

ABNORMAL CUTANEOUS REACTIONS IN DERMATITIS HERPETIFORMIS

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Abstract. In 94% of the patients with dermatitis herpetiformis, a locally applied ointment with an ester of nicotinic acid (Trafuril) induced an abnormal reaction with erythema, edema, papules, and often vesicles. The appearance of the reaction to Trafuril is similar to DH lesions. It differs markedly from the reactions to iodide where, as a rule, only one large blister results. The reaction is most pronounced 12-24 hours after application of Trafuril. The reactivity is strongest in the predilection areas for dermatitis herpetiformis. Strongly increased reactivity to Trafuril in DH is induced by pretreatment with streptokinase, streptokinase-streptodornase, or urokinase. Diminished reactivity to Trafuril is seen after pretreatment with injections of Compound 48/80, tranexamic acid, cromoglycate, or application of fluocinolone-acetonide, as well as after stroking the skin.

Key words: Cutaneous reactions; Dermatitis herpetiformis; Nicotinic acid ester; Iodide; Streptokinase; Urokinase

In recent years, interest in dermatitis herpetiformis (DH) has been stimulated both by the finding of a small bowel enteropathy in this disorder and a probable gluten hypersensitivity (2, 3, 4, 5, 9, 18). A number of new observations concerning the immunology of DH have also been reported (2). The relevance of all these findings is not yet entirely clear, however (19).

Few studies have been made on skin reactivity in DH. We have previously reported that patients with DH usually have abnormal reactions to a tetrahydrofurfuryl ester of nicotinic acid in an ointment base, Trafuril® (Ciba, Basle, Switzerland) (7). The appearance of this reaction, which is fully developed 24 hours after application, closely resembles the lesions of DH. This simple test may provide a valuable diagnostic tool for DH and be a useful model for studies of DH lesions. Various aspects of the cutaneous reactions to Trafuril and other vasoactive substances in patients with DH are the basis for this paper.

PATIENTS AND METHODS

Patients

Fifty-four patients (40 men and 14 women) who were between 22 and 86 years of age, with clinical findings and a histology considered typical for DH. The duration of their disease varied between a few months and 40 years. All of them have had a prompt response to dapsone. The ordinary dose of dapsone varied between 0.1 and 0.2 g/week and 0.2 to 0.4 g/day. None of the patients was on a gluten-free diet and no intestinal biopsies were taken from any of the patients.

Controls

Twenty-one healthy subjects between the ages of 20 and 44 years served as controls for the reaction to Trafuril. Patients with minor skin disorders served as controls for tests with other vasoactive substances.

The "Trafuril Test"

Trafuril (5% tetrahydrofurfuryl ester of nicotinic acid in an ointment base) in amounts of 30-35 mg was applied with a syringe to a 9 cm² area of normal-appearing skin. Application of the ointment was made on both the volar side of the forearm and the dorsal side just distal to the elbow and was left on for 10 min without a covering. It was then gently removed with a dry cotton swab and the area cleaned with 60% ethyl alcohol. The reaction was observed after 20 min and 24 hours, and, in a large number of patients, observations were also made at 5 and 8 hours.

The ordinary dose of dapsone was maintained during the first test procedure. In a number of patients, the tests were made before and after changes in the dapsone dose and, in two new cases, tests were made both before and after initiating the dapsone treatment.

In order to compare the sensitivity of different areas of the body, 7 patients had Trafuril applied on the upper back in the shoulder region, the lateral side of the mid-trunk, the waist, the gluteal areas, the upper ventral side of the thigh, and below the knee.

Punch biopsies from Trafuril reaction areas were taken from 6 patients 24 hours after application.

Tests with other vasoactive compounds

1. Nine ointments and liniments with initial effects similar to those induced by Trafuril were applied to the skin of the

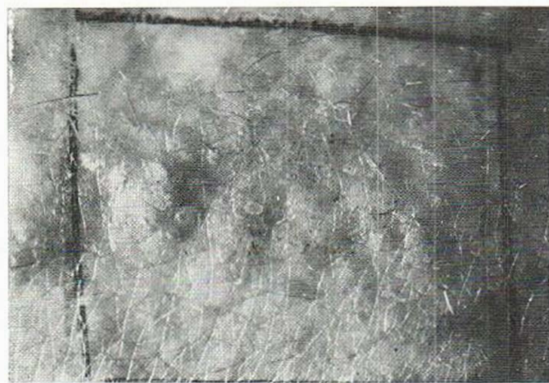


Fig. 1. Reaction to Trafuril (16 hours) distal to the elbow in patient with DH.

shoulder and/or elbow region of 8 patients in the same manner as described for Trafuril. These ointments contain one or several of the following vaso-dilating substances: methyl-diethylacetylsalicylate, diethylaminesalicylate, benzylnicotinate, *n*. Vanillylnonanamid, butoxyethylnicotinate, salicyl-ethanol, tetrahydrofurfurylsalicylate, ethylnicotinate.

2. Dithranol 0.1% in chloroform and chloroform alone were applied on the volar side of the forearm, as well as to an area distal to the elbow, and left without covering—18 patients.

3. Potassium iodide, 10 and 30%, in white petrolatum was applied as routine patch test on both the lateral surface of the upper arm and to an area distal to the elbow—21 patients. These tests were removed after 20 hours.

4. Light of wavelengths 2 800–3 000 Å in doses ranging from 0.3 to 1.5 mJ were used for testing on the dorsal side of the arm distal to the elbow—8 patients.

5. The following substances were injected in a volume of 0.1 ml on the volar side of the arm:

(a) Kallikrein (Padutin®, Bayer AG, Leverkusen, BRD) 4 U, and prostaglandin E₁ (Kindly supplied by Astra AB, Södertälje, Sweden) 0.5 µg—30 patients.

(b) Histamine (Vitrum AB, Stockholm, Sweden) 0.01 mg—30 patients.

(c) Streptokinase (SK) (Kabikinase, AB Kabi, Stockholm, Sweden) 1 U and 10 U, and a mixture of streptokinase and streptodornase (SK-SD) (Varidase, Lederle, Wayne, N.J., USA) 1 U and 10 U—24 patients. If there were no reactions, injections of 100 U and 1 000 U were also made.

(d) Urokinase (UK) (Løvens Kemiska Fabrik, Ballerup, Denmark) 10, 100, and 500 Plough units—5 patients and 6 healthy controls.

(e) Physiological saline, used as a control.

Nineteen patients with minor skin disorders such as eczematous dermatitis, psoriasis, and pustulosis palmo-planaris served as controls for tests 5a, 5b, and 5c.

6. Anti-IgA (kindly supplied by the Blood Center, University Hospital, Uppsala, Sweden) prepared from rabbit serum and equivalent to IgA 1 mg/ml and diluted in saline 1/10, 1/100, and 1/1 000 was injected into the shoulder region of 5 patients with DH and 2 patients with a minor eczematous dermatitis. Intradermal tests with anti-IgG prepared and diluted as with IgA were made in 3 of the IgA-tested DH patients and in one of the control patients.

Pretreatment procedures before application of Trafuril

In patients with DH, injections proximal to the elbow were made with 1 ml of the following substances:

1. Cromoglycate (Fisons Ltd., Loughborough, England) 10 mg/ml saline, which was infiltrated in the lower dermis 30 min before Trafuril application—7 patients.

2. Tranexamic acid (AB Kabi, Stockholm, Sweden) 1 mg/ml saline, deeply intradermally 30 min before Trafuril application—6 patients.

In 3 of the patients, a slight erythema was observed after the injections of cromoglycate and tranexamic acid.

3. Compound 48/80, 0.1 mg/ml saline, intradermally, repeated at intervals of 24 hours until no visible reaction—6 patients.

4. Lidocaine (Astra AB, Södertälje, Sweden) 1%, intradermally 30 min before Trafuril application—6 patients.

5. Saline for control—7 patients.

Other pretreatments were (1) stripping of the epidermis with tape and stroking the skin as in a dermatographic test, both of which were done 15 min before Trafuril application—5 patients, and (2) 0.2% flucinolone acetonide in a cream base (Synalar®—ICI-Pharma, Gothenburg, Sweden), and the cream base alone, both of which were applied and left on the skin with a plastic occlusion for 24 hours—7 patients.

Trafuril was also applied to areas previously treated with dithranol, chloroform, kallikrein, prostaglandin E—7 patients, and anti-IgA, anti-IgG—3 patients.

RESULTS

Reactions to Trafuril

Fifty-one of the 54 patients tested with Trafuril had abnormal (= positive) reactions to Trafuril of the type described in a preliminary report (7). None of the controls had an abnormal reaction. In 3 patients, who were tested only once, the reaction to Trafuril was negative, with no visible reaction 12 to 24 hours after application. One of them was 86 years old and had suffered from DH for 40 years but with only mild symptoms during the last 10 years. Another had an advanced internal malignancy and the third patient had a schizophrenia and was being treated with large doses of phenothiazines.

The initial reaction to Trafuril in healthy individuals consists of erythema and edema visible after 15 min and usually persisting for 1 to 3 hours. This early reaction is not significantly different in patients with DH; if anything, it tends to be moderate or weak. The abnormal reaction is a delayed one and is not visible until 5–8 hours after application. At this time, an itching erythema develops within the test area and, during the following hours, the reaction becomes more pronounced, with a formation of distinct papules which first appear around the follicle openings and often also vesicles, which are 2–4

Table 1. *Intensity of reactions to Trifuril in 48 patients tested on the elbow area and volar side of the forearm*

Location	Intensity of reaction	No. of patients
Elbow	+++	2
Forearm	+++	
Elbow	+++	7
Forearm	+++	
Elbow	+++	7
Forearm	++	
Elbow	+++	1
Forearm	0	
Elbow	+++	5
Forearm	+++	
Elbow	++	15
Forearm	++	
Elbow	++	4
Forearm	0	
Elbow	+	1
Forearm	+	
Elbow	+	5
Forearm	-	
Elbow	-	1
Forearm	+	

mm in diameter, and later may become confluent. The reaction is most pronounced at 24 hours.

Two patients, who sometimes have a purpuric component in their DH lesions, both had reactions to Trifuril, with papules and vesicles, as well as a purpura.

The intensity of the reaction varies from patient to patient. The mildest reaction, +, is erythema and usually a moderate edema. The next grade, ++, is characterized by an erythema and edema that is more pronounced and, as a rule, with a number of discrete papules. The strongest reaction, +++, is associated with a very marked edema, erythema, papules, and usually vesicles (Fig. 1).

As a result of regional differences in sensitivity between one area and another, there is considerable disparity in the appearance of the reactions within the same patient. The region around the elbow, especially just distal to it, seems to be the area that is most sensitive to Trifuril. Of the 48 patients tested both below the elbow and on the volar surface of the forearm, only one patient, who also had a Morbus Crohn, had a more pronounced reaction on the volar side. Forty-one patients had a decidedly more pronounced reaction near the elbow. The

marked differences between these two areas can be seen in Table 1.

In 7 patients, the sensitivity of other skin areas to Trifuril was compared with that of the elbow region. Strong reactions were observed in the area below the knee and in the upper lateral part of the shoulder. The sensitivity decreased towards the middle part of the shoulder area and, in 2 patients, the difference was pronounced with a +++ reaction on the lateral part and a + or 0 reaction near the spine. The sensitivity was low in the dorso-lateral part of the middle trunk and waist and moderate in the gluteal and thigh areas.

Reproducibility. The reactivity to Trifuril varies only slightly from one week, one month, or one year to the next if the degree of DH is unchanged and the dapsone dose remains the same. Twenty-three patients were given repeated Trifuril tests and the reactions were identical in 5 patients and with only minor variations in the others. Those patients with a more severe type of DH usually had more pronounced reactions than those who had a mild or moderate one.

One patient, who has been observed for several years with steadily waning symptoms of DH and is now free from symptoms and treatment, had Trifuril responses during this time that varied from moderately positive to weakly positive. They have now finally become negative. Another patient with an increasing intensity of DH now has a stronger reaction than when the DH symptoms were only moderate. As an interesting contrast, one patient became free from all DH symptoms when on a vegetarian diet but the response to Trifuril was the same regardless of diet.

Influence of dapsone. Two patients with a recently developed DH were tested before and after the dapsone treatment was started and their Trifuril responses decreased by one degree (+). A decrease in the reactivity to Trifuril was also observed in 5 patients when the doses of dapsone were increased from 0.1 g to 0.2 or 0.3 g per day. When the amount of dapsone was reduced, the reactivity again increased.

Influence of aspirin. The initial erythematous reaction to Trifuril was delayed or abolished by aspirin, but no significant lessening of the delayed reaction to Trifuril was observed in 6 DH patients who had taken 500 mg of aspirin/hour before the Trifuril test. In 2 patients, however, who took 3 000 mg of aspirin daily, there was a diminished response.

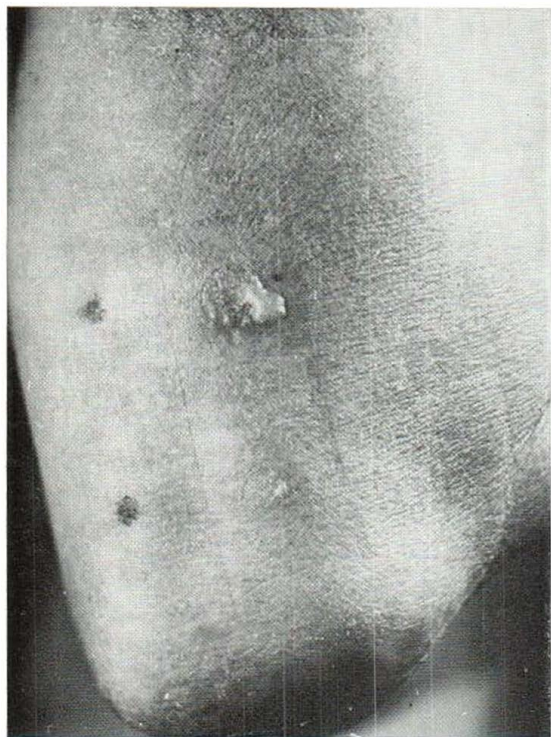


Fig. 2. Reactions to potassium iodide 10% and 30% (20 hours) distal to the elbow in patient with DH.

Biopsies

The histology of the biopsies taken from positive Trafuril test areas did not seem to differ from that of biopsies from spontaneously developed lesions of DH. Only routine stainings were made however.

Reactions to other vasoactive compounds

1. Most of the ointments containing vasodilating substances produced reactions comparable to those induced by Trafuril.

2. A papular and/or erythematous reaction to dithranol in chloroform was observed in 13 of 18 patients 3 days after testing. The appearance of the reaction was not similar to that seen after Trafuril. There was no visible edema and the papules were smaller and non-confluent; the reactions were as common under the elbow as on the volar side of the forearm. This type of reaction was not observed in patients with other skin disorders. No reactions were observed after chloroform alone.

3. The effect of potassium iodide varied according to the concentration of the iodide. Two of the 21 patients had papular and/or vesicular reactions to

10% potassium iodide, while 14 out of the 21 had such abnormal reactions to the 30% iodide. Eight of these 14 had vesicular reactions, mostly with a single, large vesicle (Fig. 2). Thus, the appearance of the reactions to potassium iodide differs from that of the Trafuril-induced reaction with its confluent vesicles, as well as from the DH lesions themselves. The difference in reactivity to potassium iodide between the elbow area and the volar side of the forearm was less pronounced than that for Trafuril. Vesicular reactions to the stronger concentration of iodide appeared both in patients with a strong reaction to Trafuril and in those with a weak one.

There was no correlation between the history of intolerance to oral iodine and the reactions to patch tests with iodide. Several of the patients with vesicular reactions to iodide have never noticed increased symptoms after oral iodine or after injections or roentgen contrast and, in 2 patients with a history of pronounced worsening after oral iodine, the local reaction to iodide was negative.

4. No abnormal reactions were observed after any of the exposures to UV-light.

5a & 5b. The reactions to kallikrein, prostaglandin E_1 , and histamine were normal in appearance and duration.

5c. The reactions to streptokinase (SK) and to streptokinase-streptodornase (SK-SD) 24 to 72 hours after the injection varied widely both in the DH group and in the control group. Two main types of reactions occurred in both the patients and controls; either there was a negative reaction to all dilutions or there were tense, tender, and erythematous infiltrated areas varying from 400 mm² after 10 U to 6 000 mm² after 1 000 U of SK-SD. The ratio reactors/non-reactors was approximately the same in the DH group as in the control group. One out of 5 had large reactions to SK-SD and one out of 6 to SK alone. One patient with severe DH had large reactions with central vesicles to both SK and SK-SD and these appeared already after 12 hours.

5d. The reactions to urokinase (UK) in 6 healthy controls differed insignificantly from those obtained after saline. No delayed reactions were observed. In patients with DH, one out of 5 developed a slightly tender infiltration after injection of 100 Plough Units and 2 out of 4 after an injection of 500 Plough Units. These infiltrations were slightly tender and erythematous and appeared 12-24 hours after injection.

Areas injected with even the lowest concentrations

Table II. Influence of pretreatment on the reactions to Trafuril in patients with dermatitis herpetiformis

Reaction to Trafuril	Not changed after pretreatment with	Increased after pretreatment with
Decreased after pretreatment with		
Cromoglycate 5/7	Saline	Streptokinase 7/7
Tranexamic acid 4/6	Lidocaine 1%	Streptokinase-Streptodornase 7/7
Compound 48/80 6/6	Dithranol 1%	Urokinase 4/6
Fluocinolone-acetonide 0.2% 7/7	Chloroform	
Stroking or stripping the skin 6/6	Kallikrein	
	Prostaglandin E ₁	
	Anti-IgA	
	Anti-IgG	

of SK-SD, as well as those treated with UK, developed a markedly increased sensitivity to Trafuril (see below).

Influence of pretreatment on reaction to Trafuril

The effects of pretreatment prior to the application of Trafuril are listed in Table II. In no case was there any change in the Trafuril response in the saline-treated area as compared with the response in non-treated skin.

Five out of 7 patients had a diminished Trafuril reaction in the cromoglycate-injected area. The decrease was + in 4 of the patients and ++ in one. In the tranexamic acid-treated areas, a diminished response of + was obtained in 4 out of 6 patients and, in the area treated with Compound 48/80, there was a + decrease in 6 patients.

The most pronounced inhibition of abnormal reactions to Trafuril was produced in areas pretreated with fluocinolone acetonide. All 7 patients had a negative reaction to Trafuril after this pretreatment. When Trafuril was applied out to the border of the non-pretreated skin, a marked reaction developed on the non-treated side of the border, whereas the pretreated side was without any visible reaction. This decreased reactivity in the fluocinolone-treated area persisted no more than 2 days, whereas the reactivity remained moderately decreased for more than one week in the areas treated with tranexamic acid, cromoglycate, or Compound 48/80.

Stroking the skin before Trafuril application did not influence the immediate response but abolished

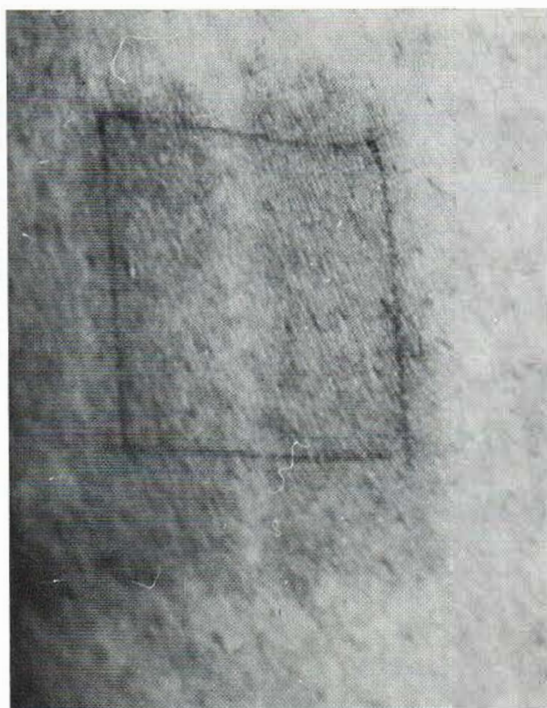


Fig. 3. Appearance of reaction to Trafuril when the middle part of test area is stroked 30 minutes before application of Trafuril. No visible abnormal reaction in stroked area.

the abnormal response to Trafuril in the stroked area in all 6 patients (Fig. 3).

Strongly increased reactivity to Trafuril was present in areas previously injected with SK, SK-SD, and UK. This greatly increased reactivity, which persisted for at least a week, was present even if there had been no visible reaction to SK or SK-SD and, in some of the patients, even in areas injected with only 1 U of SK or SK-SD. The reactions to Trafuril in these areas were tender, edematous, centrally vesicular, and very itchy (Fig. 4). The vesicles were often confluent but larger than what is seen after Trafuril alone. One of the patients tested with Trafuril a week after the SK-SD test developed generalized symptoms such as malaise and elevated body temperature in addition to the pronounced local Trafuril reactions. In 5 controls, the response to Trafuril was unchanged in areas that were previously injected with SK, SK-SD, and UK.

DISCUSSION

DH is associated with a number of abnormalities in addition to the visible skin changes. The majority



Fig. 4. Reaction to Trafuril (16 hours) in area injected with SK 1 U, 3 days before application of Trafuril.

of the patients have an enteropathy that seems to be associated with a gluten sensitivity (5). Deposits of immunoglobulin A and of C3 in uninvolved skin (15, 16) and of fibrin in the early papillary lesions are frequent findings (14). Circulating immune complexes (10), changes in the function of lymphocytes, and the occurrence of splenic atrophy (12), as well as impaired phagocytic capacity of the neutrophils (Michaëlsson, unpubl.) are other signs of immunological abnormalities in DH.

In DH, vesiculo-bullous reactions have been observed after intradermal injections of various bacterial antigens (17) and after patch tests with iodide. How these abnormal reactions are mediated or in what way they might be linked to the immunological defects is not yet known. We have previously described abnormal, delayed reactions to Trafuril that developed in 29 of 30 patients with DH and that were very similar to the DH lesions. This high frequency of reactions to Trafuril was further confirmed in the present study in which 94% of the DH patients developed reactions with one or several of the following characteristics: edema, erythema, papules, and vesicles that were best visible 24 hours after application of Trafuril and most pronounced in the elbow area, as well as in the other DH-predilection sides, i.e., the shoulder and knee regions. In other areas where DH lesions are uncommonly observed, the reactions to Trafuril were usually weak or absent.

Reactions of the same type as after Trafuril can be induced by a number of selected nicotinic-acid compounds in ointment bases. If a solution, e.g. isopropanol, glycerol, and water, that rapidly penetrates the skin is used instead of the ointment base, no delayed reaction is obtained even if the active substance gives a strong initial erythema (Michaëlsson, unpubl.). A prolonged contact between the active substance and the outerlayers of the skin thus seems to be required.

Little is known about the mediators of the reaction to Trafuril even in normal skin. Intradermal injections of neither histamine, prostaglandin E₁, Compound 48/80 (which produces a strong vasodilation within 30 minutes) nor kallikrein (which gives a more sustained reaction) induce reactions in DH that differ from those observed in healthy subjects.

Biopsies from normal skin treated with Trafuril reveal that an endothelial swelling begins 20 minutes after application of Trafuril. After 2 hours there is a pronounced endothelial swelling in both arterioles and venules and, in addition, an infiltration in and around the vessel walls by neutrophil granulocytes. The changes persist for at least 24 hours (Pettersson, unpubl.). These findings might indicate that the nicotinic acid compounds may act not only via vasodilation but also by some other mechanism.

The greatly increased sensitivity to Trafuril in areas where intradermal injections with even small amounts of SK-SD have been made may indicate an increased sensitivity in DH skin to activators of the fibrinolytic system. SK-SD influences fibrinolysis by activating plasminogen to plasmin (11, 20). It also acts as an antigen but it seems likely, however, that it is the influence on fibrinolysis that is the relevant factor in DH, since urokinase, which does not act as an antigen but only as a plasminogen activator, had the same potentiating effect on Trafuril reactions.

On the other hand, the sensitivity to Trafuril was less pronounced in skin depleted of histamine by Compound 48/80 and this may indicate that histamine is still involved in the delayed reaction to Trafuril. That there is a release of vasoactive substances in the Trafuril response might be further supported by the fact that pretreatment with cromoglycate, which has the property of inhibiting the release of vasoactive substances, made the skin less responsive to Trafuril.

The strongest inhibiting effect was obtained after fluocinolone acetonide pretreatment, which is previously known to inhibit the normal response to Trafuril (8). A decreased response was also observed after tranexamic acid, which inhibits the conversion of plasminogen to plasmin. This supports the possibility that there is an increased sensitivity to plasminogen activators in DH. An alternate explanation for the effect might be that tranexamic acid may have a histamine-releasing effect (1).

Stripping of normal skin with tape has been shown to decrease fibrinolytic activity of the upper dermis (13, 21). This decrease is observed after 6 hours and is pronounced by 24 hours. If these procedures have the same effect in DH skin, then the normalization of the Trafuril response after stripping and stroking might further strengthen the assumption that there is an enhanced tendency to fibrinolysis in DH skin.

As the majority of patients with DH have been shown to have IgA deposits either in a continuous or papillary pattern (15, 16), it might be expected that intradermally injected anti-IgA would produce a reaction differing from that in controls and also to that of anti-IgG. This assumption, however, was not confirmed. Nor was there any increased reaction to Trafuril in areas injected with anti-IgA.

Other reactions that were recorded in DH patients, but differed from those in controls, were those that occurred after dithranol and especially after potassium iodide. None, however, were like those seen after Trafuril. Dithranol has an irritating effect on normal skin and may increase the mitotic counts in the normal epidermis (6); otherwise little is known about its effects. We have no explanation for the discrete papules appearing 3 days after dithranol.

Reactions to potassium iodide in patients with DH are well known but were seen less frequently (66% with 30% KI) than the abnormal reactions to Trafuril that were present in 94% of the patients and are probably less specific than the reaction to Trafuril since strong concentrations of iodide often give irritant reactions in other skin diseases as well.

Blistering after Trafuril may also occur in patients with pemphigoid (7), but the reactions seen in these patients do not vary with anatomical area as do those of DH. In addition, the blisters are larger and, as a rule, not confluent.

In conclusion, the very simple Trafuril test in patients with a suspected DH seems to be a useful and reliable diagnostic test. It also is a valuable

model for studies of the DH lesions and how they may be influenced.

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