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QUANTITATIVE STUDIES ON THE REACTIONS OF PSORIATIC EPIDERMIS TO TREATMENT

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Abstract. An image-analysing computer has been used to assess the changes in the length of the dermo-epidermal junction and in the epidermal area in histological sections from psoriatic plaques in groups of patients undergoing various treatment regimes. The changes in these two features closely parallel one another, and measurement of the length of the dermo-epidermal junction may be a relatively simple quantitative method of gauging the course of the disease. Topical fluocinolone acetonide produced a greater improvement than did dithranol or coal tar. Variation in the number of epidermal mitotic figures was not a reliable guide to improvement or otherwise in the psoriatic lesion and reappearance of the granular layer can occur independently of any decrease in mitosis.

Key words: Psoriasis; Epidermis; Image-analysing computer; Quantitative measurements

In psoriatic skin, increased thickness of the epidermis with parakeratosis, increased mitotic activity and an increasingly convoluted dermo-epidermal junction are obvious histological features. Various methods of treatment modify these features to give an appearance more closely resembling normal skin, and although the beneficial effects of any particular regime of treatment are usually obvious to the naked eye as well as being confirmed histologically, few quantitative data (apart from those on mitotic figures and DNA synthesis) are available on the changes during reparative phases of the disease. In our current investigations we are attempting to provide rather more exact data about certain features of the psoriatic process in so far as they are affected by plastic occlusive dressings and various chemotherapeutic agents. In the present paper we record our assessment of the day-to-day changes in the length of the dermo-epidermal junction and in epidermal area, as observed in histological sections, using an image-analysing computer as a convenient measuring device, in (i) a series of patients receiving no treatment of any kind, (ii) a similar series using plastic occlusive dressings alone without any form of drug treatment, (iii) patients who have been treated with fluocinolone acetonide, dithranol, or coal tar. The whole project has been regarded not as a definitive exercise but as a pilot study to unmask any trends that might be profitably explored in greater depth in subsequent studies.

MATERIALS AND METHODS

A total of 254 biopsies formed the basis of this study. One group of 60 biopsies constituted the "untreated series" taken from psoriatic lesions on 11 forearms of 9 patients. The first biopsy from each forearm served as a control (day 0) for that patient and the remainder were taken at periods varying from 1 to 14 days later, giving 11 control and 49 later biopsies. A second group of 67 biopsies formed the "polythene series" and were taken from similar lesions on the forearms of 12 different patients. The first biopsy was the control (day 0) before the beginning of the treatment which consisted of applying plastic (polythene) film to the forearm and changing the film every 24 hours. Most of the biopsies were taken at periods up to 14 days later but 5 were up to 4 weeks later; in this group there were 12 controls and 55 later biopsies.

Three other groups were treated with daily topical applications of either fluocinolone acetonide under plastic occlusive dressings (10 patients giving 10 control or pre-treatment biopsies and 39 later biopsies), dithranol (8 patients, giving 8 control and 44 later biopsies) and coal tar (4 patients giving 4 control and 22 later biopsies). The first biopsy taken the day before the start of the treatment served as each patient's own control with which all later biopsies from that same patient were compared. As in the polythene series, most biopsies were taken during the first fortnight of treatment, though some were from the second fortnight.

The specimens were fixed in 10% formol–saline, sectioned at 7 μm and stained with haematoxylin and eosin. Care was taken to ensure that the blocks of tissue were properly orientated to produce sections at right angles to the skin surface. Sections were examined with a Quantimet 720 image-analysing computer to measure the length of the dermo-epidermal junction (hereafter referred to as

Table I

	Percentage improvement				
	Length	Area	Length+ area	Mitosis	Granular layer
Untreated					
1–14 days	47	53	50	67	24
Polythene					
1–14 days	48	62	55	48	30
1–28 days	52	65	58	49	35
Fluocinolone					
1–14 days	71	71	71	44	65
1–28 days	74	69	72	49	64
Dithranol					
1–14 days	50	67	58	30	57
1–28 days	57	70	64	32	61
Coal tar					
1–14 days	40	60	50	53	53
1–28 days	59	68	64	59	68

the length measurement) and the epidermal area (area measurement) in a unit length of skin surface. For both measurements the unit length of skin was taken as the vertical length of the Quantimet screen using a standard microscope magnification (×125) and the results were recorded as the number of "picture points", taking the mean of 10 readings. The term "epidermal area" as used in this investigation refers to the epidermis excluding the stratum corneum (or excluding the presumptive stratum corneum if this layer was nucleated) and use was made only of those histological sections that allowed a clear definition of this upper limit. This part of the epidermis as defined above, i.e. the epidermis beneath the keratin layer, has become currently known to dermatologists as the EBK.

In each biopsy the mean number of mitotic figures in a unit length of the basal three layers of the epidermis was calculated and as with the length and area measurements the count of the first biopsy from each patient served as that patients's own control with which later counts were compared.

An assessment of the state of the granular layer of the epidermis was made for each biopsy, according to criteria adopted in earlier studies (2):a grading of 0 indicated an absence of granules throughout the histological section of the biopsy, and 1 the presence of granules in less than half of the section, 2 indicating granules in more than half of the section, and 3 a complete granular layer. Again the grades of later biopsies were compared with that of each patient's first.

RESULTS

Each measurement from each patient was compared with its own control (day 0) to establish whether there was any significant difference at the 2% level, and the results on a percentage basis are summarized in Table I. In the untreated series 23 of the 49 lengths (47%) were significantly shorter than control values, with 26 higher or unchanged. Similarly 26 of the 49 areas (53%) were smaller than the control value, with 23 greater or unchanged. Thus out of a total of 98 measurements, 49 were smaller than their control values (i.e. 50% improved) and 49 unchanged or greater. In this group of 49 biopsies there were 5 in which the changes in length and area did not parallel one another.

In the polythene series, the values for lengths in the 50 biopsies of the first 2 weeks compared with their 12 control values were 24 smaller and 26 unchanged or greater (48% improved): for areas, 31 smaller with 19 unchanged or greater (62% improved). Thus for the 100 measurements after a fortnight of polythene occlusion, 55% were improved compared with control values.

When the additional biopsies from polythene patients after 3 or 4 weeks are taken into account, the percentage improvements in length and area rose to 52 and 65 respectively, so giving a combined mean of 58%. In this whole "polythene series" of 55 biopsies there were 6 in which the changes in length and area did not parallel one another.

In the patients treated with fluocinolone acetonide for 2 weeks, 24 out of 34 lengths and an identical number of areas were improved (71%) compared with control values. When third and fourth week biopsies were included, the improvements in

length and area were 74% and 69% respectively (mean 72%). In 30 biopsies in the dithranol series, 15 lengths (50%) and 20 areas (67%) were improved, the figures rising to 57% and 70% when biopsies up to a month were included. In the coal tar series, the length and area improvements were 40% and 60% (mean 50%) up to a fortnight of treatment and 59% and 68% after a month (mean 64%).

Among the 105 biopsies of the fluocinolone, dithranol and coal tar series, there were only 3 where the increases or decreases in length and area measurement did not parallel one another.

The counts of mitotic figures in all patients of each group were compared with their own controls, and note taken of whether any increases or decreases were accompanied by similar changes in the lengths and areas. Out of 209 biopsies there were 37 (17%) in which the mitotic count changes did not correspond to changes in length or area, or both. When the counts in the five groups were compared with their own controls the percentage improvements were as follows: untreated 67, polythene 49, fluocinolone 49, dithranol 32, and coal tar 59.

When the assessments of the granular layer were compared with their control values, the percentage improvements were: untreated 24, polythene 35, fluocinolone 64, dithranol 61, coal tar 68.

DISCUSSION

All types of measurement indicate that in psoriasis there is a continual change in the epidermis from day to day. In the present untreated group 50% of length and area measurements showed improvement compared with their own control values, with 50% unchanged or worse. In the polythene series over a similar period of 14 days, 55% were improved, which may not be a very impressive difference, but in the groups undergoing specific topical therapy, fluocinolone acetonide produced the greatest improvement (71%) compared with dithranol (58%) and coal tar (50%). This is in conformity with the well-known clinical observation that topical steroids clear psoriasis quicker than do other agents, and provide a quantitative basis for that observation. However, an even more striking suggestion from the present study is that in the second fortnight after the beginning of treatment, all agents—and even polythene alone—were more effective than in the first 2 weeks. In view of the relatively small numbers of biopsies that were available in the third and fourth weeks, a more extended series should be undertaken during this and even later periods.

Casual observation through the microscope suggests that in psoriatic skin the thickening of the epidermis is correlated with an increasingly convoluted dermo-epidermal junction. In the current series of measurements a change in one has almost invariably, but not completely, been associated with a similar change in the other; in the untreated and polythene groups 11 out of 104 were not correlated, and with specific treatments only 3 out of 105. Of course, in a multilayered epithelium where it must obviously taken time for a change in one feature to affect another, an exact correlation need not be expected, and a biopsy at any particular time may "capture" the skin in a transition phase. It would certainly appear that, especially when under the influence of chemotherapeutic agents, changes in the length of the dermo-epidermal junction reflect changes in epidermal area—at least as regards the EBK.

As the surface length of the epidermis is not altered, the increase in area is accommodated by alteration in the length of the dermo-epidermal junction, which seems capable of increasing or decreasing to a considerable degree from day to day. Measurement of the length of this convoluted line may be a relatively simple method of assessing quantitatively the efficacy of a treatment regime.

Increases in epidermal area may be due in part to a greater number of cells in the epidermis, particularly in the germinative cell population, and in part to an increase in cell size (2). The speed of decrease in area that occurs in some patients particularly during treatment with topical steoids suggests that the change in area is due to a decrease in cell size.

Many studies have shown that the number of mitoses in psoriatic epidermis falls during spontaneous relapse and with effective treatments, and even plastic occlusive dressings alone may cause a slight fall (1). In the present study, epidermal mitotic activity (as judged by the counting of mitotic figures) has not always closely followed rises or falls in the length and area measurements in any of the groups. In a total of 209 biopsies (excluding the day 0 controls) there were 37 instances (17%) where the mitotic count did not mirror the behaviour of either the length or area measurements or both. Again, this may simply be a reflection of

the time taken for the effects of mitosis to make themselves felt. Of course it would be very nice to know the changes that occur in the total epidermal cell population, but the phenomenon of keratinization with its accompanying loss of nuclei makes accurate cell counts impossible. The fact that 67% of serial mitotic counts in patients receiving no treatment of any kind were lower than their own initial counts was an unexpected results, perhaps indicating the capriciousness of cell division in this disease and the difficulty of drawing valid conclusions from such counts.

On the other hand, improvements in the granular layer were clearly brought about by all three topical applications (61 to 68% compared with 24% in the untreated series) and even polythene alone may have some beneficial effect (35% improved), as previously shown by Fry, Almeyda & McMinn (1).

The results of this study also suggest that the primary fault may not lie in increased cell division. The reformation of the granular layer accompanied by changes in area are features associated with the healing of psoriasis rather than with a fall in the amount of mitotic activity. It is possible that the biochemical changes responsible for psoriasis are not acting primarily on cell division but on other cellular functions such as keratinization, with changes in mitosis being of a secondary nature.

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