resembling in this respect several other disorders with epidermal hyperproliferation.

4. Reduced levels of total carotenoids are frequently found in the skin and serum of psoriatic patients.

5. Short-term treatment with etretinate, but not with carotenoids, increases the vitamin-A levels in lesional psoriatic skin.

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