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THE BIOLOGY OF PSORIASIS

An experimental study of the Koebner phenomenon

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The Koebner phenomenon, which is the development of isomorphic pathologic lesions in the traumatized uninvolved skin of patients who have cutaneous disease, was first observed in patients with psoriasis by Hebra, as reported by Wutzdorff (27) and Köbner (13) many years ago. Although it also has been described in patients with other dermatoses, especially lichen planus, lichen nitidus and Darier's disease, the Koebner phenomenon is seen most frequently in the presence of psoriasis. The clinical and histopathologic characteristics of the lesions induced traumatically are always identical to those which arise spontaneously. This conveniently reproducible clinical model, which may be observed and sampled directly, has encouraged many investigators to study the pathogenetic mechanisms in psoriasis, and several important observations have been made.

Bizzozero (1) suggested that psoriasis begins in the dermis because the Koebner reaction occurs only after the papillary body of the dermis has been damaged. Levi (15) produced positive Koebner lesions in seven of 26 patients who had psoriasis, and he emphasized vascular injury as the principal factor. Telner and Fekete (25) used the term "subclinical Koebner phenomenon" to describe the "cotton-ball" capillaries seen equally well in the apparently normal skin or in the lesions of patients with psoriasis. Kúta and Neumann (14) believed that the initial psoriatic papule originates in the follicular ostium. Nardelli (20) was able to produce the Koebner reaction by scarifying the epidermis without causing capillary hemorrhage. Because suction-induced petechiae in the normal skin of psoriatic patients do not cause psoriasis, Reinertson (23) also concluded that hemorrhage is not the primary event; but he could not rule out dermal inflammation as an important factor. Most recently Farber *et al.* (6) restudied the factors which produce and retard the Koebner reaction in psoriasis. They observed that the extent of trauma is important because scraping the epidermis until bleeding points appeared regularly produced psoriatic lesions, whereas lesions developed in a much smaller number of patients after dermal knife injury.

Our current studies were designed to determine the consistency of the relationship of the Koebner phenomenon to specific types of trauma and reproducibility of the phenomenon in patients with psoriasis, and to make additional observations on blocking agents for this reaction. We especially wished to study to evolving psoriatic lesion in the Koebner reaction and, in this manner, to evaluate the relative importance of the epidermal and dermal changes in psoriasis.

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Methods

Twenty-one patients with psoriasis, of whom 11 were females and 10 were males, were chosen at random for this study. Ages ranged from 17 to 58 years; average duration of the disease prior to the commencement of the study was 8 years, with a range of 2 to 30 years. Thirteen patients had widespread psoriasis, whereas the remaining 8 exhibited only localized plaques. Previous therapy, which had consisted of the use of emollients, corticosteroid creams, tar ointments, occlusive dressings and ultraviolet light, was discontinued 2 weeks prior to the onset of the study. Three patients had had Koebner reactions clinically in the past.

The investigation was divided into three parts: (1) the effect of various physical and chemical stimuli on the Koebner reaction, (2) the histopathologic aspects of the Koebner reaction, and (3) the histochemical aspects of the Koebner reaction.

Effects of Various Physical and Chemical Stimuli on the Koebner Reaction

Experiments were designed to deliver various physical and chemical insults to the uninvolved skin in an effort to induce the isomorphic response and, in turn, to permit study of the inhibition of this response by various physical and chemical agents. The scapular areas bilaterally were used as test sites on all patients, and were evaluated every other day for 21 days. Since we were limited to the number of test sites available, we chose to test 14 sites which were subjected to the following:

1. *Physical stimuli.*—These consisted of:

a. Scraping. A circular area 2 cm in diameter was scraped with a No. 15 (Bard-Parker) blade until minute bleeding points were seen. The lesion was left uncovered.

b. Scraping before the application of cold. Scraping was performed in the above manner and ice was then applied to the scraped area for 30 minutes, and reapplied on the third and fifth days. When ice was applied skin temperature decreased, on the average, from 33 to 12 degrees C, as measured by a Yellow Springs telethermometer with skin thermistors.

c. Scraping before the application of heat. Similar to scraping before the use of cold, except that heat was delivered to the area by a 150-watt tungsten light bulb which increased the skin temperature on the average from 33 to 38 C.

d. Freezing. Frigiderm[1] in an aerosol can was sprayed for 20 seconds to the test site 3 inches from a cardboard shield pierced with an aperture 2.5 cm in diameter.

e. Suction. Suction was applied to a skin area by means of a suction cup similar to that used in making electrocardiograms. Cambridge electrode jelly was used to assure adequate contact and suction was applied continuously for 15 minutes, at the end of which time numerous petechiae were evident.

f. Ultraviolet light. All patients were tested for a minimal erythema dose (MED) of ultraviolet light applied with the hot quartz lamp. A delayed erythema dose (DED), or eight times the MED, also was delivered to the test site on day 3.

2. *Chemical stimuli*

a. One-half cubic centimeter of 0.9 % sodium chloride injected intradermally before scraping as a control.

b. One-half cubic centimeter of 1 % lidocaine injected intradermally before scraping.

c. One-half cubic centimeter of 0.5 % colchicine injected intradermally before scraping.

d. Scraping plus the topical application of 0.5 % colchicine on the first, third and fifth days.

e. One-half cubic centimeter of 0.1 % methotrexate injected intradermally before scraping.

f. Scraping plus the topical application of

[1] Frigiderm is fluro-ethyl (75 % dichlorotetrafluoroethane and 25 % ethylchloride).

0.1 % methotrexate on the first, third and fifth days.

g. Scraping plus the topical application of 0.03 M amytal in dimethyl sulfoxide on the first, third and fifth days.

h. Scraping plus the use of antimycin A (100 µg/ml) in dimethyl sulfoxide on the first, third and fifth days.

The Histopathologic and Histochemical Aspects of the Developing Koebner Phenomenom

The histopathologic aspects of the developing Koebner phenomenon were studied by comparison of the results of examination of 22 specimens taken for biopsy with a 4-mm Keyes punch from eight patients. Of 16 specimens obtained from sites of an isomorphic response, four were taken from each of three patients at appropriate intervals, and two were taken from each of two other patients. Specimens, taken after the intradermal injection of 0.5 cc of a 1 % solution of lidocaine, were fixed in a buffered 10 % solution of formalin and were stained with hematoxylin and eosin. The tissue was obtained at 4-to-6-day intervals in the positive reactors, so that the developing Koebner reaction could be studied sequentially. Six biopsies also were done to demonstrate the reaction when clinical psoriasis did not develop at the test sites.

The histochemical aspects of the Koebner phenomenon also were studied in three of the patients in terms of a spectrum of oxidative and hydrolytic enzymes. Specimens for biopsy taken 1, 5, 15 and 22 days after the inciting stimulus were divided into two portions. One was placed in a buffered 10 % solution of formalin for sectioning and routine staining; the other portion was frozen, sectioned on a cryostat and treated according to the following procedures:

1. Method for succinic dehydrogenase (SD) (19). Substrate: Sodium succinate. Time of incubation: 3 hours at 37 C. Postfixation: 10 % solution of formol and saline.
2. Method for indoxyl esterase (IE) (22). Substrate: Five bromoindoxylacetate. Prefixation: Calcium formalin. Time of incubation: 3 hours at 37 C.
3. Method for acid phosphatase (7). Substrate: Sodium beta glycerol phosphate. Prefixation: 5 % solution of neutral formalin. Time of incubation: 45 minutes at 37 C.
4. Method for alkaline phosphatase (8). Substrate: Sodium beta glycerol phosphate. Prefixation: As for acid phosphatase. Time of incubation: 1 hour at 37 C.
5. Method for aminopeptidase (18). Substrate: L-leucyl-4-methoxy-2 naphthethylamide. Prefixation: Acetone plus chloroform. Time of incubation: 2 hours at 37 C.

Results

Only the usual consequences of inflammation, such as formation of crusts and erythema, were seen during the first 14 days after the test trauma (Fig. 1). All scraped areas initially exhibited a glazed surface with prominent papillary bodies. Superficial crusting and erythema were noted on the third day, at which time heat, ice and all topical chemical agents were reapplied. On the fifth day the two sites at which Frigiderm and colchicine had been applied topically showed a deeper necrosis. Much of the local inflammation was beginning to subside on the seventh day and the attachment of the superficial eschar was loosening. The test sites usually were healed by the ninth day in patients who did not react (those in whom a Koebner reaction subsequently did not develop) except for small areas of hypopigmentation and hyperpigmentation.

In five patients, or 24 % of the series, clinical psoriasis developed at all the sites tested except when the testing agent was suction, which merely produced a petechial reaction. Resolution of the traumatic inflammation in these subjects revealed small, erythematous, nonscaling papules (Fig. 2). All the numerous sites of injury in these patients had essentially the same appearance. Furthermore, all lesions in those who reacted positively exhibited the character-

istic psoriatic marginated erythema as the traumatic inflammation faded.

The reaction time, which we have defined as "the interval from the skin injury to that of a clinical diagnostic isomorphic response", varied from 12 to 20 days (Table 1). In each person lesions were produced at all sites simultaneously. No acceleration or delay in the Koebner reaction was caused by any of the chemical or physical methods used.

Table 1. *Reaction time (interval from skin injury to that of clinical diagnostic isomorphic response): 5 patients*

Patient	Reaction time, days
1	12
2	22
3	14
4	16
5	20

Patients who reacted negatively (psoriatic patients in whom the Koebner phenomenon did not appear) showed no histologic evidence of psoriasis. First were the early (3 to 5 days) histopathologic changes of capillary dilatation, mild perivascular inflammation in the upper portion of the dermis and an overlying crust of serum and acute inflammatory cells, which were compatible with normal inflammatory responses (Fig. 3 A). Biopsies done at 10 to 12 days from patients who did not react showed a normal-to-acanthotic epidermis, usually with loss of the rete pegs, slight proliferation of capillaries, and a mild perivascular infiltrate of neutrophils and lymphocytes in the subepidermal zone (Fig. 3 B). At 18 to 20 days, the clinical appearance was that of a flat, slightly atrophic, hyperpigmented macule with some areas of depigmentation, while the histologic picture was that of mild hyperkeratosis without parakeratosis, mild atrophy to slight acanthosis of the epidermis, which was flattened, a mild, uniformly scattered infiltrate in the upper part of the dermis of mononuclear cells and fibroblasts, and slight capillary proliferation (Fig. 3 C).

Histopathologic findings at the sites of the isomorphic responses were similar to those made in the patients who did not react in the early stages. Definite changes distinguishable from those observed in patients who did not react usually were readily seen by the fifteenth day, although they appeared as early as the twelfth day in one case or as late as the twenty-second day in another. Figure 4 depicts a representative sequential series of four specimens taken for biopsy in the developing psoriasis of the Koebner phenomenon. The late development of significant parakeratosis, marked capillary tortuosity and suprapapillary thinning is striking. Staining for elastic tissue, acid mucopolysaccharides and mast cells did not disclose unusual changes.

Results of our studies of the enzymic histochemistry of the Koebner reaction generally were predictable. They reflected an increased metabolic activity of the tissues. Succinic dehydrogenase was most prominent in the basal layer of the epidermis; it diminished progressively toward the parakeratotic horny layer, where it was absent. There was also intense staining of the enzyme localized in the cells of the inflammatory infiltrate in the upper part of the dermis. There appeared to be no significant differences of SD content in the specimens taken for biopsy at sequential intervals except for the greater amounts seen in cells of the inflammatory infiltrate.

Indoxyl esterase was present in moderate amounts on the first day after trauma in the remaining basal buds of epidermal cells. On the fifth day the reaction as presented by the eschar itself was moderately positive, but in the basal layer the reaction was definitely less positive than on the first day. By the tenth day the reaction was most intense in the upper layers of the acanthotic epidermis. On the eighteenth day striking esterase activity was present in the transitional and parakeratotic horny layers. Results of staining for acid phosphatase were similar to those of staining for indoxyl esterase, in that moderate activity in the few basal epidermal cells remained on the first day, but the reaction was most pronounced in the parakeratotic layer and granular layer of the epidermis on the eighteenth day.

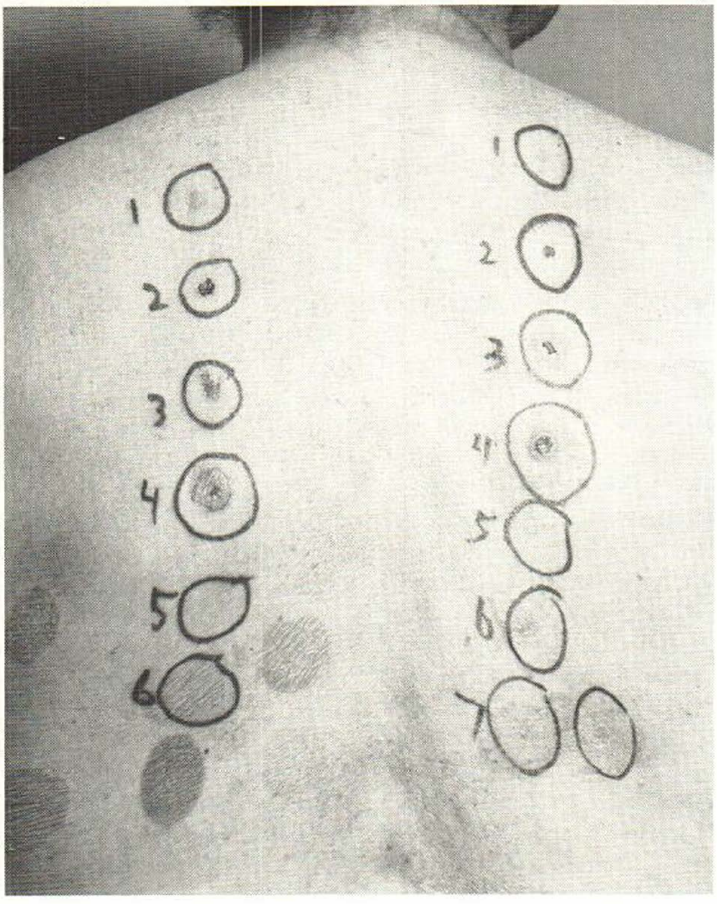

Fig. 1. Results of test trauma in a negative reactor on the sixth day. More necrosis is noted at the site of application of Frigiderm in the fourth circle on the left and at the site of the intradermal and topical application of colchicine in the third and fourth tests on the right.

Alkaline phosphatase was localized to only a few scattered capillaries in the upper part of the dermis on the first day. By the tenth day the capillaries were more elongated and showed marked alkaline-phosphatase reactivity. Those capillaries which extended to the uppermost portion of the dermal papillae showed still more intense AP activity by the eighteenth day.

Results of studies for leucine aminopeptidase were intensely positive in the debris of serum and inflammatory cells overlying the dermis during the crusted phase of the Koebner phenomenon, but the enzyme was not especially prominent in the border zone. In the fully developed psoriatic lesion the activity was localized to the border zone of the epidermis and dermis, but in greater amounts than in normal skin.

Comment

There seems to be no question that the Koebner phenomenon actually is true psoriasis because the clinical and histopathologic features of a fully developed lesion always reveal classic psoriasis. The excitant stimulus usually is mechanical trauma to the skin, but it also may be chemical. We have confirmed the observation that the stimulus must cause traumatic alteration of the epidermis and an associated inflamma-

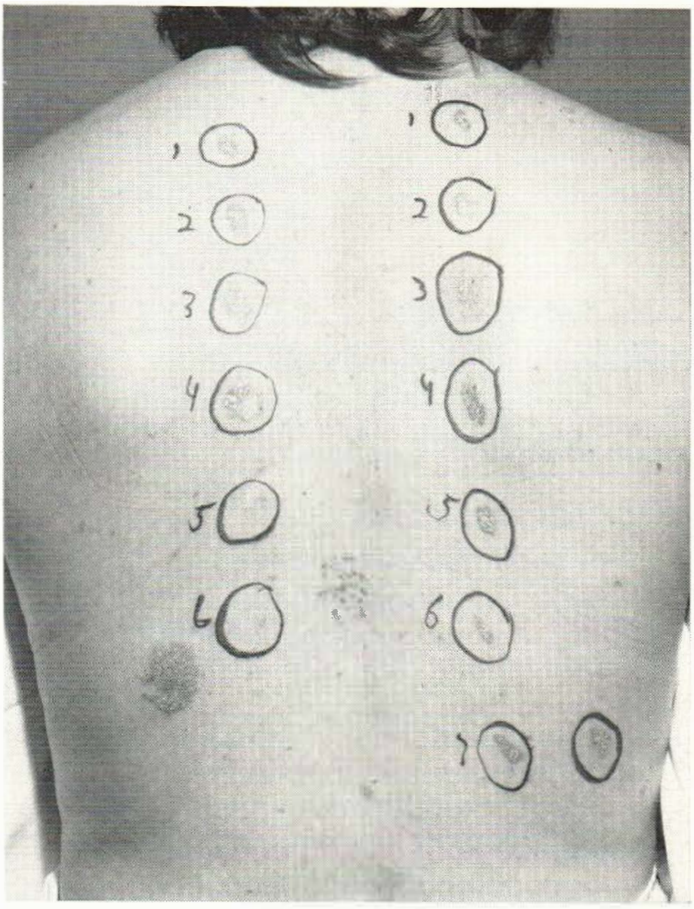

Fig. 2. Results of test trauma in a positive reactor on the twentieth day. A negative reaction is seen in the fifth site on the left, where suction was applied. The delayed erythema dose of ultraviolet light was applied below and laterally to the left of the sixth circle, where only a minimal erythema dose was given.

tory response. Capillary hemorrhage alone is not a sufficient stimulus.

In a select group of 25 psoriatic patients with the active form of the disease or a history of a Koebner phenomenon or both, Eddy and associates (5) were able to elicit positive reactions in 74 % of the patients by scraping sufficiently to produce minute bleeding points. Farber and his colleagues (6) found the incidence of positive reactions to be 44 % in a random selection of 100 psoriatic persons among whom scraping to produce minute bleeding points also was employed. Of the 21 patients in our series chosen at random, only five (24 %) exhibited positive Koebner reactions. All positive reactions were seen in the group of 13 patients who had widespread psoriasis, whereas isomorphic responses did not develop in any of eight patients who had mild localized psoriasis. This suggests again that whether or not a Koebner reaction will develop is dependent on the severity or stage of the psoriasis. A few instances have been reported (4, 11, 17, 24) in which the Koebner reaction occurred in patients with stable localized psoriasis, so that additional testing of larger numbers of patients seems indicated for confirmation of our results. It is conceivable that persons who react positively are a unique group who have distinctive epidermal or dermal responses differing from those of persons who do not react. It also

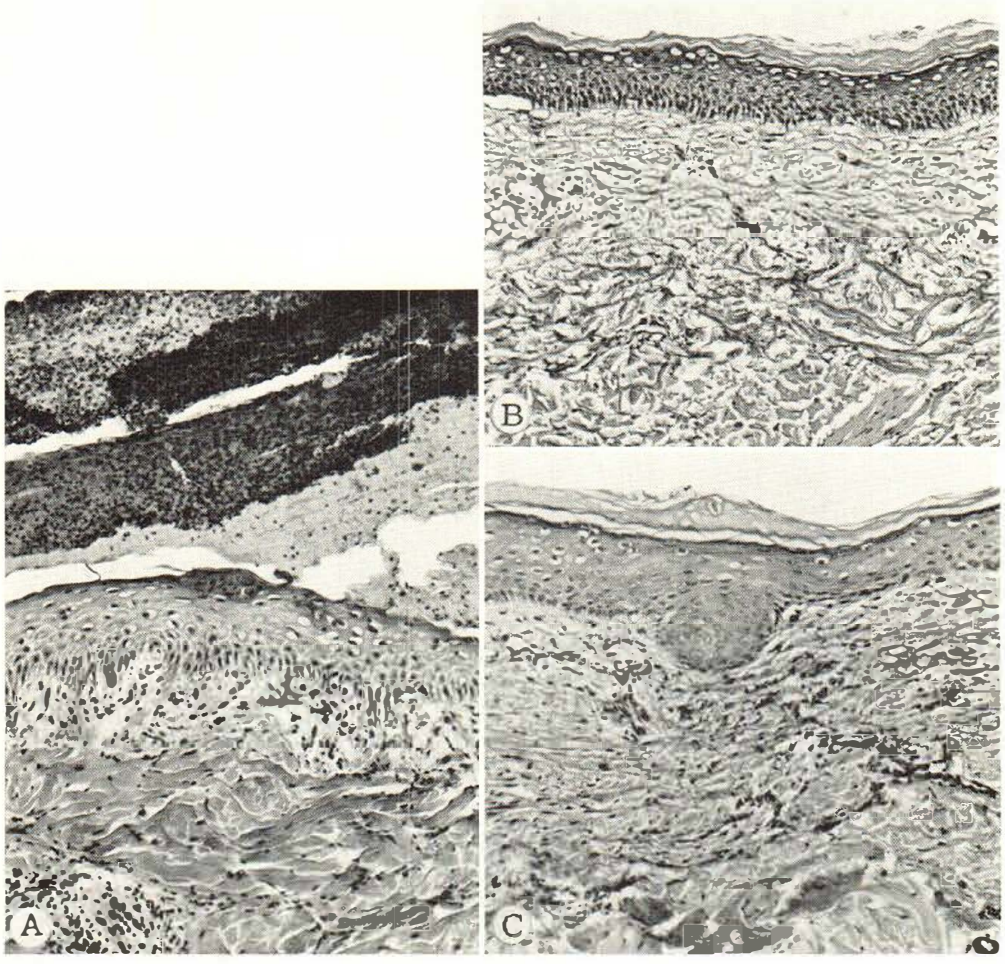

Fig. 3. Sections of skin taken for biopsy from test sites in negative reactors at (A) 5 days (hematoxylin and eosin; ×115); (B) 12 days (hematoxylin and eosin; ×120) and (C) 20 days (hematoxylin and eosin; ×120).

seems logical that positive reactivity may be lost during the recovery phase of psoriasis. Koebner reactions have been postulated to occur more frequently in the winter than in the summer (20). Our studies were done in the fall and winter. Our clinical impression is that the Koebner reaction usually is seen only in the ascending phase of the eruption and that similar reactivity as a rule is not present during resolution.

Eddy *et al.* (5) observed reaction times of 2 to 3 weeks, similar to those which we recorded in our study. The reaction time is likely to be a unique characteristic peculiar to the patient's skin, and it could reflect the degree of sensitivity for the development of isomorphic responses. It should be remembered, also, that regional differences in cutaneous reactivity may be present in the same patient, but we have no experimental data at present to support this possibility.

The effect of treatment on the development of the Koebner reaction is not known, but it might provide important pathogenetic data. Moreover, knowledge of the factors which cause inhibition or acceleration of the Koebner reaction undoubtedly would give new insight into the pathogenesis and

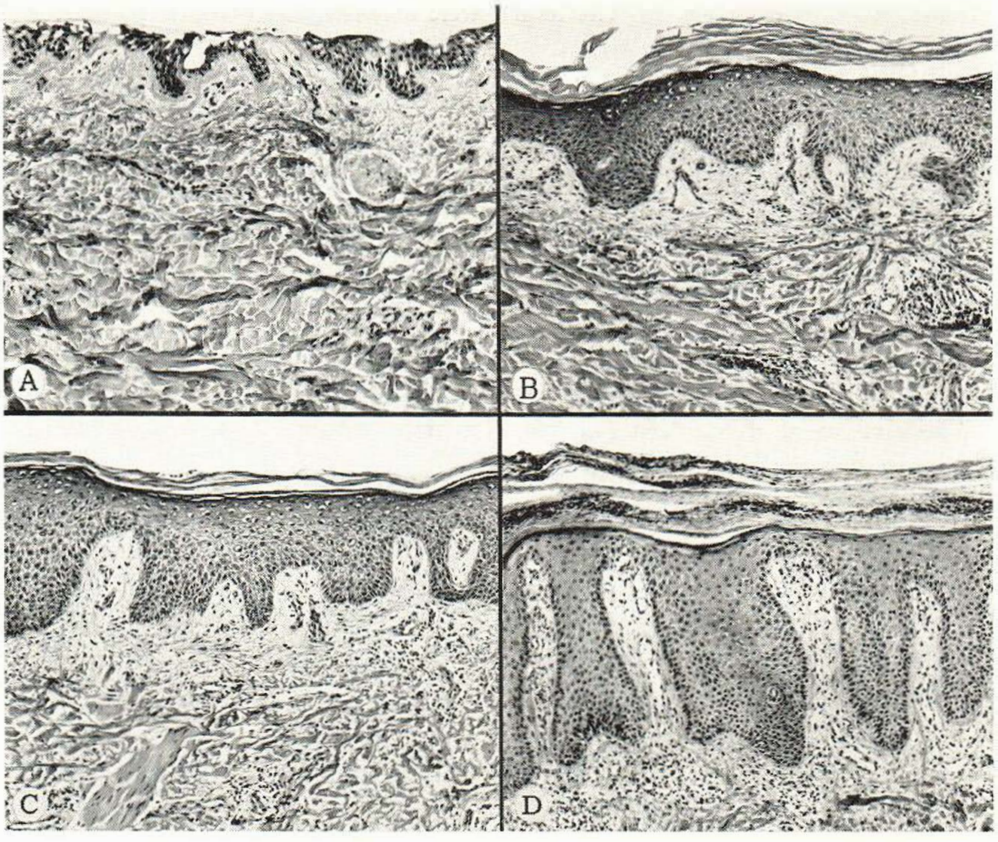

Fig. 4. Histopathologic aspects of the Koebner phenomenon.

A, First day: the test site immediately after scraping (hematoxylin and eosin; reduced from ×110.)

B, Ninth day: hyperkeratosis without parakeratosis, an irregular acanthosis, loss of papillary bodies and edema of the upper part of the dermis with dilatation and an increase in the number of capillaries. A slight perivascular infiltrate of lymphocytes and reticular cells also is present (hematoxylin and eosin; reduced from ×75).

C, Fifteenth day: slight spotty parakeratosis, irregular acanthosis, beginning formation of the papillary bodies and dilatation and slight tortuosity of the upper dermal vessels, reaching to the uppermost portion of the new papillary bodies. Leukocytic infiltration of the epidermis and suprapapillary thinning are absent (hematoxylin and eosin; reduced from ×75).

D, Twenty-second day: full development of the psoriatic lesion. There are present lamellar parakeratosis, Munro microabscesses, elongation and clubbing of the rete pegs, suprapapillary thinning of the epidermis and excellent formation of papillary bodies with dilatation and tortuosity of the capillaries. A moderate perivascular infiltrate of lymphocytes is present in the dermis (hematoxylin and eosin; reduced from ×75).

treatment of psoriasis. Eddy and his associates (5) believed that the topical application of colchicine is psoriasigenic and that the intradermal injection of lidocaine appeared to inhibit the reaction, an action which they postulated was caused by the local vasoconstriction induced by lidocaine. Van Scott and Reinertson (26) applied colchicine with occlusion on psoriatic plaques for 18 to 24 hours, and noted partial clearing after 7 days. Similar topical applications of methotrexate were ineffective. Our test sites treated with lidocaine, methotrexate or colchicine all showed positive reactions identical to those seen in the control sites. The positive isomorphic response could not

be inhibited by such treatment. The local application of cold or heat also had no effect in inhibiting or accelerating the reaction.

That the patients exhibited an "all-or-none" response was significant. If a patient reacted to one stimulus, he reacted to all of them. Conversely, lack of a positive response to a known Koebner-inducing stimulus predicted failure of the other stimuli in the series. Thus, the patients could be divided into positive and negative reactors. Thirteen of the 14 test sites exhibited psoriasis of equal development and, although the reaction times varied in the five positive reactors, test sites in each patient manifested a simultaneous onset of psoriatic lesions. Colchicine and Frigiderm caused more tissue necrosis than did the other physical and chemical agents, but did not alter the temporal or morphologic expression of the psoriatic process. We therefore believe that the type or amount of trauma is not vital in the pathogenesis of the Koebner phenomenon, but rather that the important determining factor is inherent in the patient's skin itself.

Eddy and associates (5) found microscopic and macroscopic agreement in their Koebner reactors in all but two instances in a total of 28 histologic sections taken from a select group of 25 patients who had psoriasis. Madden (16) wrote that the uninvolved portion of skin participated in the psoriatic process because of the leukocytic infiltrate, capillary dilatation and lengthening of the rete pegs and papillary bodies which he observed in the uninvolved skin of patients who had psoriasis. Gordon and Johnson (9) found minor histologic abnormalities in the clinically normal-appearing skin of patients with psoriasis. Our studies, which were done immediately after scraping away the epidermis, did not reveal significant alterations between the normal skin of reactors or nonreactors.

Our microscopic findings substantiated the view that patients vary in their individual clinical-reaction times. Therefore, histopathologic samples cannot be compared on a day-for-day basis. However, it was evident that the same histologic events were occurring in all positive reactors. The earlier significant changes of hyperkeratosis and acanthosis appeared to overshadow the dermal alterations which, except for dermal edema and slight capillary dilatation, were seen after the onset of epidermal change. The histopathologic changes seen in the negative reactors were indistinguishable from those of the positive reactors until after exfoliation of the crust had taken place and possibly a few days longer. After the crusted phase, the positive reactors continued to show proliferation and psoriasis developed, whereas the negative reactors healed. Burks and Montgomery (3) wrote that the earliest changes in a new papule of psoriasis were mild hyperkeratosis, acanthosis and edema of the papillary tips which had an increased number of fibroblasts. This is in agreement with our findings and we interpret these changes as favoring the notion of a primary epidermal origin of the clinical lesion of psoriasis.

The sequential histochemical findings of the Koebner phenomenon in patients with psoriasis are those of evolving psoriasis. The epidermis in a fully developed psoriatic lesion is characterized by an increase in the enzymes of the glycolytic and citric-acid cycle which are not specific for psoriasis but, instead, are increased in any acanthotic epidermis. The localization of indoxyl esterase and acid phosphatase at or near the transitional zone was normal except for the greater intensity of the staining probably related to the increased rate of cell turnover.

The dermis in psoriasis is characterized by marked enzymatic staining of alkaline phosphatase and aminopeptidase, an action which probably is caused by the dilated and tortuous capillaries and the fibroblasts in the papillary bodies. Alkaline-phosphatase staining clearly demonstrated the evolution of normal capillaries, present at the time of scraping, to elongated vessels characteristic of psoriasis. Braun-Falco (2) reported similar histochemical changes in the psoriatic dermis, consisting primarily of increased aminopeptidase and alkaline-phosphatase activity.

Neumann and Kúta (21) thought that the adnexa of the skin might be important in the pathogenesis of psoriasis because of the initial changes in the succinic-dehydrogenase activity in these areas. Hashimoto *et al.* (10) found increased concentrations of dehydrogenases in all layers of the epidermis and wrote that the intensity of the dehydrogenases was proportionate to the degree of the acanthosis of the epidermis. Jones *et al.* (12) found increased succinic-dehydrogenase activity in the lower third and basal layer of the epidermis in psoriatic lesions. Our studies showed localization of the succinic-dehydrogenase in the basal layer and in the adnexa. There was no significant succinic-dehydrogenase staining in the upper two-third portions of the epidermis. Braun-Falco (2) speculated that the increase in succinic dehydrogenase in psoriatic skin might possibly be related to the increased utilization of oxygen because of the correlation between the oxygen consumption of the tissues and the intensity of the formazan deposits. We would agree that the increased activity, as well as the localization of the enzyme to the basal layers of the epidermis, is not specific and that it is related only to the degree of acanthosis and increased metabolic activity which characterizes the skin of patients who have psoriasis or other proliferative disturbances.

SUMMARY

An experimental, clinical, histopathologic and histochemical study of the Koebner phenomenon was made in a group of 21 patients who had psoriasis. The Koebner phenomenon, which was seen only in patients with widespread psoriasis, was produced in 24 % of the patients tested. The reaction time—which was the time from epidermal injury to the first clinically detectable psoriatic lesion—was approximately 2 to 3 weeks. Identical lesions of psoriasis occurred simultaneously in all test sites of positive reactors, regardless of the initiating trauma, so long as epidermal injury had been incurred. Enough suction to produce petechiae always failed to induce a Koebner reaction. The intradermal injection or topical application of lidocaine, amytal, antimycin A, colchicine or methotrexate did not prevent or adversely affect, in any way, the development of the Koebner reaction nor did the transient application of physical modalities, such as cold and heat.

The histologic progression of the Koebner phenomenon suggests that psoriasis is an epidermal process which is dependent on the tortuous and dilated state of dermal capillaries. The histopathologic aspects of the developing Koebner reaction favor the assumption of an epidermal genesis of psoriasis because of the early development of acanthosis, hyperkeratosis and spotty parakeratosis. The formation of papillary bodies and dilatation and tortuosity of the capillaries occur after the epidermis has begun to proliferate. The histochemical nature of the psoriatic epidermis is not specific; it probably is related to the degree of acanthosis plus the rapid rate of cell division and protein synthesis.

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