

Occupational dermatitis from *Lactuca sativa* (lettuce) and *Cichorium* (endive)

Simultaneous occurrence of immediate and delayed allergy as a cause of contact dermatitis

GÖSTA KROOK

Department of Dermatology, University of Lund, Malmö, Sweden

Four patients with occupational contact dermatitis to *Lactuca sativa* had cross-sensitivity to *Cichorium endivia*. One of the patients also had contact urticaria to *Lactuca* and *Cichorium*, and another reacted positively to scratch tests with these plants as a sign of immediate allergy. In two cases such immediate allergy was considered the cause of a vesicular, intense itching eruption within a few minutes of contact with fresh leaves of *Lactuca* on previously eczematous skin. The severe chronic dermatitis of the hands of these patients is ascribed to combined delayed and immediate allergy.

Key words: *Cichorium* (endive) – contact dermatitis of immediate type – contact urticaria – immediate vesicular reaction – *Lactuca* (lettuce) – occupational contact dermatitis.

Received for publication September 20, 1976

Contact dermatitis from *Lactuca sativa* (lettuce) is probably rarely diagnosed and it seems that the diagnosis has been confirmed by patch tests in only a few cases (Rinkel & Balyeat 1932, Morris 1954, Krook 1973, Vail & Mitchell 1973, Friis et al. 1975).

Since 1973, when the first case was reported from our clinic (Krook 1973), another three cases have been diagnosed. Two of the patients also had immediate allergy to lettuce and *Cichorium endivia* (endive) and two reacted with immediate vesicular eruptions after contact with lettuce leaf.

Case Reports

Case 1

In 1965 a 56-year-old gardener without known heredity for atopy had cultivated lettuce for 3 years when he acquired dermatitis with itching, erythema, edema and desquamation on the hands, face, arms and legs. The patient noticed a flare-up of the dermatitis after contact with lettuce (only full-grown plants, not young ones) or even after a visit to the greenhouse. In winter, when he did not work with lettuce, he had no dermatitis. He had never used insecti-

cides or the like. He could eat lettuce without consequent mucosal or skin symptoms and he had never noticed skin eruptions after contact with other plants.

In 1971 he reacted positively to a patch test with a fresh lettuce leaf and in 1973 to an endive leaf (Table 1). Control tests on 10 healthy persons were negative.

Patch tests with our standard series were negative. (The series was supplied by K. Trolle-Lassen, A. N. Hansen alle 6 B, 2900 Hellerup, Denmark.) The patient was also patch-tested with plant oleoresins of a number of Compositae species with several positive reactions (Table 3).

In April 1975 the patient was tested again, this time to find out whether he had immediate hypersensitivity to lettuce or endive. He had by then retired and not worked as a gardener for 2 years, during which he had been free from dermatitis. Open epicutaneous tests on the arms and fingers with juice squeezed from fresh leaves of lettuce and endive did not elicit any urticarial or other reactions within 30 min, but scratch tests with the same allergens were positive (Tables 2 & 4). Control tests with lettuce in six healthy persons and with endive in five were negative. The patient had never before been in contact with, or eaten, endive.

Case 2

In March 1973 a 48-year-old woman who had for some months been packing lettuce into

plastic bags in a supermarket acquired vesicular dermatitis on her hands. She had never before had dermatitis and she had no heredity for atopy. The dermatitis disappeared when she had stopped working with lettuce. In August 1973 she returned to work with lettuce and the hand dermatitis recurred on the fingers and palms. The patient had not noticed any skin symptoms after contact with plants other than lettuce.

In October 1973 patch tests with lettuce and endive leaves were positive (Table 1). Patch tests with our standard series were positive only to para-phenylenediamine, but there was no history of skin symptoms due to this or allied substances. Patch tests with plant oleoresins were positive only to a Compositae mix (Table 3).

In April 1976, by which time she had been free from dermatitis for about 2 ½ years, open epicutaneous tests on normal skin on her arm with juice squeezed from fresh leaves of lettuce and endive produced no urticarial reactions within 30 min. Also scratch tests with the same allergens were negative (Table 2). Open epicutaneous tests with fresh, crushed lettuce leaf gently rubbed on her previously eczematous fingers did not provoke any reactions (Table 4).

Case 3

The patient was a 63-year-old woman, who had worked as cold-buffet manageress since the age of 15. Her mother had had asthma, one sister had had asthma as a child and

Table 1. Results of 48-h patch tests* with *Lactuca* and *Cichorium*

	Case 1	Case 2	Case 3	Case 4	Number of controls
<i>Lactuca sativa</i>					
fresh leaf as is	+++	++	++	++	10
<i>Cichorium endivia</i>					
fresh leaf as is	++	+++	++	+++	10

* read after 72 h.

Table 2. Results of immediate hypersensitivity tests*

Allergen	Open epicutaneous tests on normal skin				Scratch tests		Number of controls
	Case 1	Case 2	Case 3	Case 4	Case 1	Case 2	
<i>Lactuca sativa</i> juice squeezed from fresh leaf	Neg.	Neg.	weal 3 × 4 mm	Neg.	weal 3 × 5 mm	Neg. 8 × 10 mm	10
<i>Cichorium endivia</i> juice squeezed from fresh leaf	Neg.	Neg.	weal 6 × 10 mm	Neg.	weal 4 × 5 mm	Neg. NT	10
							6
							5

* read 15–30 min after epicutaneous application of a few drops of the allergen.
NT = not tested.

another sister has dermatitis of the hands.

The patient had never before had any skin diseases, asthma, allergic rhinitis or other atopic symptoms.

Since the age of about 40 the patient had suffered from chronic relapsing vesicular and desquamating dermatitis of the hands. The dermatitis was always worse after working with lettuce and her hands itched already after a few minutes' contact with lettuce. Once, when she had eaten an endive leaf, her throat was suddenly swollen and she was nearly suffocated. Ever since then she had avoided all contact with endives. She had never noticed any such reactions of the skin or mucous membranes after eating lettuce. Exposure to plants other than lettuce or endive had never provoked any such symptoms.

In November 1974 patch-tests with lettuce leaf and endive leaf were negative. About 15 min after the patch test with lettuce leaf had been placed on her back she experienced intense pruritus at the site of the test, where an urticarial reaction, 3 × 4 mm, was observed (Fig. 1).

In January 1976 a scratch test on her arm with juice squeezed from lettuce leaf provoked an urticarial reaction, about 8 × 10 mm, with an erythematous flare about 40 × 40 mm (Fig. 2 & Table 2).

An open epicutaneous test on the arm with a few drops of juice squeezed from a fresh endive leaf caused intense pruritus within a few minutes and after 15 min there was an urtica 5 × 8 mm, which after a further 15 min was 6 × 10 mm (Table 2). She was patch-tested again with endive leaf and crushed lettuce leaf (Fig. 3 & Table 1). A biopsy specimen from the site of the test revealed a picture consistent with an allergic contact dermatitis (Fig. 6).

An open test performed by gently rubbing crushed leaves of lettuce on the left arm and hand, resulted in intense pruritus on both sites in about 3 min. After about 10

Table 3. Results of 48-h patch tests¹ with plant oleoresins²

	Case 1	Case 2	Case 3	Case 4
Compositae Mix (A)	++	—	—	—
Compositae Mix (B)	+++	++	++	++
Compositae Mix (C)	+++	—	—	++
<i>Franseria acanthicarpa</i>				
False ragweed	—	—	—	—
<i>Achillea millefolium</i>				
Yarrow	+++	+	++	+++
<i>Parthenium hysterophorus</i>				
Wild Feverfew	++	—	—	—
<i>Tanacetum vulgare</i>				
Tansy	+++	—	+	++
<i>Chrysanthemum</i>	—	—	—	—
<i>Ambrosia eliator</i>				
Short ragweed	+++	—	—	++
<i>Anthemis cotula</i>				
Dog Fennel	—	—	—	—

¹ read after 72 h.² obtained from Hollister-Stier Laboratories, Box 3145, Spokane, Wa. 99220, USA.

min a few small vesicles appeared on the ulnar and radial aspects of the fingers, where the skin had previously been eczematous but where it had looked normal to the naked eye before the test. Still more vesicles developed within 15 min (Figs. 4 & 5, Table 4) and a biopsy specimen of the skin was obtained. Histological examination of the specimen revealed an intra-epidermal vesicle containing lymphocytes extending to the corneal layer, where a small area of parakeratosis was seen just

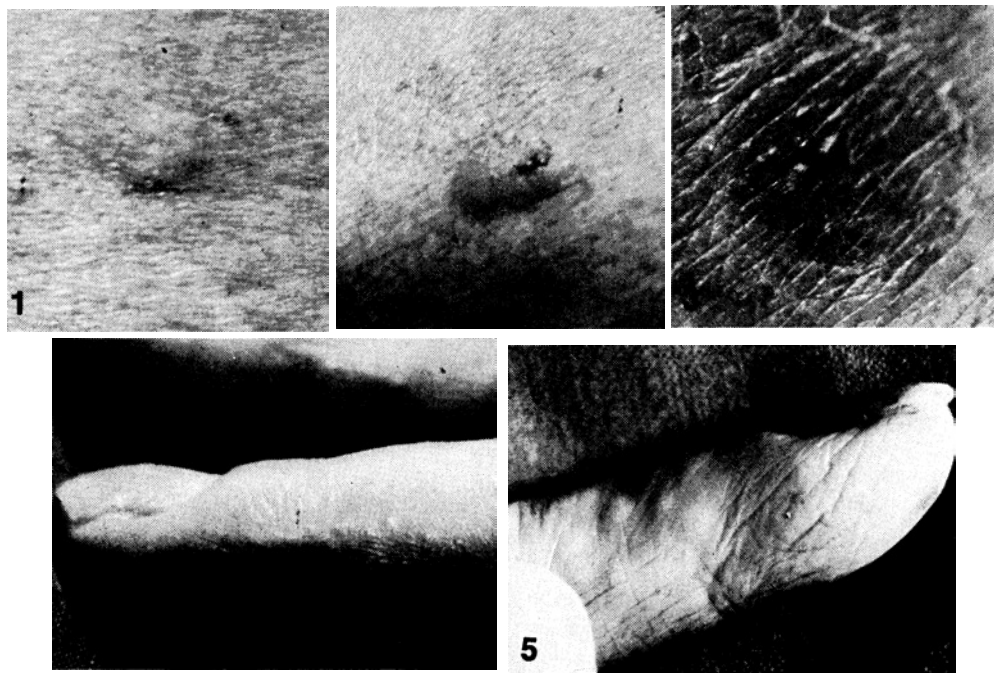
above the vesicle. There was also spongiosis. In the upper part of the corium just beneath the vesicle was a rather dense infiltrate of lymphocytes spreading up into the epidermis (Fig. 7). A separate frozen biopsy specimen taken at the same time and from the same area was studied by direct immunofluorescent techniques with antihuman IgG, IgA, IgM, IgD, IgE and complement C. The results were negative. The exposure trial on the arm provoked itching and erythema, but no vesicles.

Patch tests with the standard series were positive only to balsam of Peru. Patch tests with plant oleoresins were positive to Compositae mix B and yarrow (Table 3).

Complete blood cell counts were normal, including the eosinophilic polymorphonuclear counts. The serum protein electrophoretic pattern was normal and the serum IgE was 300 µg/l (estimated normal value < 900 µg/l).

Table 4. Results of open epicutaneous tests with crushed lettuce leaves on previous eczematous fingers

Case 1 no reactions	
Case 2 no reactions	
Case 3 intense pruritus	after 3 min
vesicles	after 10 min
Case 4 intense pruritus	after 5 min
vesicles	after 10 min



Figs. 1-5. Tests with crushed lettuce leaf (case 3).

1. Contact urticaria
2. Positive scratch test
3. Positive patch test
- 4-5. Open tests with immediate vesicular reactions.

Case 4

The patient was a 43-year-old woman who had worked as a cold-buffet manageress and cook since her teens. She has no heredity for atopy. As a child she had acute urticaria, but no dermatitis. Since the age of 27 she had suffered from chronic relapsing, often vesicular, dermatitis of the hands. Repeated patch tests with our standard series and spices, tomato, lemon peel, onion, and pepper were all negative. The dermatitis was usually worse during wet work and contact with different food-stuffs, but she had never observed exacerbation after contact with any particular substances until the winter 1976, when she repeatedly experienced intense itching of the fingers a few minutes after handling lettuce in the kitchen. She had never observed skin symp-

toms after eating lettuce or endive or after contact with other plants.

Patch tests with crushed leaves of lettuce and endive were positive (Table 1). In April 1976 open epicutaneous tests and scratch tests with juice squeezed from fresh leaves of lettuce and endive on normal skin were negative (Table 2). An open test by gently rubbing crushed leaves of lettuce on previously eczematous, but now normal fingers resulted in itching within 5 min and in several small vesicles, erythema and some edema within 10 min (Table 4).

A biopsy specimen of one vesicle was obtained 30 min after the beginning of the experiment. Histological examination of the specimen revealed a small subcorneal vesicle just beneath a small area of parakeratosis. In the corium below the vesicle was

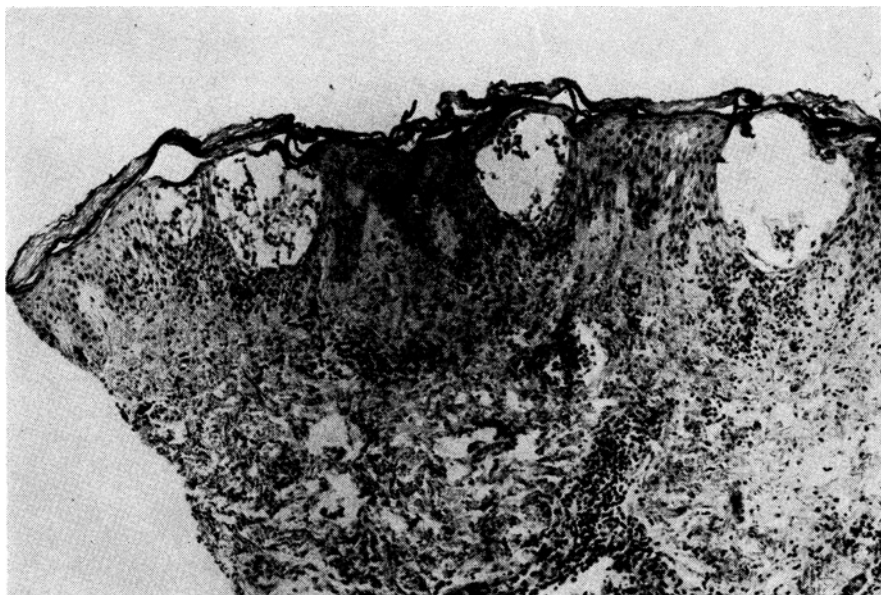


Fig. 6. Positive reaction to 72-h patch test with lettuce (case 3). Multiple vesicles and spongiosis in epidermis. Corium contains perivascular infiltrates of lymphocytes, plasma cells and some histiocytes. In some areas fairly superficial infiltrate of abundant inflammatory cells spreading up into the basal part of the epidermis.

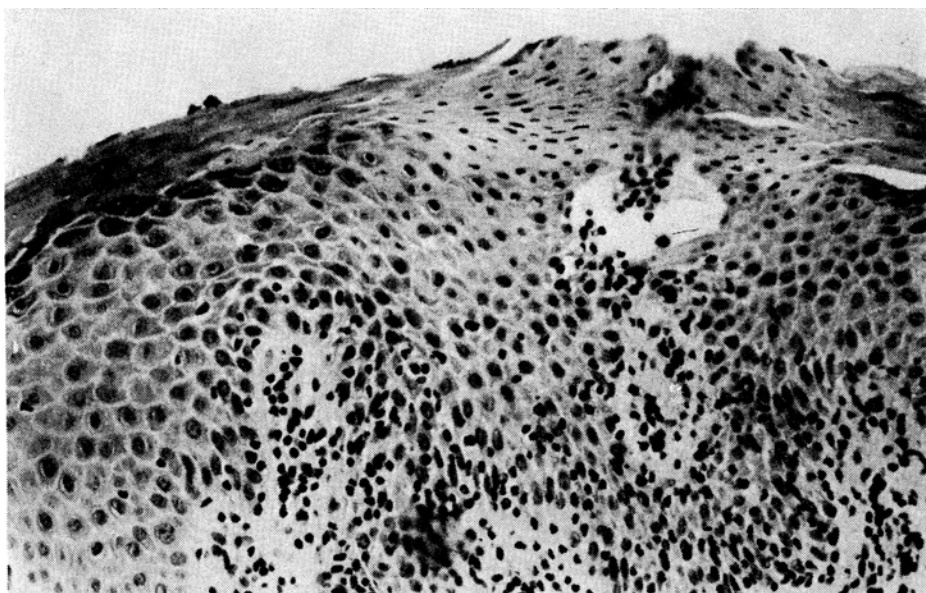


Fig. 7. Immediate vesicular reaction 30 min after open test with lettuce on previously eczematous finger (case 3). Epidermis shows slight spongiosis, an intra-epidermal vesicle containing lymphocytes and parakeratosis over the vesicle. From the corium fairly numerous lymphocytes spread up into the epidermis.

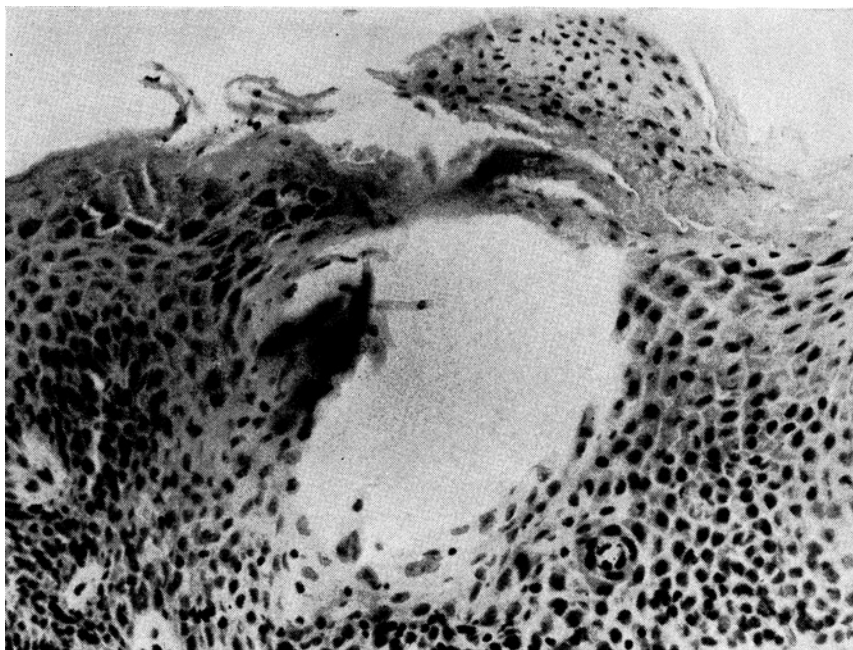


Fig. 8. Immediate vesicular reaction 30 min after open test with lettuce on previously eczematous finger (case 4). Histologic appearance resembles that in Fig. 7.

a dense infiltrate of lymphocytes and some polymorphonuclear leucocytes. There were also lymphocytes immigrating into the epidermis and some degree of spongiosis (Fig. 8).

In order to find out whether immediate vesicular reactions could be provoked not only on previously eczematous fingers, open tests with fresh endive juice were performed on the back of the patient on:

1. an almost healed previous patch test site (remaining weak erythema) tested 2 weeks previously with the same allergen and read as positive after 72 h (papules and vesicles), and
2. normal skin close to test site 1.

After a few minutes the patient experienced itching on test site 1 and after about 15 min there were barely visible papules, but

no vesicles. On test site 2 there were no symptoms or signs.

Half an hour after the start of the tests biopsy specimens were taken from the two test sites and, as a control, from a site which had 2 weeks previously been patch-tested in the same manner as test site 1, but not now. The histological examination of test site 2 and the control revealed a normal epidermis and only small perivascular infiltrates of lymphocytes. In test site 1, however, there were spongiosis and disseminated lymphocytes in the epidermis, but no vesicles or parakeratosis (in contrast with the biopsy specimens from the fingers in cases 3 and 4, Figs. 6 & 7). The corium showed a dense and diffuse infiltration of mainly lymphocytes (Fig. 9).

Complete blood cell counts were within normal limits, including the eosinophilic polymorphonuclear counts. Serum electro-

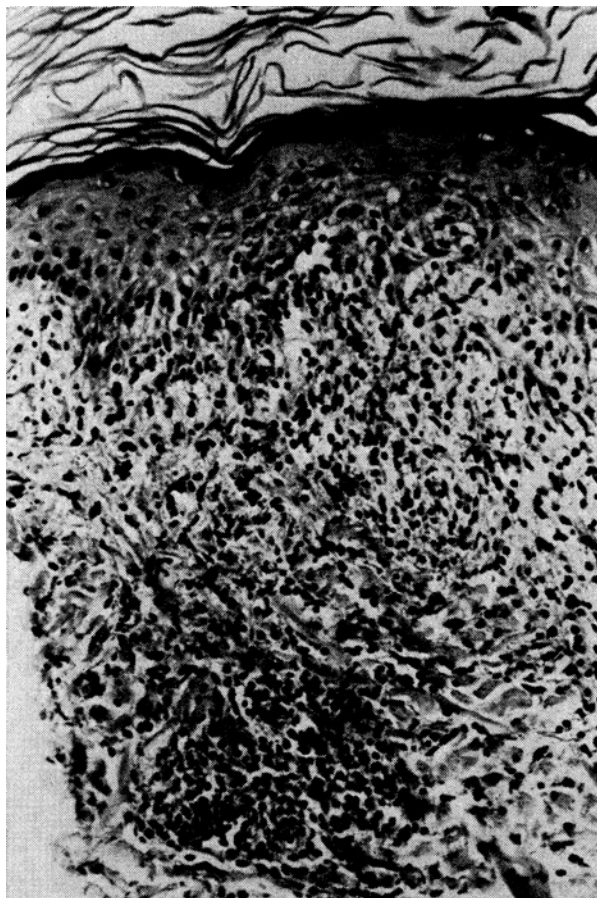


Fig. 9. Open patch test with endive after 30 min at site of a previously positive 72-h patch test (case 4). Moderate spongiosis of epidermis, but no vesicles. Fairly dense and diffuse infiltration of mainly lymphocytes in corium and spreading up into the epidermis.

phoresis revealed nothing remarkable and the serum IgE was 1500 $\mu\text{g/l}$.

All four patients were also patch-tested with many different extracts of lettuce and endive (water-, ether-, methanol-, methylethylketone extracts, etc.), but so far it has not been possible to ascribe the allergen to any particular fraction.

Discussion

So far, all known patients with dermatitis caused by *Lactuca* and *Cichorium* had contact allergy of delayed type (Rinkel & Ballyeat 1932, Morris 1954, Krook 1973, Vail

& Mitchell 1973, Friis et al. 1975). Cross-sensitivity between *Lactuca* and *Cichorium*, as in all four cases, has also been demonstrated by others (Vail & Mitchell 1973, Friis et al. 1975), but one patient with a positive patch test for *Cichorium* was negative for *Lactuca* (Hjorth & Roed-Petersen 1976).

These plants yield sesquiterpene lactones which have been identified as the allergens also of other Compositae species (Mitchell 1975a). This may explain why all four patients reacted positively to patch tests with Compositae species when tested with the plant oleoresins (Table 3). However, it

should be observed that case 2 and 3 were negative for *Compositae* mix C in spite of its content of *Lactuca*. This may depend on too low a concentration of the allergen in the mix. In case 1 the patient experienced skin symptoms only after contact with full-grown plants, but not from young ones, possibly because of the small content of lactones in the latter (Mitchell 1975b).

A remarkable finding in the four patients with delayed allergy was the simultaneous occurrence of signs of immediate type allergy presenting as contact urticaria (case 3) positive scratch tests (cases 1, 3) and immediate vesicular reactions on previously eczematous sites (cases 3, 4).

Rinkel & Balyeat's (1932) case with a positive patch test to *Lactuca* also had signs of immediate allergy presenting as urticaria and positive intradermal test, but in all other published cases of allergy to *Lactuca* and *Cichorium* the patients have not had signs of immediate allergy.

The simultaneous development of both immediate and delayed contact allergy to the same allergen in the same patient is probably rare. For instance, it has been reported from sulisobenzene (Ramsay et al. 1972) and from contact with flesh of fish and chicken (Hjorth & Roed-Petersen 1976).

The vesicular reaction on previous eczematous skin 10–15 min after contact with the allergen as in cases 3 and 4 has hitherto apparently been described only by Hjorth & Roed-Petersen (1976), who observed vesicles after an open 20-min patch test with tomato on affected skin. In four patients with hand dermatitis the same type of test with different protein allergens (fish, lobster, shrimp, cheese) provoked itching, erythema and urticaria, but no vesicles. Protein allergens, beef and pork, have also been reported to elicit vesicular (and papular) reactions comparatively soon (2–5 h) after contact or ingestion of the allergens

causing positive patch tests but negative intradermal tests in four patients (Seeberg 1952).

A prerequisite for the appearance of the immediate vesicular reactions observed in cases 3 and 4 seems to be that the allergen comes into contact with previously eczematous skin even if it appears normal to the naked eye.

The penetration of the allergen seems to be facilitated in the previously affected skin. In the biopsy specimens from the fingers in cases 3 and 4 (Figs. 7, 8) there was parakeratosis above the vesicles, indicating a previous inflammatory reaction at that very site with probably residual lesions of the epidermis.

In the biopsy specimen taken 30 min after the open tests from the fingers (cases 3 & 4) and the back (case 4) there was spongiosis and infiltration of lymphocytes both in the lower epidermis and the corium. In the fingers there were also subcorneal vesicles. Judging from the normal histologic appearance of the control site on the back in case 4 before the open test there, these histologic changes probably appear within 30 min. In patient 1 who had immediate allergy to lettuce (positive scratch test) no vesicular reaction appeared on the fingers after the open test, perhaps because his hand dermatitis had been healed for as long as 2 years.

The histologic appearance of the immediate vesicular reaction (cases 3 & 4, Figs. 7, 8) does not differ very much from that of contact dermatitis of the usual delayed type (case 3, Fig. 6), but in the latter there is more pronounced spongiosis and more vesicles. The mechanism of allergy eliciting the immediate vesicular reaction is not known, but is probably of immediate type. It is emphasized that in contact allergy a cell-mediated immunological response rarely occurs in complete isolation and there will be local production of humoral antibodies

at the site of a previous cell-mediated immune reaction in the skin (Turk 1972). It is suggested that the immediate vesicular reaction should be named contact dermatitis of immediate type.

One might expect patients with allergy of immediate type to be atopics. Case 3 had heredity for atopy and case 4 had a high level of IgE, but otherwise there were no atopics signs or history in any of the four patients. IgE could not be discovered by direct immunofluorescent examination of the biopsy specimen from the finger in case 3. Only six of the 25 patients with hand dermatitis and immediate reactions of Hjorth & Roed-Petersen (1976) had a personal and/or family history of atopy and only two had suffered from atopic dermatitis. Contact urticaria as a causal factor of hand eczema in the atopic has been discussed by Maibach & Johnson (1975). The severe hand dermatitis in cases 3 and 4 is considered to be a result of contact allergy of both immediate and delayed type.

Elucidation of the mechanism of the immediate vesicular reactions, which are undoubtedly involved in many cases of occupational dermatitis in persons handling foodstuffs, for example, must await further research. It is important to test these patients not only with 2-day patch tests, but also with scratch tests and open tests.

Acknowledgements

Thanks go to Professor Folke Linell, Dr. Rolf Holst and O. Ljunggren for the histologic, and Dr. Helge Löfberg for the immunofluorescent, examinations; and to Dr. Holger Hansson for placing case 4 at my disposal and to Dr. Sigfrid Fregert for the extracts of lettuce and endive.

References

- Friis, B. (1973) Occupational dermatitis from chicory salad (*Cichorium intybus* var. *foliosum*). *Contact Dermatitis Newsletter* 13, 349.
- Friis, B., Hjorth, N., Vail, J. T. Jr. & Mitchell, J. C. (1975) Occupational contact dermatitis from *Cichorium* (chicory, endive) and *Lactuca* (lettuce). *Contact Dermatitis* 1, 311–313.
- Hjorth, N. & Roed-Petersen, J. (1976) Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 2, 28–42.
- Krook, G. (1973) Contact dermatitis due to lettuce (*Lactuca sativa*). *Contact Dermatitis Newsletter* 13, 346.
- Maibach, H. I. & Johnson, H. L. (1975) Contact urticaria syndrome. *Archives of Dermatology* 111, 726–730.
- Mitchell, J. C. (1975a) Biochemical basis of geographic ecology: part 2. *International Journal of Dermatology* 14, 301–321.
- Mitchell, J. C. (1975b) Personal communication.
- Morris, G. E. (1954) Dermatoses among food handlers. *Industrial Medicine Surgery* 23, 343–344.
- Ramsay, D. L., Cohen, H. J. & Baer, R. L. (1972) Allergic reaction to benzophenone. Simultaneous occurrence of urticarial and contact sensitivities. *Archives of Dermatology* 105, 906–908.
- Rinkel, H. J. & Balyeat, R. M. (1932) Occupational dermatitis due to lettuce. *Journal of the American Medical Association* 98, 137–138.
- Seeberg, G. (1952) Eczematous dermatitis from contact with, or ingestion of beef, pork and mutton. *Acta Dermato-venereologica* 32, Suppl. 29, 320–322.
- Turk, J. L. (1972) *Immunology in Clinical Medicine*, 2nd ed., p. 163. London: William Heinemann.
- Vail, J. T. Jr. & Mitchell, J. C. (1973) Occupational dermatitis from *Cichorium intybus*, *C. endivia* and *Lactuca sativa* var. *longifolia*. *Contact Dermatitis Newsletter* 14, 413.

Address:

Dr. G. Krook
Department of Dermatology
General Hospital
S-214 01 Malmö
Sweden