Role of the Microcirculation in the Treatment and Pathogenesis of Psoriasis

IRWIN M. BRAVERMAN, M.D., AND JANE SIBLEY, B.A.

Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

Controversy exists whether the initiating events in psoriasis are primarily epidermal or dermal (vascular). To study this point, serial biopsies from 6 patients were taken from the periphery of individual plaques before, and at 1 to 3 day intervals during, Goeckerman and PUVA treatments. Part of the biopsy was studied by electron microscopy to determine the fine structure of the capillary loops and part was incubated with tritiated thymidine to determine the labeling index (LI) of the basal cells. Normal appearing buttock skin of 11 other psoriatic patients not under treatment was studied by identical methods. In 4 of the 6 treated patients, the capillary loops began to return toward normal 3 to 8 days before the LI began to decrease. Two patients did not show a return toward normal of either capillaries or LI during the period of the experiment. The LI was elevated in the normal appearing buttock skin of 6 of 11 untreated psoriatics. In 4 of the 6, the loops were normal arterial capillaries. We did not observe abnormal (venous) capillaries associated with a normal LI in the other 5 untreated patients. These data support the concept that the initiating factors in psoriasis are in the epidermis, but epidermal hyperplasia cannot occur without vascular proliferation. Understanding the factors responsible for shortening the capillary loops during epidermal normalization and for inhibition of capillary growth in the presence of an increased LI could lead to other ways of controlling psoriasis.

The major emphasis in psoriatic research has been directed toward the epidermal hyperplasia. Whether the accelerated epidermal cell turnover is a primary defect or a secondary response to an unidentified stimulus is still unresolved. The possibility that a vascular defect plays a major role in the pathogenesis of psoriasis has been debated for many years. Morphologic studies employing capillary microscopy and cleared whole mounts of skin have supported this notion with the following observations. The capillary loops in the dermal papillae of psoriatic lesions have been observed to become dilated and tortuous, before epidermal hyperplasia has been detected morphologically [1,2]. Abnormally dilated capillary loops have frequently been found in the normal appearing skin of psoriatic patients [1]. Convoluted capillaries have persisted for 1 to 9 mo after the skin had returned to normal [3,4]. Based upon light microscopic studies of developing psoriatic lesions, Pinkus and Mehregan concluded that initial vasodilatation accompanied by an exudate of inflammatory cells and serum in the papilla was the initiating event in psoriasis [5]. Several investigators, who studied developing psoriatic lesions 1 mm in

size, found that there was an upward proliferation of the dermal papillae at the edges of psoriatic lesions. They believed this enlargement was one of the initiating events, although the stimulus was unknown [6,7].

In chronic psoriatic plaques, several studies have shown that there is marked vascular and lymphatic dilatation, with an increased blood flow that is twice normal [8–11]. Endothelial cell gaps which are present in the venous capillaries of the capillary loops and post-capillary venules of the superficial horizontal plexus [11–13] provide a morphologic basis for the proposals that capillary loop dilatation with a presumed protein rich exudate is responsible for initiating epidermal hyperplasia [1,5].

Our previous studies on the normal dermal microcirculation [14,15], confirmed by others [16], showed that it is possible to distinguish arterioles, arterial capillaries, venous capillaries and post-capillary venules from one another by their ultrastructural features. Reconstruction of the capillary loops within the dermal papillae of normal skin showed them to have the fine structure of arterial capillaries: homogeneous appearing basement membrane material in the wall and an absence of bridged fenestrations in the endothelial layer. In psoriasis, the capillary loops within the dermal papillae display the characteristics of venous capillaries: single or multilayered basement membrane material in the wall and the presence of bridged fenestrations in the endothelial cell layer. It is possible to describe each loop in a psoriatic lesion by the extent of its venous capillary component (Fig 1) [17]. In earlier studies, we noted that the venous capillary loops in psoriatic plaques were replaced by arterial capillaries after the skin had returned to normal following Goeckerman therapy, and that the capillary loops had begun to revert toward a normal pattern within 24 to 72 hr after the initiation of Goeckerman therapy. In these studies, biopsies were taken at 24-hr intervals for the first 96 hr only [17].

In this report, we have combined autoradiography, histologic evaluation by light microscopy, and ultrastructural reconstruction of capillary loops in sequential biopsies of psoriatic plaques over a longer period in order to determine whether the histologic features of psoriasis and epidermal hyperplasia as measured by the basal cell labeling index precede or follow the return of venous capillary loops toward normal during Goeckerman and PUVA therapy. In addition we studied the normal appearing buttock skin of untreated psoriatic patients by this combined approach in order to relate the ultrastructural pattern of the capillary loops to the labeling index and the histologic appearance of the epidermis. We also applied these techniques to the acute lesions of pustular psoriasis of von Zumbusch in order to identify the segments of the microvasculature responsible for capillary elongation in the enlarging dermal papillae of developing psoriatic lesions.

MATERIALS AND METHODS

Four patients (3 women and 1 man) undergoing in-patient Goeckerman therapy with coal tar (Zetar) and UVB irradiation, and 2 men being treated by photochemotherapy with 8-methoxypsoralen and UVA (PUVA) volunteered for these studies which were approved by the Human Investigation Committee at the Yale School of Medicine. In each patient, biopsies were taken just inside the edge of a plaque the day before therapy was begun and subsequently, at similar sites along the edge of the same plaque at intervals during therapy. The sampled
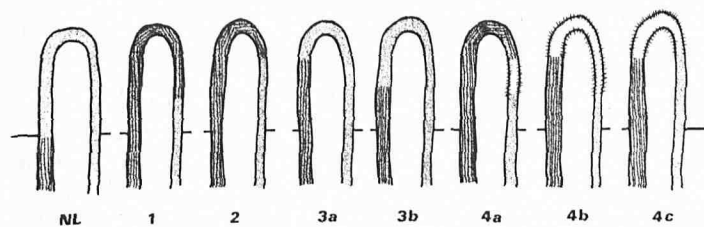
FIG 1. Capillary loop patterns in normal and psoriatic skin. *NL* = normal loop. *1-4c* = psoriatic patterns. *Horizontal line* delimits the intrapapillary portion from extrapapillary portion of the loop. *Striped areas* = venous ultrastructure. *Stippled areas* = arterial ultrastructure. *Clear areas with slashes* = transitional zone vessel in which the basement membrane has both homogeneous and multilaminated features and bridged fenestrations and is probably equivalent to a venous capillary in physiological function [17].

plaques were on the buttock or trunk. In 3 of the 4 Goeckerman treatment patients, biopsies were obtained daily for the first 2 or 3 days, and at intervals of 3 to 4 days thereafter. In the fourth patient, biopsies were obtained at 4 day intervals because the response to treatment initially was very slow. In the PUVA-treated patients, who were treated twice a week, biopsies were obtained at 3 or 4 day intervals just before their next scheduled treatment. Three percent coal tar in plastibase was the only topical treatment used in the Goeckerman-treated patients. No topical preparations were applied by the PUVA-treated patients to their plaques. These experiments continued for 6 to 29 days until the plaques almost disappeared or showed marked improvement characterized by flattening, loss of scale, and decreased erythema. Anesthesia using 1% lidocaine without epinephrine was injected as an intradermal ring around the site to be biopsied and the center was removed with a 3-mm skin trephine. The plaques selected for study were large enough so that the subsequent areas to be biopsied were not infiltrated by the previous rings of anesthesia.

Each biopsy was split in half. One piece was placed in half-strength Karnovsky's fixative and processed for electron microscopic examination by procedures described previously [11]. The ultrastructural patterns of 4 to 5 capillary loops were reconstructed by correlating 1 μm sections studied by light microscopy with the corresponding ultrathin sections used for electron microscopy. Our previous studies have shown that all the capillary loops in a given area of psoriasis (1–2 mm diameter) have the same ultrastructural characteristics. The other half of the specimen was processed for autoradiography by the *in vitro* technique of Lachapelle and Gillman in order to determine the labeling index of the basal (germinative) cell layers [18]. The biopsy specimens were cut by hand with a razor blade into pieces less than 1-mm thick. The slices were placed in 20 ml of Ham's F-10 culture medium within 10 to 15 min after having been removed from the skin and were incubated in a water bath at 37°C for 2 hr. The culture medium contained tritiated thymidine in a concentration of 10 μCi/ml (New England Nuclear, NET-027Z, concentration 1 mCi/ml, specific activity 51.8 C/mmol). The flask containing the tissue and medium were connected to a source of 95% O_2 and 5% CO_2 which passed through at a rate of 60 bubbles/min. After incubation, the tissues were washed 3 times for 10 min each with nonradioactive Ham's F-10 medium. The specimens were blotted on filter paper (Whatman #50), flattened on a cover glass, and fixed in buffered formalin overnight. After dehydration and wax embedding, the specimens were serially sectioned at 5 μm before being coated with Kodak NTB-2 emulsion for autoradiography. The slides were kept at 4°C in the dark for 4 weeks before being developed and subsequently stained with hematoxylin and eosin. We found it necessary to use tritiated thymidine in a concentration of 10 μCi/ml of tissue culture fluid, instead of 2 μCi/ml as recommended by Lachapelle and Gillman in order to obtain consistent labeling of epidermal cells. All the biopsies and incubations were performed at 9 AM and the labeling index was calculated from slides exposed for 4 weeks. The basal (germinative) cells were counted through the microscope with a hand tally counter. The basal cells were easily recognized because they were stained more deeply blue with hematoxylin and eosin than the overlying Malpighian cells. In psoriasis, the basal (germinative) cell pool was present in the lowest 2 to 3 layers of the epidermis. A minimum of 2,000 basal cells were counted, but in most instances 2,500–3,000 cells were tallied. The tritiated thymidine diffused into the skin slices for distances of 200 to 400 μm to produce a regular labeling of epidermal nuclei. Every sixth section was counted so that

labeled cells were not tallied twice. Each labeled nucleus was overlaid with at least 15 coarse grains and the background grain count was less than 6. Only the basal cells between appendages were scored. The labeling index (LI) was calculated as follows.

$$LI = \frac{\text{number of labeled basal cell nuclei}}{\text{number of counted basal cell nuclei}} \times 100$$
$$= \text{mean percentage of labeled basal cells in epidermis.}$$

Lachapelle and Gillman established that their *in vitro* technique is as accurate as *in vivo* labeling methods [18]. The LI for normal skin by the *in vitro* method ranges from 2 to 5% [18,19]. In our own controls, the LI of skin from the buttocks and forearms of 6 healthy adult men and women ranged from 2.4 to 3.9%.

The autoradiographs were also scored for the presence of histologic abnormalities using the following notations. PS indicates the presence of parakeratosis, loss of the granular layer, acanthosis and in most instances the presence of Munro's microabscesses. Nl indicates the presence of orthokeratosis and the presence of a granular layer. The epidermis was either slightly to moderately acanthotic or of normal thickness. The other half of the biopsy which had been processed for electron microscopy, showed the same histologic features in 1 μm plastic embedded sections as the corresponding autoradiographs.

Biopsies were also obtained from normal appearing buttock skin of 8 men and 3 women who were being evaluated for PUVA or Goeckerman therapy. These individuals had been applying only lubricants to their skin for the preceding 2 to 3 weeks. The LI, capillary loops and histology were evaluated in these biopsies as well.

We also biopsied an early pustule and an erythematous macule in a man with pustular psoriasis (von Zumbusch) for study by the same techniques in order to determine the LI of the epidermal cells and the pattern of endothelial cell labeling in the microvasculature. Capillary loops were reconstructed from serial 5 μm autoradiographic sections in order to determine the localization pattern of endothelial cell labeling.

RESULTS

In 5 of the 6 patients treated by the PUVA and Goeckerman regimens, the psoriatic plaques became flatter with less scaling within 2 to 3 days after therapy was begun. Fine wrinkling developed around the edges of the plaques as they became flatter within the first 2 to 3 days. In the sixth patient (UV-tar-1) improvement was not seen until day 8. However in 2 of the 6 (UV-tar-3 and -4), the histologic appearance, LI, and configuration of the capillary loops did not return toward normal even though the plaques were flatter and less scaly at days 13 and 7 respectively (Fig 2). The results obtained from these 2 patients who were the first ones studied, prompted us to continue serial biopsies for 3 to 4 weeks in the other patients until the plaques had almost healed completely. In the other 4 patients, the capillary loops began to revert toward normal at days 1, 7, 14, and 21 respectively, and correspondingly, their plaques had almost healed by days 6, 22, 23 and 28.

In all instances, the return of the capillary loops toward normal proceeded in a uniform, orderly and identical way. The arterial characteristics of the ascending limb increased progressively in length with a reciprocal decrease in the venous features of the rest of the loop. By the end of these studies, the intrapapillary portion of the capillary loop was almost completely arterial except for the short terminal segment of the intrapapillary descending limb which still showed venous characteristics. At no time did arterial features develop as isolated segments within the venous portions of the loops. In all 6 patients, only an occasional endothelial cell was labeled by autoradiography, even though the epidermis of these chronic psoriatic plaques was heavily labeled.

Figure 2 displays the correlation between LI, histologic appearance of the biopsy and ultrastructural configuration of the capillary loops. For the sake of conciseness, the data for days 3 and 7 in PUVA-1, day 4 in PUVA-2, and days 4 and 8 in UV-tar-1 have not been included in the chart. There were no signs of improvement in the LI or loop configurations at these times. However, every LI determined in the 6 patients is listed in the Table. In the successfully treated patients, the capillary loops
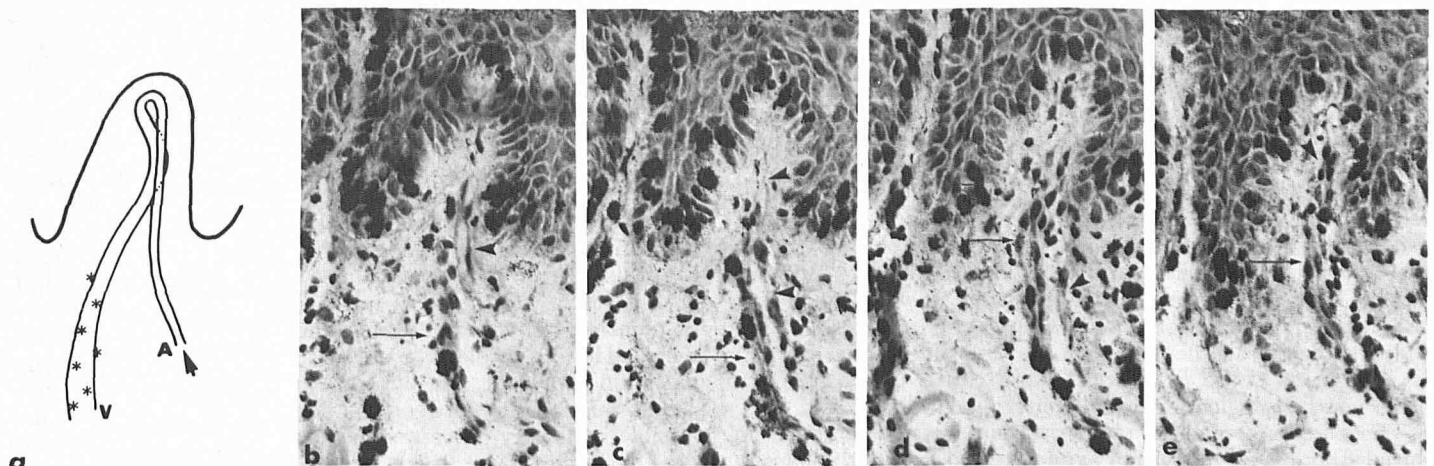
began to return toward normal 3 to 8 days before the LI did. The histological features of psoriasis in the biopsies began to show signs of improvement concomitant with the return of the capillary loops toward normal. The first change was a spotty and focal return of the granular cell layer with overlying orthokeratosis. Complete restoration of the granular layer with orthokeratosis in the entire biopsy took 3 to 8 days. At this point, marked Nl on Fig 2, the epidermis was still slightly to moderately acanthotic. In patients UV-tar-3 and -4, none of the 3 parameters showed any change toward normal even though the plaque was thinner and less scaly at the time the experiment was ended.

In 4 of the 6 subjects, the LI in the serial biopsies fluctuated over a 2-fold range in the early and midportions of the experiments (Table).

In 11 patients with extensive psoriasis who had not yet begun treatment with either PUVA or Goeckerman therapy, the same 3 parameters were evaluated in biopsies from their normal appearing uninvolved buttock skin. Figure 3 shows these data. In 6 normal controls, the LI of buttock and flexor forearm skin ranged from 2.4 to 3.9%, and the capillary loops in the papillae were arterial in configuration. In 5 of the 11 psoriatic patients, both the LI (1.8 to 3.4%) and capillary loops were normal. In 6 of the 11, the LI (5.1 to 8.6%) was abnormally elevated, but in only 2 of these individuals (LI 5.9% and 7.4%) did the capillary loops have venous features. The other 4 had arterial loops.

The histological appearance of the skin in both the controls and in 8 of the 11 psoriatics was normal. In the 2 psoriatics who had both an elevated LI and venous capillary loops, the epidermis was normal except for a few small foci of basal cell hyperplasia. In both individuals, a granular cell layer and orthokeratosis were present. In one psoriatic with an elevated LI (7.3%) and *arterial* loops, the epidermis also showed a few small foci of basal cell hyperplasia as the only histological abnormality. Thus, we found an elevated LI in association with normal capillary loops and normal epidermal histology in the clinically uninvolved buttock skin of 3 psoriatics. In a fourth psoriatic, a few foci of basal cell hyperplasia were present in association with an elevated LI and arterial loops.

In the pustular and macular lesions of von Zumbusch disease, there was extensive labeling of the endothelial cells by tritiated thymidine in the superficial horizontal plexus and the vessels passing from the dermal papillae to this layer. Three well-labeled capillary loops were reconstructed in 3 dimensions from

Fig 2. Correlation of capillary loop configuration labeling index (LI) and histology in serial biopsies. Only the intrapapillary portions of the loops are shown. *Black area* = venous component. *Clear area* = arterial component. *Ps* = psoriatic features present. *NL* = normal epidermal. LI expressed in percent. — = not determined.

Fig 3. Correlation between labeling index and capillary loop configuration in normal appearing buttock skin of 11 psoriatics and 6 controls.

Labeling indices of serial biopsies expressed in percent

Subjects	Day																				
	0	1	2	3	4	5	6	7	8	11	12	13	14	15	18	19	21	22	23	25	28
PUVA-1	14			11.3				9.5		16.5					8.9		21			10.5	8.8
PUVA-2	10.3				10.2			9.8		13.7				2.5	2.5			3.0			
UVA-tar-1	9.7				22.7				11.1		20		9.5			4.4			5.7		
UVA-tar-2	12	12	12.5	7.3		5.8															
UVA-tar-3	12.3	14.9	13.8			19.5						8.6									
UVA-tar-4	12.3	16.4	22	10.9				9.8													

FIG. 4. Reconstruction of loop showing arterial limb (A) and direction of flow (*arrow*) and localization of labeled endothelial cells (*asterisks*) to extrapapillary portion of descending venous limb (V). b–e. Serial sections from which the loop shown in A was reconstructed. *Arrow* indicates descending venous limb. *Arrowhead* indicates ascending limb × 800.

the 5 μm autoradiographic sections. Identical findings were present in all 3 loops, an example of which is illustrated in Fig 4a. The labeled or dividing endothelial cells (*asterisks*) were limited to the extrapapillary portion of the descending venous limb of the capillary loop and to the vessels in the superficial horizontal plexus (not shown). Labeled endothelial cells were never found in the intrapapillary portion of the loop. Figures 4b–e are the serial sections from which the drawing was reconstructed. Not included is the last section in the series showing the apex of the loop.

DISCUSSION

An initial rapid flattening of psoriatic plaques with decreased scaling after the first few days of Goeckerman therapy is a frequent observation in our experience. We had interpreted such changes as indicating a return toward normal, but the histologic findings, LI, and ultrastructure of the capillary loops in patients UV-tar-3 and -4 belied this hypothesis. Closer visual inspection of the plaques disclosed fine wrinkling on their margins where the flattening was most evident. Because of this wrinkling it seems most likely that papillary dermal edema contributes significantly to the elevation of psoriatic plaques. The initial rapid flattening of plaques is probably related to a decrease in the abnormal vascular permeability which is present in psoriasis. The apparent decrease in scaling in our Goeckerman treated patients was most likely related to the frequent applications of the lubricating bases in which the tar was incorporated.

The infrequent labeling of endothelial cells in the psoriatic plaques probably reflects the chronicity and stability of such lesions. In contrast, the pustules and red macules of von Zumbusch disease which are very active and rapidly evolving lesions, displayed marked vascular labeling. de la Brassinne and Lachapelle had reported that labeling of endothelial cells by tritiated thymidine can be seen in all forms of psoriasis (vulgaris, erythroderma, and von Zumbusch disease), but they did not state whether the extent of labeling differed among these 3 varieties of the disease [20].

Based upon the pattern by which the loops in psoriasis vulgaris return to normal, and the pattern of vascular labeling in von Zumbusch disease, the mechanism illustrated in Fig 5 is offered as an explanation of the process of elongation of the capillary loops in psoriasis. The endothelial cells in the extrapapillary portion of the venous limb divide to supply the cells required for the lengthening of the loop within the enlarging dermal papilla. Since the venous limb is the source of the endothelial cells, the intrapapillary venous limb enlarges and the arterial limb becomes proportionally shorter. Eventually,
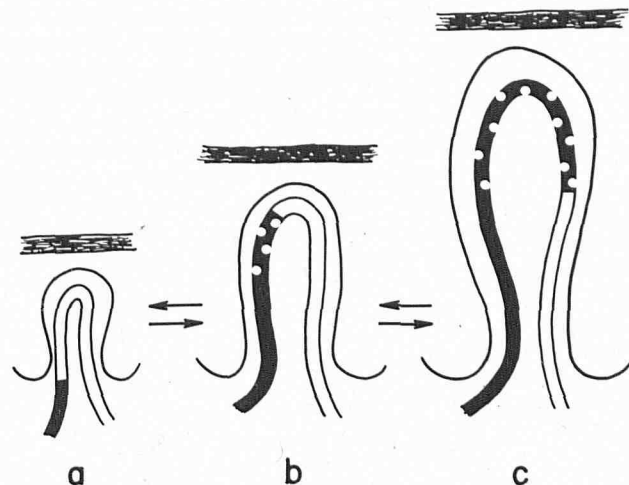

FIG. 5. Proposed mechanism for shortening and elongation of capillary loops in psoriasis. a = normal loop. b = partial elongation or shortening depending upon direction. c = maximal elongation. *White dots* indicate area of bridged fenestrations. *Black zone* = venous component. *Clear zone* = arterial component.

almost the entire intrapapillary loop has the ultrastructural features of a venous capillary. The *white dots* indicate the region of the bridged fenestrations. Successful antipsoriatic therapy is associated with a decrease in the volume of the dermal papillae and a concomitant shortening of the capillary loops. As the extra endothelial cells in the venous limb are resorbed, the venous limb shortens and the arterial limb becomes proportionally longer. The bridged fenestrations decrease in number until they are no longer present in the normal arterial loop. We never observed necrosis of endothelial cells in the intrapapillary loops or a spotty return to normal within these loops. The loss of endothelial cells could occur from the segment that was the site of proliferation, or from the intrapapillary portion. However, it seems more likely that the segment responsible for hyperplasia would also be the site from which endothelial cells would be lost. An analogous phenomenon develops in the microvasculature of rat skin during the hair growth cycle [21]. The capillary network around actively growing follicles increases in size by endothelial cell proliferation. Virtually all the endothelial cells are supplied by the capillaries. (In human skin, both glabrous (Braverman, IM, unpublished data) and scalp (22), the capillary network around the hair follicles has a venous ultrastructure—bridged fenestrations and a laminated basement membrane.) When the rat hair follicle

enters catagen, the vascular network is greatly reduced in size, partly through loss and partly through collapse.

Morphologically, the return of the capillary loops toward normal preceded improvement in the LI by 3 to 8 days. In 2 patients, there was neither significant healing of the plaques nor improvement in the 3 parameters during the experimental period. Of the 4 patients who did show improvement, 3 still had an elevated LI (8.8%, 5.8% and 5.7%) even though the loops had returned almost to normal and the histological features of psoriasis were no longer present. Similarly, the studies of normal appearing buttock skin in psoriatics showed that an elevated LI may exist in the presence of both a normal epidermal histology and a normal capillary loop configuration. In one of these subjects, an elevated LI was associated with normal arterial loops and a few foci of basal cell hyperplasia in an otherwise histologically normal epidermis.

These 2 complementary studies support the concept that the initial stimulus for epidermal hyperplasia in psoriasis resides in the epidermis and not in the microvasculature. We never observed venous capillaries in the papillae of clinically uninvolved psoriatic skin that had a normal LI and was also histologically normal. These studies do not support previous proposals that epidermal hyperplasia may be initiated by a protein rich exudate in underlying papillae resulting from venous capillaries made more permeable by endothelial cell gaps and bridged fenestrations [1,5].

Rather, our studies suggest that the microvasculature plays a modulating role in psoriasis. Morphologically, the therapeutic response to PUVA and Goeckerman therapies appears to be mediated through the microvasculature rather than through any observable antiproliferative effect on the basal cells. The combination of normal capillary loops with a histologically normal epidermis that has an elevated LI suggests that there may be inhibition of endothelial cell proliferation. Such inhibition would prevent basal cells from multiplying to produce a psoriatic lesion by failing to generate an adequate blood supply.

PUVA and Goeckerman therapies are believed to produce beneficial effects in psoriasis through mechanisms related to phototoxicity, but never clearly defined. Although the inhibition of DNA synthesis in epidermal cells has been shown to occur *in vivo* following phototherapy [23,24], this may not be the major or only mechanism by which these modalities are effective. In our studies, the psoriasis began to improve before the LI showed a return toward normal as measured by autoradiographic techniques. Concomitant with the return of the capillary loops toward normal and before the LI began to decrease, the granular layer began to reform in a spotty fashion. Fry and McMinn made the same observation in their studies, in which serial biopsies were taken from psoriatic plaques treated topically with methotrexate, dithranol, fluocinolone acetonide or coal tar coupled with UVB [25]. The earliest morphologic change was a return of the granular layer before the elevated mitotic count showed a significant fall. Goldberg, Cox, and Abel made similar observations in their study of the mitotic index in psoriatic plaques treated by PUVA therapy [26]. The vessels were not studied in these 2 experiments. These observations suggest that an important mechanism may be the correction of a metabolic defect leading to a resumption of normal epidermal growth. Since both UVA and UVB penetrate the dermis to the level of the capillary loops, it is possible that UV irradiation is exerting its beneficial effects by inducing endothelial cells in the venous limbs to be resorbed, thereby shortening the loops. In effect, this would increase the length of the arterial limbs which lack the bridged fenestrations that are believed to represent the large pore system of the capillaries responsible for facilitating the transport of nutrients [27]. Such a change in the morphology of the capillary loop would result in less nutrient support for the ongoing epidermal hyperplasia, and the epidermal proliferation might thus be dampened by a restriction of its energy sources. The mechanism by which UV irradiation exerts these effects is unknown. Both PUVA and Goeckerman therapy require an average of 23 treatments to produce healing of psoriasis. The number of UV interactions with the skin, not the total duration of therapy, appears to be the significant feature of these 2 forms of phototherapy.

An alternate hypothesis for the beneficial effects of UV irradiation might be as follows. UV irradiation produces an epidermal signal that causes the microvasculature to regress which in turn results in normalization of the epidermis. Our data do not exclude such a possibility.

The microvasculature has been implicated in the pathogenesis of psoriasis by previous studies employing light and capillary microscopy in which the capillary loops remained dilated for months after the skin lesions had healed [3,4]. Our studies of healed lesions by electron microscopy, indicate that although dilatation is present, the loops are arterial rather than venous [17]. A relationship between the persistent vasodilatation and possible inhibitory processes on the microvasculature remains to be determined.

The data shown in the Table indicate that the LI fluctuated by 2-fold in 4 patients. Fry and McMinn found the same 2-fold fluctuations in the mitotic counts in their experiments which assessed the therapeutic effects of topically applied agents [25]. In our studies, it is unlikely that UV irradiation is responsible for the fluctuations of LI through epidermal stimulation, since identical phenomena were observed by Fry and McMinn in their studies with topically applied agents. We believe the fluctuating LI indicates that the rate of epidermal proliferation in psoriatic plaques varies and is not constant. Other phenomena suggesting that the activity of psoriatic plaques is variable are the histological observations that layers of orthokeratosis may alternate with layers of parakeratosis vertically, and small areas of parakeratosis may be separated by orthokeratotic zones horizontally in the same section [28].

The epidermis and microvasculature act as a unit once the epidermal hyperplasia of psoriasis begins. Understanding the factors responsible for the shortening of the capillary loops that leads to epidermal normalization and for the inhibition of capillary growth in the presence of an increased LI could lead to other methods of controlling psoriasis.

REFERENCES

1. Kulka JP: Microcirculatory impairment as a factor in inflammatory tissue damage. Ann NY Acad Sci 116:1018–1044, 1964
2. Telner P, Fekete Z: The capillary responses in psoriatic skin. J Invest Dermatol 36:225–230, 1961
3. Lawler JC, Vineyard WR: The effect of treatment on the vascular component of the psoriatic lesion. Arch Dermatol 82:190–193, 1960
4. Gordon M, Johnson WC, Burgoon Jr, CF: Histopathology and histochemistry of psoriasis. II. Dynamics of lesion during treatment. Arch Pathol 84:443–450, 1967
5. Pinkus H, Mehregan AH: The primary histologic lesion of seborrheic dermatitis and psoriasis. J Invest Dermatol 46:109–116, 1966
6. Van Scott EJ, Ekel TM: Kinetics of hyperplasia in psoriasis. Arch Dermatol 88:373–381, 1963
7. Braun-Falco O, Christophers E: Structural aspects of initial psoriatic lesions. Arch Dermatol Forsch 251:95–110, 1974
8. Nyfors A, Rothenborg HW: Cutaneous blood flow in psoriasis measured by [133]Xenon clearance. J Invest Dermatol 54:381–385, 1970
9. DiLorenzo PA, Brown DW, Walker SH, Deern PL, Goltz RW: Technetium—99m pertechnetate disappearance studies in normal and psoriatic skin. J Invest Dermatol 56:39–43, 1971
10. Braverman IM: Electron microscopic studies of the microcirculation in psoriasis. J Invest Dermatol 59:91–98, 1972
11. Braverman IM, Yen A: Microcirculation in psoriatic skin. J Invest Dermatol 62:493–502, 1974
12. Braverman IM, Cohen I, O'Keefe E: Metabolic and ultrastructural studies in a patient with pustular psoriasis (von Zumbusch). Arch Dermatol 105:189–196, 1972
13. Mottaz J, Zelickson AS, Thorne EG, Wachs G: Blood vessel changes in psoriatic skin. Acta Dermatovener (Stockh) 53:195–198, 1973
14. Yen A, Braverman IM: Ultrastructure of the human dermal microcirculation: The horizontal plexus of the papillary dermis. J Invest Dermatol 66:131–142, 1976
15. Braverman IM, Yen A: Ultrastructure of the human dermal micro-

circulation. II. The capillary loops of the dermal papillae. J Invest Dermatol 68:44–52, 1977

16. Higgins JC, Eady RAJ: Human dermal microvasculature: A morphological and enzyme histochemical investigation at the light and electron microscope levels. Microvasc Res (abstr) 80:280, 1979

17. Braverman IM, Yen A: Ultrastructure of the capillary loops in the dermal papillae of psoriasis. J Invest Dermatol 68:53–60, 1977

18. Lachapelle JM, Gillman T: Tritiated thymidine labelling of normal human epidermal cell nuclei. Br J Dermatol 81:603–616, 1969

19. Lachapelle JM: Isotopic labelling of cutaneous structures. Br J Dermatol 81:299–305, 1969

20. de la Brassinne M, Lachapelle JM: Epidermal and dermal cell renewal in pustular psoriatic erythroderma, Psoriasis, Proceedings of the Second International Symposium. Edited by EM Farber, AJ Cox. New York, Yorke Medical Books, 1977, pp 368–370

21. Sholley MM, Cotran RS: Endothelial DNA synthesis in the microvasculature of rat skin during the hair growth cycle. Am J Anat 147:243–254, 1976

22. McLeod WA: Observations of fenestrated capillaries in the human scalp. J Invest Dermatol 55:354–357, 1970

23. Walter JF, Stoughton RB, DeQuoy PR: Suppression of epidermal proliferation by ultraviolet light, coal tar and anthralin. Br J Dermatol 99:89–96, 1978

24. Walter JF, Voorhees JJ, Kelsey WH, Duell EA: Psoralen plus black light inhibits epidermal DNA synthesis. Arch Dermatol 107:861–865, 1973

25. Fry L, McMinn RMH: The action of chemotheapeutic agents on psoriatic epidermis. Br J Dermatol 80:373–383, 1968

26. Goldberg LH, Cox AJ, Abel EA: The mitotic index in psoriatic plaques and their response to PUVA therapy. Br J Dermatol 102: 401–405, 1980

27. Simionescu N, Simionescu M, Palade GE: Permeability of intestinal capillaries. Pathway followed by dextrous and glycogens. J Cell Biol 53:365–392, 1972

28. Cox AJ, Watson W: Histological variations in lesions of psoriasis. Arch Dermatol 106:503–506, 1972

Announcements

The third international conference on the Biology of Skin arranged by the European Society for Comparative Skin Biology will be held at the Jagellonian University, Krakow, Poland, from September 6 to 10, 1982, and will consist of submitted papers and posters on function and structure of skin, review lectures, and long plenary discussions. Details may be had from Professor M. Jakubowski, Department of Comparative Anatomy, Jagellonian University, ul. Krasia, 6, 3o-060 Krakow, Poland.