

Histological differences between irritant and allergic patch test reactions in man*

J. P. NATER¹ AND PH. J. HOEDEMAEKER²

¹ Department of Dermatology and ² Department of Pathology, State University Hospital, Groningen, The Netherlands

The results of a study of the histological aspects of the application of DNCB on the skin of unsensitized and sensitized persons are discussed. The nature of the histological changes in primary irritant and allergic reactions to DNCB in human skin appeared to be identical. The differences appeared to be primarily of a quantitative character.

It is furthermore concluded from data in the literature that the skin of some persons may react with a primary irritant reaction to concentrations of a compound thought to cause only allergic reactions. In these persons histological examination of the patch test result may give insufficient clues as to the nature of the reaction.

The practical consequences of the data presented are discussed.

Key words: Contact allergy – DNCB – histology – primary irritant.

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Every physician engaged in the diagnosis and treatment of eczema must, in our opinion, have some knowledge of the history of modern dermatology, in order to find out what is meant by this concept.

Writers on the subject almost invariably regard Ferdinand von Hebra as the real father of our present concept of eczema. Although scientists like Willan and Devergie made some study of the phenomenon, it was really von Hebra who gave the diagnosis eczema a sound foundation.

According to von Hebra there is only one eczema. To illustrate the clinical characteristics of a typical eczematous reaction, he described the development of what he called an artificial eczema. To this end von

Hebra took croton oil and rubbed it into the skin. After a few hours, reactions were noted. The morphology of this reaction differed, according to the author, and depended primarily on the localization. The morphological reaction furthermore depended on the amount, the concentration and the chemical nature of the compound that was used to elicit such a reaction. Von Hebra also mentions some other factors which may have an influence, such as the duration of the contact and the individual susceptibility. In a comment on this text Kreibich (1927) proposed to confine the use of the word dermatitis only to those reactions to external influence which differ morphologically from eczema.

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Thus, more than 100 years ago, von Hebra proved that a primary irritant, a substance which damages the skin by direct cytotoxic action, may cause an eczematous eruption. An eczema caused by a contact allergen, as we know now, is incited by an indirect immunological reaction involving changes in the whole organism. The fact that toxic materials may cause morphological reactions which are difficult to differentiate from an allergic response adds an element of uncertainty to patch test readings.

Large control series of allergens have been tested by the members of the International Contact Dermatitis Research Group (ICDRG) in order to ascertain the concentrations of the most commonly used test allergens which do not cause toxic reactions. Some uncertainties remain, however.

In a recent publication of Kligman & Epstein (1975) the difficulties and problems of the maximization test are discussed. In their paper they state that the variability in the response to irritants is greater in whites than in blacks. The skin of a small percentage of apparently healthy Caucasians has an extraordinary vulnerability to mild irritants like propylene glycol, aluminium chlorhydroxide and benzoic acid. There is as yet no definite way to recognize these sensitive persons. Thus the possibility exists, that in persons belonging to this group, reactions occur to patch tests with substances in concentrations which are entirely harmless for the greater majority of a normal control group.

For instance, a compound which may cause special difficulties in the interpretation of patch tests is propylene glycol. It is widely used as a vehicle for local therapeutics, cosmetics and lotions. The concentration of propylene glycol may be as high as 70 %. Hannuksela et al. (1975) encountered problems in the interpretation of patch tests with this compound. Some of the clin-

ical positive reactions observed by them could hardly be explained on the basis of a true contact hypersensitivity. Reactions due to primary irritation, for instance those caused by the hygroscopic properties of propylene glycol, apparently were undistinguishable from a true allergy.

Other causes of error have been reported by Mitchell (1975) in his paper on the diagnostic problems caused by a hyperreactive skin. According to him, one positive patch test reaction may create a state of hyper-reactivity of the skin elsewhere. One of the possible consequences mentioned by Mitchell is that patch test chemicals which are marginal irritants – and this is the case with many compounds – may become frankly irritant for this hyperreactive skin. This may cause false positive reactions, primary irritant reactions, in fact, which cannot be differentiated from an allergic reaction.

In addition, negative patch test results in a group of control persons may strengthen the false impression of a contact allergic reaction. In this connection a remark of Kligman & Wooding (1967) should be called to mind. They state: "It is urgent to abandon the convention of thinking in terms of irritants versus non-irritants or allergens versus non-allergens. A sounder biological view is to regard all substances as potential irritants."

At this stage a histological differentiation between a primary irritant and an allergic reaction might be of great help. The histology of primary irritant and allergic reactions has been studied extensively by well-known authors like Bandmann (1960) and McCallum (1957). Data on this subject have been summarized ably by other authors, for example Lachapelle (1973) (see Table 1).

All investigations thus far, however, were performed with *different compounds* causing either irritant or allergic reactions. The possibility must be excluded that some of the histological differences which have been

Table 1. Distinctive histological criteria between allergic and irritant patch test reactions in man

	Allergic Reactions	Irritant Reactions
<i>Epidermis</i>		
Spongiosis	+ to +++	Not frequent
Exocytosis	+ to +++	
Vesicles	+ (Spongiotic)	+ (Not spongiotic)
Formation of bullae	Facultative (Spongiotic)	Facultative (Not spongiotic)
Pustules	—	+ or —
Necrosis	—	+ to +++
Acantholysis	—	+ or —
<i>Dermis</i>		
Perivascular infiltrate	Mononuclear	Mononuclear
Eosinophilic leucocytes	+ or —	— (Rarely +)
Dilatation of lymphatic vessels	+ or —	—
Dilatation of blood capillaries	+ or —	—
Oedema	+ or —	Not frequent

noted were caused by the different chemical structure of the compounds. We therefore investigated the histological aspects of primary irritant and allergic reactions to the same compound, namely DNCB (Hartman et al. 1976).

Investigation and Results

In the *first* place we patch-tested a group of Caucasian volunteers, without preliminary sensitization, with 3, 10, 30, 50 and 90 μg DNCB/cm². Almost all showed an erythematous reaction to 30 μg DNCB and the higher amounts. This reaction must be attributed to a primary irritant effect. Histologically we found slight spongiosis after application of 30 μg DNCB/cm². This spongiosis increased after application of 50 μg DNCB/cm² and a slight perivascular infiltrate in the dermis was also seen. The application of 90 μg DNCB/cm² resulted in perivascular infiltrate as well as degenerative changes of the surface epithelium (Fig. 1).

In the *second* place the histological changes were studied after application of 3, 10, 30 and 90 μg DNCB/cm² in patients

who prior to challenge had been sensitized to DNCB. It appeared that the histological changes were definitely more pronounced when compared with the reactions in unsen-

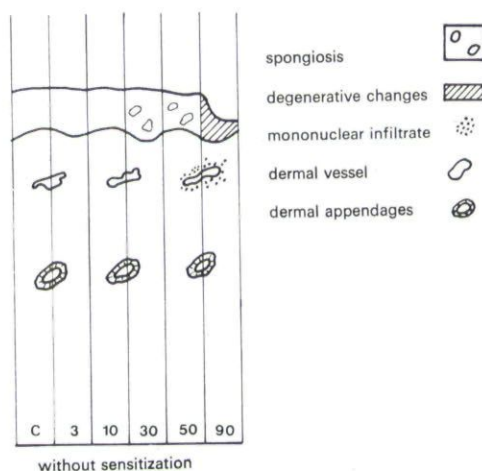


Fig. 1. Schematic drawing of changes after dermal application of 3, 10, 30, 50 and 90 μg of DNCB without prior sensitization, compared with the control skin of the same patient (C). Surface epithelium changes appear in the form of spongiosis after application of 30 μg and increase to degenerative changes after application of 90 μg . At 50 and 90 μg perivascular dermal infiltrate can also be observed.

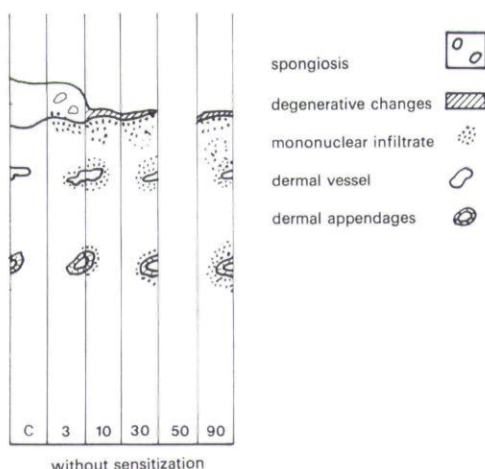


Fig. 2. Schematic drawing of changes after dermal application of 3, 10, 30 and 90 μ g of DNCB after prior sensitization, in comparison with the control skin of the same patient (C). The dermal changes are more pronounced in comparison with those seen in Fig. 1. Changes in the surface epithelium start after application of 3 μ g and are more severe after application of increasing amounts of DNCB. Already with 3 μ g mononuclear infiltration at the dermal-epidermal junction can be observed, as well as some perivascular infiltrate. After application of 10, 30 and 90 μ g an extensive dermal infiltration of mononuclear cells as well as degenerative changes of the surface epithelium are observed.

sitized persons. With 3 μ g DNCB/cm² a mononuclear cell infiltration of the dermal epidermal junction could be noted, as well as some perivascular infiltrate. After application of the higher amounts, an extensive dermal infiltrate of mononuclear cells, as well as degenerative changes of the surface epithelium were seen (Fig. 2). Thus the principal difference between the reaction of the sensitized and non-sensitized skin appeared to be primarily of a quantitative character: the sensitized skin reacts to lower amounts. The basic morphology of the reaction, however, was identical.

In the *third* place we studied the dermal changes after application of a sensitization

dose of 2 mg DNCB on 3.14 cm². To this end biopsies were performed during 17 consecutive days. It could be observed that the histological changes were biphasic in character. The first changes appeared after a few hours and became more pronounced from day 1 to day 5, when spongiosis, degenerative changes of the surface epithelium and a dermal lymphocytic infiltrate developed. After day 6 these changes subsided to reappear from day 9 to day 13 (Fig. 3). Although in general no differences could be noted, the dermal infiltrate during the second phase, the flare-up phase, was more severe and the degenerative changes of the epithelium somewhat less pronounced.

Discussion

In this study on the effect of DNCB on the skin, it was not possible to differentiate histologically between an allergic and a primary irritant reaction to the compound. Both reactions consist of an identical cutaneous inflammation process. One must keep in mind, of course, that no "overkill" of the epidermis was caused by application of high concentrations of this primary irritant.

In view of the conclusions from our own investigation it is interesting to consider briefly the results of other techniques which have been used in this field.

In vivo skin perfusion techniques have been employed to study the pharmacological activity in the skin of patients with allergic contact eczema and primary irritant dermatitis. A review has recently been given by Goldyne (1975). The experimental evidence so far presented suggests that there may be a common denominator – the prostaglandins E and F – present in cutaneous inflammation which results from the application of allergens as well as primary irritants. Thus it is possible that a primary irritant as well as an immunologic trigger mechanism

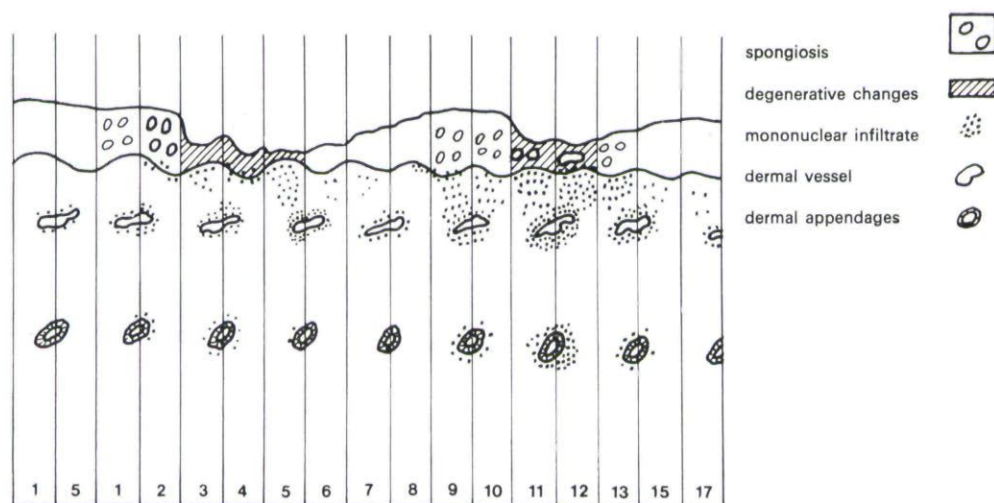


Fig. 3. Schematic drawing of dermal changes after application of 2 mg DNCB after varying periods. In the first two columns the numbers (1, 5) represent hours, in the rest of the columns the numbers represent days. It can be seen that the dermal changes are biphasic in character. The first changes appear after a few hours and become more severe from day 1 until day 5, in which spongiosis, degenerative changes of the surface epithelium and dermal infiltrate appear. Then after day 6 these changes subside, to reappear from day 9 to day 13. Although generally there is no difference from the changes occurring from day 1 to day 5, the dermal infiltrate is more severe and the degenerative changes of the surface epithelium are somewhat less pronounced.

both result in the production of prostaglandins as a mediator of the inflammation. The question of the origin of these prostaglandins, release by invading leucocytes or production by the epidermis itself, lies outside the scope of this paper.

Based on the literature data, the results of our own investigation might be explained in the following way: contact allergens as well as tissue irritants may trigger lymphocytic and/or non-lymphocytic mediator systems. Both systems produce leucocyte chemotaxis, vasodilation and increased vasopermeation. This process leads to changes in the skin which, light microscopically at least, cannot be differentiated.

Summarizing, in the first place, the previously mentioned literature one may conclude that the skin of some persons under certain conditions may react with a primary irritant reaction to concentrations of a com-

pound supposed to cause only allergic reactions. Secondly, from our own investigations it appears that histologically no basic differences can be found between the allergic and toxic reactions to the same compound.

Finally, I should like to draw some practical conclusions from the presented data. In daily medical practice it is a common experience that in most industries the following situation exists (Fig. 4):

- the vast majority of employees work without skin complaints
- a minority appear to become sensitive or to remain sensitive, but not allergic, to mild irritant compounds which most other workers in the same industry are capable of handling without developing skin trouble. In some of these people hardening (accommodation is a better

The case of the (new) employee

A. No (skin) problems

B. Dermatitis:

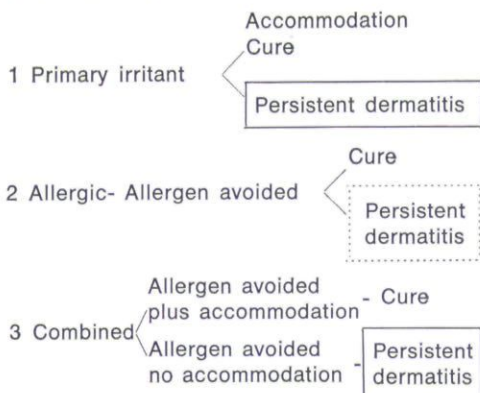


Fig. 4. The case of the (new) employee.

prescription) occurs; other less fortunate workers develop a persistent orthoergic dermatitis

c. a minority may acquire a contact allergy.

The minority who develop a contact allergy constitute essentially a social problem, as a trained dermatologist must be able to solve the medical side of many, though not all, of these cases. Based on his report, society tries to find a solution for these patients. The group of patients with negative patch tests, however, remains a medical as well as a social problem. The beacon of the positive patch test is missing. In spite of these negative patch tests, resumption of work reactivates the orthoergic eczema.

In these cases two difficulties may arise. In the first place some physicians tend to repeat the process of investigation and especially of patch testing. In this way one patient may be tested by several dermatologists with the same materials; thus, the chance of patch test sensitization becomes quite real. A second difficulty may also occur: undue importance is attached to doubtful patch test reactions, especially those

caused by tests with little-known materials, often marginal irritants. As we have pointed out, histological examination as well as patch tests in a small control group, may give inadequate clues as to the real nature of the reaction.

In each case a combination of observations is necessary: a careful evaluation of the medical history and a study of the morphological aspects of the eruption as well as patch tests. This is the only way to make a diagnosis with a reasonable amount of certainty and only dermatologists with an extensive experience of contact allergic investigations and with a thorough knowledge of the literature in this field can be expected to be able to do so.

Eczema is one of the most frequently encountered skin diseases in general practice. In a dermatological clinic 20–30 % of the patients suffer from some kind of eczema. In our modern industrialized society great economical and social interests are at stake. In my opinion a reasonable amount of the training period of the young dermatologist ought to be reserved for study in this field of dermatology. This must not only comprise patch testing but also morphology, histology, epidemiology, occupational and social aspects and, last but not least, the immunological aspects and the new techniques for diagnosis which are being developed in this discipline.

Acknowledgments

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Address:

J. P. Nater
Department of Dermatology
State University Hospital
Oostersingel 59
Groningen
The Netherlands

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