Involved and Uninvolved Skin from Psoriatic Subjects: Are They Equally Diseased?

ASSESSMENT BY SKIN TRANSPLANTED TO CONGENITALLY ATHYMIC (NUDE) MICE

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ABSTRACT A highly significant, but unanswered, question in the pathogenesis of psoriasis relates to how normal appearing and diseased skin can coexist, undergo spontaneous flares and remissions, and yet appear to be genetically acquired. A plausible explanation for these disparate observations is that there is a basic defect in epidermal proliferation of skin of subjects with psoriasis and that disease expression is governed by other host factors. To address this question, we compared epidermal proliferation of skin involved and uninvolved with psoriasis with normal skin before and after transplantation to congenitally athymic (nude) mice, a biologic milieu free of humoral factors unique to the donor host.

Results demonstrated that (*a*) before transplant, synthesis of DNA by the epidermal cells from skin uninvolved and involved with psoriasis is significantly higher than normal, 1.6 and 3.6 times, respectively; (*b*) 6 wk after transplantation, synthesis of DNA by epidermal cells is unchanged for normal skin, increased for uninvolved skin, and decreased for involved skin. These increases and decreases are of such a magnitude that at 6 wk the number of epidermal cells synthesizing DNA per 1,000 basal cells is identical, and is 2.2 times that of normal skin. When removed from the milieu of the afflicted host, skin involved and uninvolved with psoriasis appear equally "diseased." These data support the notion that there is aberrant epidermal proliferation in skin of patients with psoriasis and that host factors appear to play a role both in the expression and nonexpression of this disease.

INTRODUCTION

Psoriasis is characterized by scaly, unsightly, mildly pruritic, erythematous plaques which are, at least in part, secondary to the benign hyperproliferative state of the germinative layer of the epidermis (1). Although the disease can involve the entire surface (exfoliative erythroderma), the majority of patients have <5% of their skin involved with disease (2). Since psoriasis is thought to be a genetic disease (3, 4) and can occur on any site of the body, it is likely that even phenotypically normal skin is abnormal. The nature and location of the factor(s) that transforms uninvolved skin to active lesions, or allows the coexistence of involved and uninvolved skin is unknown.

Studies comparing uninvolved skin of psoriatic subjects with skin of normal subjects are limited (5–14). These studies indicate that although uninvolved skin appears normal, abnormalities are present. Examples of such abnormalities include: an increase in the number of germinative cells of the epidermis undergoing DNA synthesis (5–9), a prolonged S phase of the germinative cells stimulated to proliferation by tape stripping (12), a stratum corneum with increased cohesion (13), and an abnormal proliferative response to the intradermal injection of propranolol and saline (10). Because these studies have been performed in vivo, the question of whether the abnormalities are inherent to the skin, or are generated by humoral factors unique to the host, remains unanswered.

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This report demonstrates that involved and uninvolved psoriatic skin acquire equally elevated epidermal cell proliferative activity, compared to normal skin, when transplanted to the congenitally athymic (nude) mouse. With this system, we find that the number of epidermal cells synthesizing DNA in involved skin decreases as a function of time, while that of uninvolved skin increases. Normal skin remains unchanged.

METHODS

Nude mouse grafting procedures. The congenitally athymic (nude) mice used in these experiments were reared and housed as previously described (15). At 2–3 mo of age, nude mice were grafted with one of three types of skin: normal human skin, or skin from psoriatic subjects, involved or uninvolved with disease.

Procedures to harvest skin grafts. The objective of this study was to transplant enough skin from each subject to have one specimen for analysis at each time interval (3 wk intervals). Control normal skin was provided by the excess portions of split-thickness skin grafts used to transplant burn patients, obtained with an electrokeratome set at 0.4 mm. Since these skin grafts originated from burn patients, it was necessary to document that this epidermis had normal numbers of cells undergoing DNA synthesis. Grafts prepared from the skin of these patients had labeling indices (LI),[1] an index of DNA synthesis (see below) equal to those of split-thickness specimens removed from the sacral skin of three normal adult male volunteers (16).

After obtaining informed consent, split-thickness skin grafts were obtained from 34 patients with psoriasis whose age and sex distribution were the same as our "normal" subjects. A total of 107 uninvolved and 84 involved skin grafts were taken from the area between the xiphoid process and the midthigh. To obtain the graft, a weal ~1.5 cm Diam was raised by the superficial intradermal injection of 1% xylocaine without epinephrine. Using a hand-held keratome (Silver's keratome, right-handed, Downs Surgical, Inc., Decatur, Ga.), a split-thickness skin graft was taken from the anesthesized area, measuring ~0.4 mm in thickness and 1.2–1.5 cm Diam. For involved sites a similar procedure was followed, but only plaques that could be harvested completely were utilized; plaque size ranged from 0.8 to 1.8 cm. All patients donated uninvolved skin. The amount and location of disease in nine subjects made donation of involved skin impossible.

Assessment of histologic parameters and incorporation of [^3H]thymidine. Before grafting, using techniques previously described (15), grafts were trimmed and 1–2-mm pieces of tissue were pulsed with [^{3}H]thymidine, specific activity 20 Ci/mM (New England Nuclear, Boston, Mass.) for 3 h at 37°C. These specimens were processed for autoradiography to determine the LI (15). An epidermal cell was defined as synthesizing DNA if it contained 5 or more grains (a labeled cell) over the nucleus when viewed at ×1,000 by light microscopy. The LI was defined as the number of labeled cells in the epidermis per 1,000 basal cells counted.

Histologic assessment was by routine light microscopy of the autoradiographic sections. Quantitation of the epidermal mass (acanthosis) was carried out with an ocular micrometer. Parakeratosis was quantitated as continuous, i.e., throughout the stratum corneum vertically and horizontally, or intermittent, i.e., present in localized areas. Background deposition of emulsion and improper orientation did not allow this type of assessment on every specimen.

Grafting and biopsy procedures. The methodology to transplant the skin grafts to the nude mouse has been described (15). At 3 and 6 wk after grafting, biopsies (2–3 × 3–4 mm) were taken from each graft site while the mouse was under light halothane anesthesia. A previously unbiopsied graft was always biopsied, and where possible previously biopsied sites were rebiopsied. After removing the biopsy, the dermis was trimmed so that the biopsy was ~0.4 mm thick. Biopsies were sectioned into 1–2-mm pieces, pulsed with [^{3}H]thymidine for 3 h, and analyzed autoradiographically as above.

Data are presented as a mean LI±SD of the total number of grafts per patient at the indicated times. Where available, the LI of biopsies from one graft pregrafting, 3 and 6 wk postgrafting, are also presented. Analysis of the LI of grafts biopsied for the first time, vs. those grafts previously biopsied, reveals that there is no difference, i.e., the trauma of a biopsy taken 3 wk previous does not affect findings 3 wk later.

RESULTS

Comparison of epidermal LI, group data, normal, involved, and uninvolved psoriatic skin vs. time. To determine whether the epidermis of involved and uninvolved skin from psoriatic subjects acquire or retain abnormal proliferation in the absence of host factors, involved and uninvolved skin were transplanted to nude mice, and epidermal DNA synthesis (LI) determined at 3 and 6 wk. These results were compared with those of normal skin transplanted to the nudes. Table I presents the mean LI±SD and the range of the LI of grafts tested; the median and mean were equivalent. Initially, uninvolved skin had a higher LI than normal, and involved skin had a LI which was greater than two times that of the uninvolved skin. Although the range of the LI was considerable, only 2 of 34 patients had a LI of uninvolved skin that was above 100. Similarly, only 4 of 25 had a LI of involved skin that fell below 100. The reason(s) why two patients had a LI of their uninvolved skin that was in the range of the LI of involved skin (130±30 and 106±23) remains unknown. The initial LI of these two subjects were mean values derived from three and five graft specimens, respectively, and thus appear to accurately reflect epidermal proliferation in those patients at that time. Pulse labeling of a biopsy of uninvolved skin of the patient with the mean LI of 130, 4 mo after harvesting of the grafts, revealed a LI of 132. In this patient, mean LI of his skin involved with psoriasis was identical to that of the uninvolved skin, 130±32.

During the 6-wk period, normal skin transplants will typically present with a slight increase in the LI at 3 wk; however, at 6 wk the values were similar to the initial values (Table 1). Over this same period of time, the LI of uninvolved skin continued to increase and that of involved skin decreased. At 6 wk, the LI of uninvolved skin had increased by 35 over initial values, a 68% increase; this contrasts with only an 18% increase

[1] *Abbreviation used in this paper*: LI, labeling index.

TABLE I

Comparison of LI of Epidermis Relative to Time, Normal and Psoriasis, Involved vs. Uninvolved

	Initial			3 wk			6 wk		
Types of skin	n‡	LI§	Range	n‖	LI	Range	n	LI	Range
Normal	20	40±11	19–58	17	53±11	41–71	15	47±13	31–72
Uninvolved¶	34	65±20	29–130	26	92±33	40–170	26	109±56	35–276
Involved**	25	145±40	90–213	21	101±29	61–192	24	98±28	44–165

Initial LI of types of skin vs. time‡‡

	Initial vs. 3 wk	*Initial vs. 6 wk*	*3 wk vs. 6 wk*
Involved	$P < 0.001$	$P < 0.001$	NS
Uninvolved	$P < 0.001$	$P < 0.001$	NS
Normal	$P < 0.005$	NS	NS

LI at various times vs. types of skin

Time	Normal vs. uninvolved	Normal vs. involved	Uninvolved vs. involved
Initial	$P < 0.001$	$P < 0.001$	$P < 0.001$
2 wk	$P < 0.001$	$P < 0.001$	NS
6 wk	$P < 0.001$	$P < 0.001$	NS

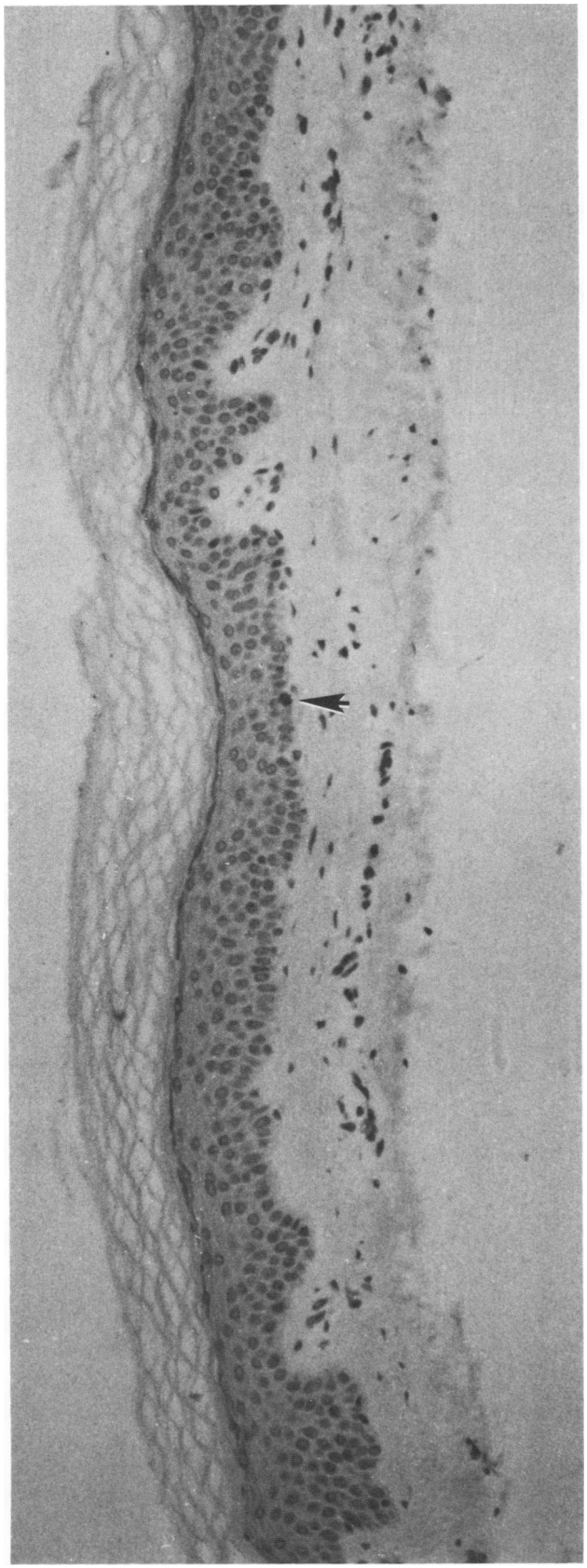
* LI, number of epidermal cells synthesizing DNA/1,000 basal cells by autoradiographic analysis.
‡ *n*, number of donor subjects.
§ Mean LI±SD.
‖ *n*, reflects number of donor subjects whose grafts were analyzed at that time. The number of grafts evaluated, per patient varies from one to five.
¶ Uninvolved, normal-appearing skin from psoriatic subjects.
** Involved, skin from psoriatic subjects involved with disease.
‡‡ Statistical significance was determined by Student's two-tailed *t* test.

TABLE II

Comparison of Epidermal Mass (Acanthosis) with the LI of Involved, Uninvolved Skin of Patients with Psoriasis with Normal Skin, as a Function of Time

		LI*			
Types of skin	(n)	Initial	(n)	3 wk	(n)	6 wk
Normal						
Epidermal mass‡						
<42 μm	(13)§	42±11	(3)	42±6	(3)	42±7
>42 μm	(1)	40	(5)	45±6	(3)	43±6
Uninvolved						
Epidermal mass						
<42 μm	(10)	62±18	(1)	48	(4)	45±13
>42 < 126 μm	(7)	72±27	(14)	83±38	(20)	86±38
Involved						
Epidermal mass						
<42 μm	(2)	119	(0)	—	(0)	—
>42 < 126 μm	(6)	126±26	(4)	132±47	(3)	92±9
>126 μm	(9)	170±52	(4)	102±9	(2)	106±20

* Data represent mean±SD.
‡ Epidermal mass: values represent the epidermal thickness as measured by an ocular micrometer, the distance from the stratum corneum to the tips of the epidermal papillae.
§ Evaluations carried out on all specimens of the first test group that were oriented correctly for histologic interpretation, and did not have excess emulsion as a background. This group contained 14 normals, 25 uninvolved, and 17 involved.



for normal skin, a fourfold difference. Contrariwise, the LI of involved skin increased by 47 from the initial value, a 32% decrease. At 6 wk, the increases and decreases were of such magnitude that essentially no differences existed between the LI of involved and uninvolved skin.

These data provide insight into two critical concepts of the clinical expressions of lesions of psoriasis: first, that some factor(s) is present in all skin of psoriatic subjects that permits/causes abnormal epidermal proliferation; second, that unknown host factors may be critical to disease expression, to wit, on the host involved and uninvolved areas coexist.

Histologic assessment and correlation. For a short time after grafting, grafts of skin involved with psoriasis usually can be visually distinguished from those grafts from uninvolved sites and those from normal subjects. This distinction, based upon a thicker stratum corneum, becomes increasingly difficult with time so that after 3 wk it is impossible to visually determine the origin of grafts. Because of this, histologic assessment of the autoradiographs of the initial group was used to confirm the observation that the epidermis of the uninvolved and involved skin become similar. The most common histologic aberrations in the epidermis involved with psoriasis are: regular acanthosis (an increase in the epidermal mass), parakeratosis (delayed maturation of the stratum corneum), and a decrease in the granular layer (absent keratohyaline granules).

At the time of grafting, histologic assessment showed $^{7}/_{17}$ (41%) of the uninvolved specimens had minimal acanthosis. At 3 wk, grafts from $^{14}/_{15}$ (93%) different patients had acanthosis (arbitrarily defined as an epidermal mass >42 μm (Table II). At 6 wk, $^{20}/_{24}$ (83%) had this degree of acanthosis (cf. Figs. 1 and 2). For normals, these values were $^{1}/_{14}$ (7%) initially, $^{5}/_{8}$ (62%) at 3 wk, and $^{3}/_{8}$ (50%) at 6 wk (cf. Figs. 3 and 4). For involved skin at the time of grafting, $^{9}/_{17}$ involved lesions showed regular psoriasiform acanthosis. By 6 wk, this had decreased to $^{2}/_{5}$ (Table II). Changes in acanthosis and the accompanying changes in the LI support the concept that both involved and uninvolved skin grafts were evolving to a similar point while being maintained on an independent biologic support system.

The histologic assessment of parakeratosis provides a more dramatic assessment of the changes which occur (Table III). Of the 14 grafts from normals, none had parakeratosis before transplant (Fig. 3). Similar results were noted in the uninvolved skin (Fig. 1); this contrasts with parakeratosis in $^{11}/_{17}$ donor grafts of involved skin (Table III). At 6 wk, none of the normal grafts had

FIGURE 1 Photomicrograph (×80) of an autoradiographic specimen from a split-thickness graft of uninvolved skin of psoriatic subject M.B., pregrafting. Arrow points to a heavily labeled epidermal cell.

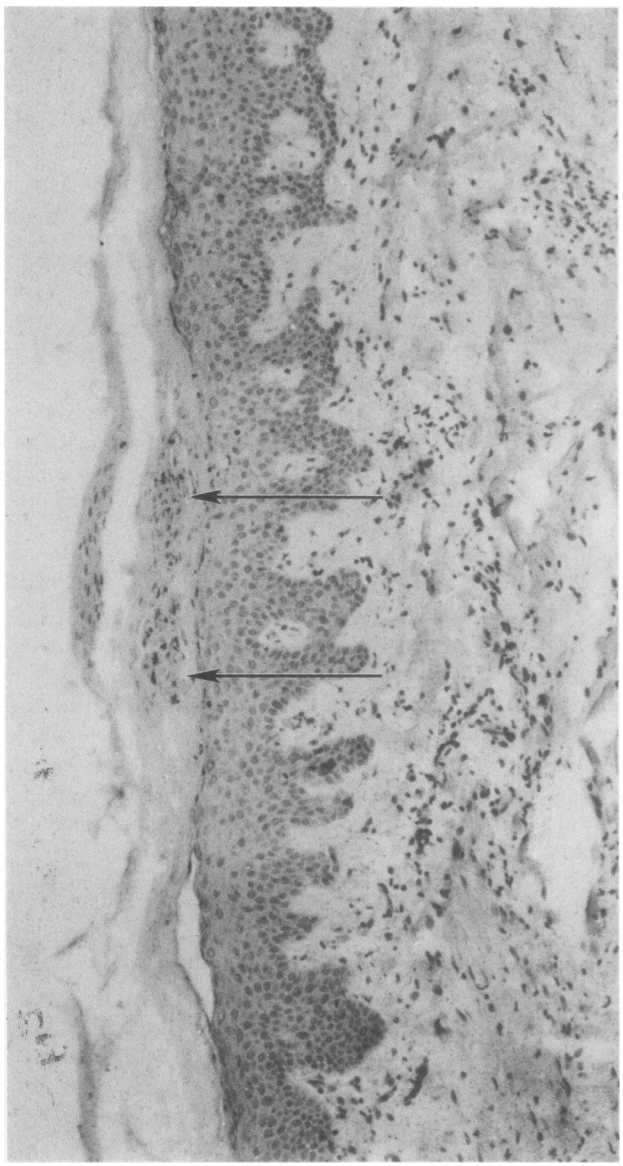


FIGURE 2 Photomicrograph (×45) of an autoradiographic specimen from a split-thickness graft of uninvolved skin of psoriatic subject M.B., 6 wk postgrafting. Arrows are to the area of parakeratosis. Note the generalized increase in epidermal mass (acanthosis).

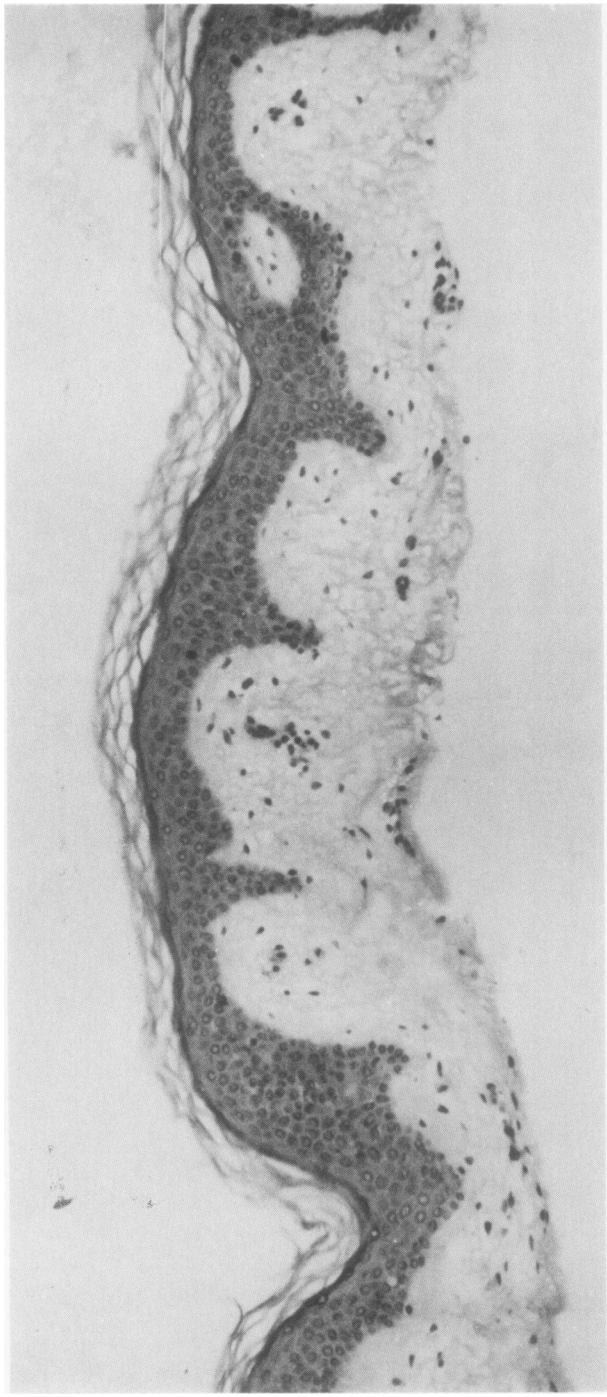


FIGURE 3 Photomicrograph (×60) of an autoradiographic specimen from a split-thickness skin graft of control subject 43, before grafting.

parakeratosis (Fig. 4). However, $^{11}/_{25}$ uninvolved grafts (Fig. 2) and $^{9}/_{11}$ involved grafts had equal degrees of parakeratosis. A statistical analysis of the number of patients whose grafts developed differing amounts of parakeratosis is presented in the lower part of Table III.

Dividing parakeratosis into three categories, none, intermittent (through the stratum corneum vertically or horizontally), and continuous, showed that the highest LI occurred in the presence of continuous parakeratosis, regardless of whether it was in involved or uninvolved specimens. In like fashion, a decrease in parakeratosis had an accompanying decrease in the LI (Table III).

After 3 wk, a mature granular layer reappeared and

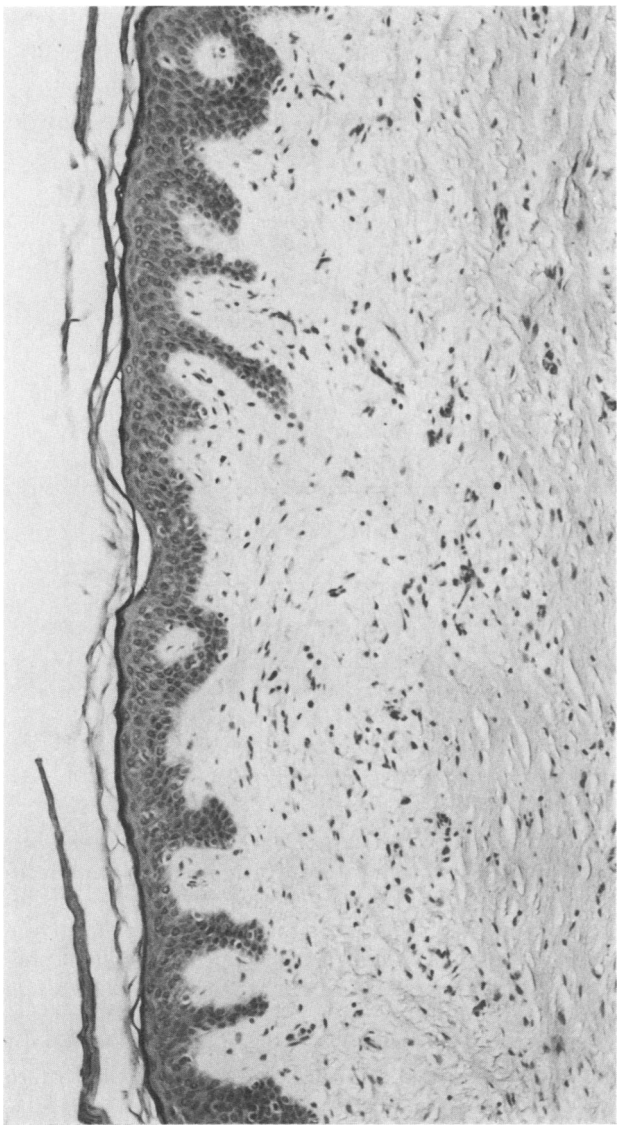


FIGURE 4 Photomicrograph (×45) of an autoradiographic specimen from a split-thickness skin graft of control subject 43, 6 wk after grafting.

remained in all the grafts of involved skin. Thus, although this keratohyaline rich layer of the epidermis is frequently aberrant in the *in situ* lesion of psoriasis, its presence appears to be independent of the abnormal epidermal proliferation in patients with psoriasis. This histologic assessment is in agreement with the autoradiographic data, i.e., the increases and decreases in psoriasiform changes in the involved and uninvolved skin occur in concert.

Analysis of those patients whose initial LI were deviant from the mean. The data presented led to the consideration of whether the increases or decreases in the LI of grafts from psoriatic subjects are inherent, i.e., if they start high, do they remain high; if they start low, do they remain low? The question is important to considerations of the influence of host factors on disease expression. If host factors are not influential, i.e., LI are inherent, we would predict that changes in the LI postgrafting should be of the same magnitude (the percent change should be the same), regardless of the LI at the time of grafting. To address this question, we compare the change in the LI of those whose initial LI are high, vs. those that are low. The decision as to whether they are in the high or low category is dependent upon where their initial LI falls relative to the mean for the entire group. The data utilized for this analysis are those which are paired; the LI of a specific graft from a patient at 0, 3 and 6 wk. These data are presented in Table IV. This analysis shows that although the initial LI are disparate, they are not different after being on the nude mouse for 6 wk, suggesting a high or low initial LI does not predict the LI at 6 wk. Thus, the LI of either involved or uninvolved skin is apparently not inherent to that patient. The epidermis, which is rapidly incorporating [^{3}H]thymidine, reaches a stabilization point that is of the same magnitude as that seen in skin with less aggressive epidermal proliferation. By extension, these data suggest that unknown host factors are responsible for the initial values of DNA synthesis by the epidermis.

Correlative analysis. Because psoriasis presents with considerable biologic diversity, e.g., percent of skin surface covered, spontaneous remission and exacerbation, and because of the rather wide ranges in the initial and subsequent LI (Table I), several correlative analyses have been made. The 34 psoriatic subjects donating skin grafts were adults with classic plaque-type psoriasis for a duration of 2–15 yr (mean = 20 yr). None had pustular, inverse, or guttate psoriasis, or total body psoriasis (exfoliative erythroderma). 43% of patients complained of arthralgias or frank arthritis. Initially, only untreated patients were selected. However, after a comparative evaluation of involved and uninvolved skin of treated and untreated patients revealed no differences in the LI of grafts before transplants (Table V), all qualified volunteers were utilized.

Various parameters of disease activity are used to characterize psoriasis at any given time. As noted in Table V, comparing these with the LI at the time of grafting fails to demonstrate any correlation. A decrease in the LI in those with "resolving disease" and those on treatment might be expected; the decreases we find are not significant. It thus appears that determining the LI at one point in the course of disease may not accurately reflect clinical activity at that time. However, because of the infrequency of LI of involved skin being below 100, and that of uninvolved skin being above 100 (see above), it does serve as an effective objective discriminator. The use of the LI as a discriminator of increased

TABLE III

Comparison of Frequency of Parakeratosis and LI of Involved, Uninvolved Skin of Patients with Psoriasis with Normal, As a Function of Time

	(n)	Initial	(n)	3 wk	(n)	6 wk
Normal						
Continuous	(0)	—	(0)	—	(0)	—
Intermittent	(0)	—	(1)	41	(0)	—
None	(14)	42±11	(12)	50±10	(7)	41±10
Uninvolved						
Continuous	(0)	—	(1)	170	(0)	—
Intermittent	(0)	—	(9)	91±27	(11)	133±74
None	(17)	71±32	(9)	55±27	(14)	80±53
Involved						
Continuous	(2)	280±85	(0)	—	(0)	—
Intermittent	(9)	155±48	(9)	114±32	(8)	114±48
None	(6)	119±26	(0)	—	(3)	68±24

Significance of Changes in Parakeratosis (Number of Individuals Changing Categories) by Fisher's Exact Test

	Normal		Uninvolved		Involved	
	Initial	6 wk	Initial	6 wk	Initial	6 wk
Parakeratosis	0	0	0	11	11	8
No parakeratosis	14	7	17	14	6	3
	$P = 1.00$		$P = 0.001$		$P = 0.49$	

epidermal proliferation is also supported by the general correlation between the histologic findings and the LI after transplantation (see above).

There is no correlation, either positive or negative, between the initial LI of involved and uninvolved skin, i.e., high values in one are not associated with high or low values in the other, and vice versa.

TABLE IV

Comparison of the Mean LI of the Grafts Whose Initial LI Were Either Greater Than or Less Than the Mean for the Group at 0, 3, and 6 Wk

		LI*		
	n	Initial	3 wk	6 wk
Uninvolved‡				
>65§	7	84±27	88±29	106±40
<65	11	52±11	83±21	105±72
Involved‡				
>145§	6	184±19	98±24	107±15
<145	5	116±19	107±50	93±25

* Values are mean LI±SD.

‡ All data are generated from one graft from one patient, i.e. LI determined before grafting and from two subsequent biopsies from that graft.

§ Selection for > or < based upon mean for group LI at initial time, see Table I.

In agreement with the observations of others, our data attest to the inherent variability between individuals with and without psoriasis (1–14). Nevertheless, an analysis of LI of multiple specimens from one patient does reveal clustering; the mean LI of five specimens of uninvolved tissue from one subject is 42 (range 30–58); in another subject the mean LI is 80 (range 62–89). The mean percent variation ±SD of the LI amongst the initial base-line values, where two or more specimens were analyzed, for involved skin is 24±13, and for uninvolved skin is 25±18. Repeat counts of the same specimen are within 12% of one another. These points are further illustrated by one patient who consented to donate a second set of grafts. The mean initial LI for the first set of uninvolved skin was 71±6, and for the second set was 79±8. At 3 wk, the LI were 83 and 92, respectively (6-wk data are unavailable for the second set, as these grafts were utilized for different experiments).

In assessing the LI of the same graft, initially and at 6 wk, we noted that 4 of 34 patients had a LI in uninvolved grafts that decreased instead of increasing. Exclusion of these four patients does narrow the range of the 6-wk LI to 65–276 (Table I). Similarly, there are two patients whose LI in involved skin increases instead of decreasing. Excluding these two patients also narrows the range for this group to 44–126. No clinical features characterize these two groups of pa-

TABLE V

Comparison of LI of the Epidermis at the Time of Transplant of Skin Involved and Uninvolved with Psoriasis with Four Parameters of the Disease

	LI*			
	(n)‡	Uninvolved	(n)	Involved
State of disease§				
Flare	(15)	65±19	(13)	153±28
Static	(13)	67±21	(8)	149±27
Resolving	(6)	58±20	(4)	112±25
Body surface involved				
1%	(8)	72±30	(3)	135±20
1–5%	(8)	61±18	(8)	143±27
6–50%	(13)	65±18	(10)	138±37
50%	(5)	65±19	(4)	180±50
Arthritis/arthralgias				
Present	(14)	61±15	(9)	150±38
Absent	(20)	67±20	(16)	136±42
Treatment at time of grafting				
Any treatment	(16)	63±24	(13)	140±40
No treatment‖	(18)	67±23	(12)	150±37
Means of all patients	(34)	65±20	(25)	145±40

Data represent mean±SD.

* For methodology see text.

‡ (n), number of patients in each group.

§ State of disease, historical, i.e., patient's assessment of disease activity at the time of grafting.

‖ No treatment, topical or systemic treatment for at least 2 wk before grafting.

tients. The LI are available at 3 wk for grafts of four of these patients. In each case, the LI of that graft at 3 wk is in harmony with the 6-wk data. This suggests that these values are not spurious.

These six patients prompted an assessment of the change in LI, 0 vs. 6 wk. This comparison was made in normals as well as those psoriatic subjects who had an initial LI and a 6-wk LI of one graft of uninvolved skin and one graft of uninvolved skin from the same patient (Table VI). This analysis shows that in normal subjects some have LI that increase and others have LI that decrease with time. The mean change is essentially zero, seven having an increase and seven having a decrease. For uninvolved skin, the picture is dramatically different. Here only 2 of 19 had a decrease in the LI, a highly significant difference (Table VI). In these two cases, the change in LI was in the range of changes seen in normals. In this group, none of the grafts of involved skin had an increase in the LI, initial vs. 6 wk. There is no correlation, either positive or negative, between the changes in the LI of the involved skin with those of the uninvolved skin grafts, $r = 0.42$. It is concluded that although there is inherent biologic variability in epidermal LI of individual specimens, the net assessment supports our conclusions.

DISCUSSION

Since psoriasis occurs more frequently in particular regions of the body, e.g., elbows, knees and scalp, the suspicion that some body regions are more prone to disease has evolved. A correlary to this is that some areas are resistant to disease. Our data demonstrate that uninvolved skin of most patients with psoriasis is inherently abnormal. Although data from a modified in vivo setting are used to make this conclusion, this, to our knowledge, represents the first direct evidence that involved and uninvolved skin from patients with psoriasis have equal potential for disease. These observations have further significance in that they provide the first direct evidence that host factors are important in the clinical presentation of the active lesion of psoriasis, as well as functioning in the control of uninvolved skin. This point is illustrated by the patient who had very similar LI in involved and uninvolved skin at the time of, and 4 mo after grafting. In further support are those patients whose LI of uninvolved skin are very high, in the range of lesions of psoriasis, but without visible disease.

An analysis of the changes in the LI of the groups whose initial LI are either above or below that of the entire group also suggests that uninvolved skin is inherently prone to increased proliferation. In the group whose initial LI is below the mean for the group, there is a mean increase of 31 at 3 wk. In the group whose initial LI is above the mean for the group, the increase is only 4. Similar differences are noted at 6 wk. These data indicate that if epidermal proliferation is near its inherent level, a further increase after the grafting procedure is not observed. This argues against the grafting procedure, its accompanying inflammation, and increased blood supply as causative factors of the abnormal epidermal cell proliferation of uninvolved skin. If grafting had triggered the proliferation, a similar increase in the LI of the group of patients with a high LI in uninvolved skin at the time of grafting would be expected.

It has been demonstrated that psoriatic lesions have capillary dilatation and that capillaries of skin of patients with psoriasis have increased numbers of endothelial gaps (18–20). As judged by light microscopy, the transplants of involved lesions lose the abnormal tufting of the superficial capillary network that accompanies an active lesion of psoriasis (unpublished observations). For these reasons, a partial explanation of our observations could be related to nutrient supply. If the change in the LI of involved skin is related to a change in nutrient supply, it is difficult to explain why uninvolved skin moves to the same level of epidermal proliferation as that of involved skin. In now classic histologic examinations of rabbit skin grafts, Medewar (21) observed that after 8 d the vasodilatation accompanying grafting decreases toward normal, reach-

TABLE VI

Paired Comparison of the Change in LI, 0 vs. 6 wk of 14 Control and 19 Psoriatic Subjects

Control identification	*Δ LI, 0 vs. 6 wk	Patient	Δ LI, 0 vs. 6 wk	
			Uninvolved	Involved‡
41	+34§	N.W.	+163	−30
34	+12	A.B.	+107	−50
33	+10	M.A.	+99	−10
42	+9	D.R.	+93	−30
40	+5	A.A.	+81	−29
38	+2	L.G.	+70	−105
44	+1	C.D.	+51	−9
36	−1	G.R.	+34	−15
37	−3	D.M.	+31	−3
32	−3	S.C.	+31	−68
43	−10	D.F.	+29	−24
31	−16	C.R.	+24	−35
39	−18	C.V.	+23	−7
35	−26	R.M.	+19	−41
		E.S.	+9	−81
		S.W.	+3	−124
		B.P.	+1	−95
		L.B.	−23	−72
		K.O.	−33	−66
Mean Δ LI±SD 0 vs. 6 wk	0.29±15‖		+43±48‖	−47±36
Number + or −/total	7/14 (50%)		−2/19 (20%)	+0/19 (0%)
Mean LI of this group				
Initial	47±7		65±20	147±40
6 wk	47±10		107±54	101±22

* Δ LI are ranked for both normal and uninvolved specimens.

‡ The Δ LI of the involved specimen accompanying the uninvolved values are the changes which occurred in that patient's involved skin.

§ + Connotes an increase in the LI 0 vs. 6 wk, − connotes a decrease.

‖ $P < 0.002$ by Mann Whitney U rank sum test.

ing normal levels in 24 d. Our observation that the LI of grafts of normal skin at 3 wk are increased over base line ($P < 0.005$) supports his observations. The percent increase from the initial LI to the LI at 3 wk for normal skin and uninvolved skin of patients with psoriasis is quite similar. Thereafter, however, uninvolved skin of patients with psoriasis continues to increase while that of normals returns to a level which is not different from the base-line LI.

Our data are in agreement with those of Harper et al. (9) who noted that the LI of epidermis of involved and uninvolved skin were very similar when assessed in vitro 8 d after placing skin explants in tissue culture media. In their study, normal skin had a LI that was also significantly lower than that of involved or uninvolved skin of psoriatic subjects. These explant studies did not assess DNA synthesis before placing tissue in explant and thus, were unable to detect changes in both involved and uninvolved tissue that could have occurred during the time they were held in culture. In a recent preliminary communication Fraki et al. (17) have partially confirmed and extended our findings. They demonstrated that following transplantation to nude mice, the LI is increased in uninvolved skin, and that plasminogen activator activity increases to that of involved skin, while normal skin did not change relative to the plasminogen activator activity. Briggaman and Wheeler (22) have also reported that grafts of lesional skin with psoriasis transplanted to the nude mouse had increased LI at 9 wk, compared with grafts from normal subjects. They did not do pregraft analysis, and did not study uninvolved skin. However, using epidermal-dermal recombinant graft techniques, they demonstrated that abnormal LI were only present in those combinations of involved dermis and epidermis.

Our data confirm the general belief that an increase in epidermal proliferation, herein determined as an increase in the LI of epidermis, results in an increase in the epidermal mass (23). The LI also appears to correlate with another of the histologic parameters used to define psoriasis, parakeratosis (Table III). This is in harmony with unpublished data from our labora-

tory which demonstrate that parakeratosis will develop in normal human skin grafts after the induction of epidermal proliferation by topically applied agents. The presence of parakeratosis follows the peak epidermal DNA synthesis by 24–48 h. Peak levels of parakeratosis are reached by day 5, and decrease thereafter. Because the involved grafts do not revert to a LI of normal skin, one would anticipate no significant change in the frequency of parakeratosis; such is the case.

When we originally described this system to study psoriasis (24), we were struck by the persistence of the acanthosis of grafts of involved skin and ignored the increase in epidermal mass (acanthosis) of grafts of uninvolved skin. A comparison of the histology of the grafts and the LI in this study suggests the LI provides a more accurate reflection of epidermal proliferation at a given point in time. In addition to arguments already presented, relative to the LI in discriminating psoriasis from nonpsoriasis, is the observation that even with active therapy, an area involved with psoriasis has an abnormal LI (Table V).

In summary, it appears that the genetic defect(s) that permit the development of psoriasis involves all of the skin of patients with psoriasis with equal propensity and that other factors must be involved in the evolution of the clinical lesions of psoriasis. Definition of the host factors important in the clinical presentation of disease or nondisease, and whether the defect in uninvolved skin is primarily epidermal or dermal, await further dissection.

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