

Compositae sensitivity among patients with contact dermatitis

Value of Compositae oleoresins in a standard test series

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Patch tests with 24 Compositae species were performed on 81 patients suspected of having a plant dermatitis, of whom 16 had positive reactions to various species.

When Compositae were included in the standard series, 10 of 488 consecutive patients (2%) were found to be sensitive to one or more species. Most of the positive test reactions were relevant.

Fourteen of 16 sensitivities could have been detected by testing with two mixtures of Compositae. Alantolactone could not serve as a screening agent, since four of seven Compositae-sensitive patients had negative reactions to it. Concomitant reactions to balsams were found in four of 10 patients with unexpected sensitivity to Compositae.

The clinical pattern of Compositae dermatitis may be that of a lichenified photo dermatitis. These cases are invariably missed, unless patch tests with Compositae are performed. Another group of patients have hand eczema and also require patch tests with Compositae for etiological diagnosis. Because positive, relevant reactions are common, inclusion of a safe and reliable Compositae screening test in the standard series is urgently required. At the present stage, however, our test materials are sometimes irritant and they have occasionally caused active sensitization.

Key words: Compositae – contact dermatitis – oleoresins – plant dermatitis.

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The frequency of plant dermatitis is unknown. Occupational dermatitis from plants is rarely brought to the attention of a dermatologist. Thus, although tulip bulb sensitization is very common indeed, only two cases had been registered at the Dermatological Department of the University of Leyden in Holland (v. Mijnsen 1968). *Primula obconica* used to be the major cause of non-occupational dermatitis in Europe (Hjorth 1965), but has now become rare because florists are reluctant to stock it. For the same reason *Chrysanthemum parthenium* is rarely found in the Copenhagen flower market. Dermatological interest has

centered mainly on indoor plants and cultivated garden plants. In one series, 2108 patch tests were performed with plants and of these, indoor plants accounted for 72% of tests, cultivated garden plants for 25%, while only 3% had been performed with wild plants. Among 250 species tested, 23 accounted for all positive reactions, while 227 species gave negative reactions throughout (Hjorth 1965, 1969).

Rook (1962) stressed the importance of knowledge of the limited number of plant families which often cause dermatitis. Among these, allergenic sensitivity may be restricted to single species.

The ignorance of botany among dermatologists results in large numbers of patch tests with plants in patients suspected of plant dermatitis, without finding the offending species. This also has led to neglect of wild plants.

Dermatological interest has recently focused on the Compositae family of plants. Members of this family are common weeds as well as popular cultivated plants. Mitchell (1969) reviewed the literature on sensitizing Compositae and listed all species involved. Species within only three of 12 Compositae tribes account for most cases. In recent years Compositae dermatitis has been reported from the U.S. (Epstein 1960, Shelmire 1940), Canada (Mitchell et al. 1971), Australia (Burry et al. 1973), India (Lonkar et al. 1974) and Europe (Rook 1961, 1962; Schulz et al. 1975; Bergh 1975; Bleumink et al. 1976) so it is obviously a worldwide disease.

Isolation and identification of the Compositae allergens showed them to be sesquiterpene lactones with one common antigenic determinant, which is a requirement for the sensitizing properties (Fig. 1) (Mitchell et al. 1971, Mitchell & Dupuis 1971). Cross-reactions between allergenic species are common, since about 250 sesquiterpene compounds are distributed within this family (Mitchell et al. 1972). A single species may contain several different sesquiterpene lactones as shown by Hausen & Schulz

(1976), who found 12 different substances of this character in *Chrysanthemum indicum*. Four of these proved to be allergenic, revealing positive patch tests in guinea pigs sensitized with an extract of the plant.

Among Danish patients Compositae dermatitis may have either an airborne pattern, simulating photo dermatitis as described by Hjorth et al. (1976), or appear on areas directly in contact with the plants. In the following pages we present our results of patch testing with the lipid soluble extracts from the plants, the oleoresins. These have been used first for aimed patch testing, and many of them have been included in our standard series.

Materials and Methods

In 1972 the International Contact Dermatitis Research Group included a series of 24 Compositae extracts (oleoresins) among their patch test substances, through the courtesy of Dr. Robert Stier of Hollister-Stier Inc. These oleoresins were supplied in two vehicles, acetone and petrolatum. The concentration of plant extract in the test material was unknown, and so was the concentration of sesquiterpene lactones in them.

For the first two years the Gentofte Hospital performed only aimed patch tests on selected patients suspected of plant sensitivity.

Since 1974 Compositae species have been included in the standard tests series, one by one. The purpose of this was:

- 1) to evaluate possible irritancy of the test substances

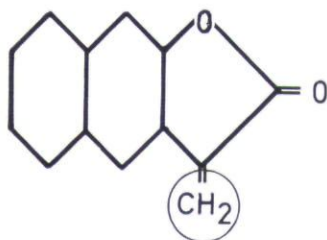


Fig. 1. Alantolactone: essential antigenic determinant is circled.

Table 1. Open and closed patch tests with Compositae oleoresins in acetone

Open patch tests positive	0/11
Closed patch tests positive/ open patch tests negative	2/2
Closed patch tests positive	6/34

- 2) to form an estimate of the frequency of the Compositae sensitivity in Denmark
- 3) to confirm the sensitivity in patients with an unexpected positive reaction by further tests with the remaining 23 Compositae species.

All patients were also examined by a series

of standard patch tests as recommended by the International Contact Dermatitis Research Group. The test substances were supplied by Trol-Lab., A. N. Hansensvej 8, Hellerup, Denmark. The tests were fixed with Finn chambers® on Scanpore® tape.

Table 2.

No. of positive and negative reactions to various Compositae species in 22 Compositae sensitive patients

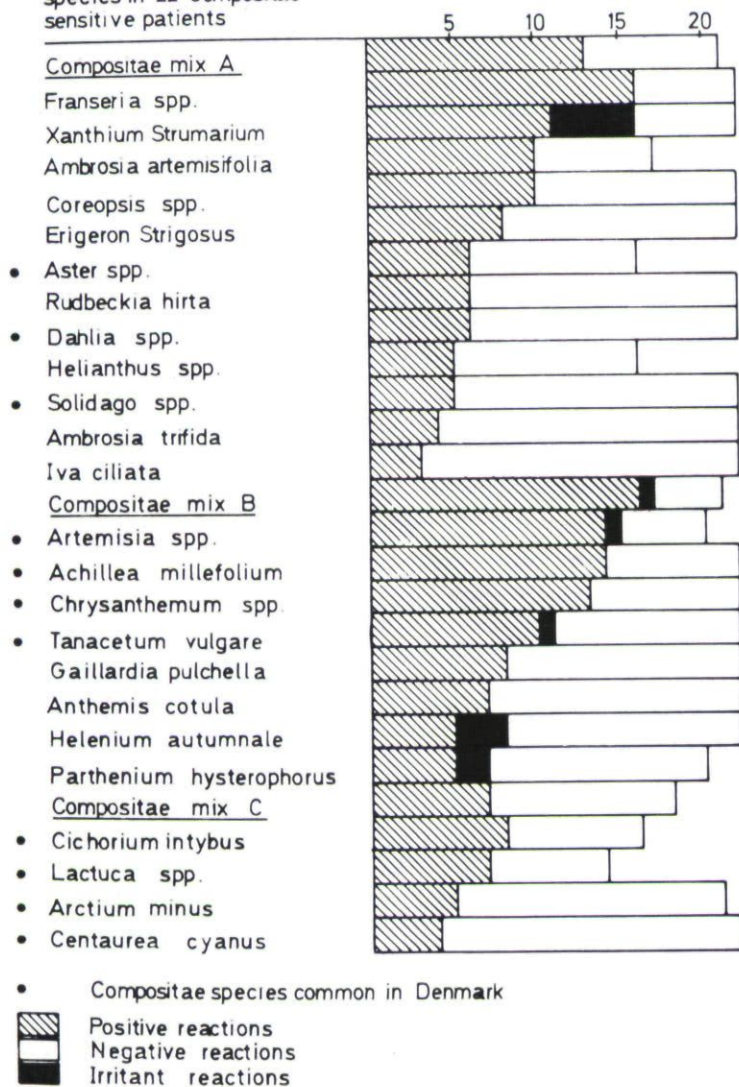


Table 3. Patch tests with alantolactone in petrolatum and Compositae oleoresins in petrolatum or acetone

Alantolactone concentration					0.1 %	0.5 %	1 %
Compositae positive	—	Alantolactone positive			1	0	2
—	—	—	—	negative	1	0	3
—	negative	—	—	positive	0	0	0
—	—	—	—	negative	6	6	1

3/7 Compositae-sensitive patients had positive patch tests to alantolactone.

Results

Open patch tests with Compositae oleoresins in acetone gave false negative reactions in two cases and were then abandoned (Table 1).

Closed patch tests with extracts of all the 24 Compositae species gave positive reactions in 22 out of 88 patients, 12 females and 10 males, of whom six out of 34 were positive to oleoresins in acetone and 16 out of 54 were positive to oleoresins in petrolatum; 16 out of 22 were found by aimed patch testing and six out of 22 by standard patch testing. The number of positive reactions varied from two to 21 (mean nine),

and every patient had his own pattern of sensitivity. This pattern is independent of exposure to the extracted plants, since we found just as many positive reactions to species not found or only growing sporadically in Denmark as to species common to the Danish environment (Table 2).

Helenin or alantolactone (the allergen in *Inula helenium*) (Fig. 1) gave positive reactions in only three out of seven Compositae-sensitive patients. Increase in patch-test concentration from the safe 0.1 % in petrolatum to a sensitizing 1 % did not influence the number of positive reactions to alantolactone in Compositae-sensitive patients (Table 3).

Table 4. Compositae species in the standard series. Vehicle: petrolatum

Species	No. positive/No. tested		
<i>Artemisia</i> spp.	5/120		
<i>Xanthium strumarium</i>	1/14	8 IR	
<i>Parthenium hysterophorus</i>	2/38	11 IR	
<i>Rudbeckia hirta</i>	0/37		
<i>Dahlia</i> spp.	0/21	1 late reaction	
<i>Coreopsis</i> spp.	0/21	1 late reaction	
<i>Aster</i> spp.	0/23		
<i>Anthemis cotula</i>	1/9		
<i>Helenium autumnale</i>	0/10	1 IR	
<i>Solidago</i> spp.	0/18		
<i>Gaillardia pulchella</i>	0/18		
<i>Chrysanthemum</i> spp.	1/23		
<i>Ambrosia artemisiifolia</i>	0/136	10 late reactions	
Total	10/488	12 late reactions	20 IR

IR: irritant reaction.

Table 5. Active sensitization to Compositae oleoresins in petrolatum

5/54 (9.3 %) tested with 24 species had late reactions
 11/488 (2.3 %) tested with one species had late reactions

Table 6. Active sensitization to Compositae oleoresins in petrolatum in 4/54 patients tested with 24 species

Patient no.	Day 2 and 4	Day	No. of species positive
1	negative	14	6 plus 1 IR
2	1 IR	13	2 plus 1 IR
3	1 IR	20	6
4	16 species positive, 2 IR	8	19 plus 2 IR

IR: irritant reaction.

Inclusion of Compositae in the standard series, one species at a time, revealed that 10 out of 488 consecutive patients were sensitive to Compositae (Table 4). The irritant and sensitizing properties of the test substances appear in Tables 4-7. *Xanthium strumarium* gave an irritant reaction in about half of those tested, when petrolatum was used as the vehicle. No obviously irritant reactions were noticed when acetone was used as the vehicle.

Patch testing with mixes of the Compositae oleoresins in petrolatum could have detected 14 out of 16 sensitive patients

Table 7. Active sensitization to Compositae oleoresins in petrolatum. One patient retested with 24 species on day 33

Day	No. of species positive	negative
2	1	23
8	0	24
35	7	17
43	20	4

when two mixes composed of a total of 20 species were used (Table 8).

Mixing of different Compositae species may result in false negative reactions by a dilution of the single allergens. A summation effect of related chemicals in the mixture may have been the cause of two positive reactions and possibly one irritant reaction to one of the mixes with negative reactions to the individual components (Table 9).

Patients who reacted to a Compositae in the standard series (four out of 10) also reacted to one or more balsams (Table 10), while reactions to aimed patch tests apparently were not associated with balsam sensitivity (Table 11).

Discussion

The present study indicates that the frequency of sensitivity to the Compositae family of plants is considerable and warrants inclusion in the standard series of a safe and reliable screening test. Although desirable, it is still premature to recommend ex-

Table 8. Results of patch tests with mixes (components are in Table 2) of Compositae oleoresins in 16 patients positive to individual Compositae. Vehicle: petrolatum

Mixture	No. positive/No. tested
Mix A only	2/16
Mix B only	2/16
Mix C only	0/16
Mix A and B	3/16
Mix A, B and C	7/16
Mix A and/or B	14/16
False negative to mixes	2/16

Table 9. Patch tests with Compositae species and mixes of species. Vehicle: petrolatum

	Mix A	Mix B	Mix C
Mix positive/components positive	12	12	7
Mix positive/components negative	0	2 ^{*)} **)	0
Mix negative/components positive	2	2	4

^{*)} negative to all 24 species tested.

^{**) plus one irritant reaction.}

Table 10. Consecutive patients patch-tested with a Compositae species, balsam of Peru, colophony and wood tars in the standard series

Compositae	No. of patients	Balsam of Peru pos/no. tested	Colophony pos/no. tested	Wood tars pos/no. tested
Positive	10	3/10	3/10	4/10
Negative	446	21/446	6/446	4/320
IR	20	1/20	1/20	0/20
Late reaction	12	0/12	0/12	0/2

IR: irritant reaction.

tracts of Compositae species in the standard series of the practicing dermatologist. Isolation of allergens and standardization of the test material are still on an experimental level.

Screening for Compositae sensitivity

Inclusion of a Compositae extract (pet.) in the standard series gave unexpected positive reactions in 10 out of 488 consecutive patients. Five of these were tested with the remaining 23 Compositae species and had several positive reactions. Two patients with irritant reactions also had further patch tests. A carpenter with an irritant reaction to *Parthenium hysterophorus* had negative reactions to all other Compositae species

tested, but positive reactions to rosewood, balsam of Peru and wood tars. One patient had an irritant reaction to *Xanthium strumarium* and several positive reactions to other Compositae species.

Among the six patients who had positive reactions (including the irritant reaction above) to Compositae in the standard series and also to other Compositae species, one was a farmer with a seasonal dermatitis of an airborne pattern. Two were housewives who also reacted to chicory salad (leaf), one of whom worked in a greengrocer's shop. Chicory salad belongs to the Compositae family, so the primary sensitization might derive from contact with this vegetable. It must be mentioned that in this series we

Table 11. Aimed patch tests with 24 Compositae species, balsam of Peru, colophony and wood tars

	No. of patients	Balsam of Peru pos/no. tested	Colophony pos/no. tested	Wood tars pos/no. tested
Compositae positive	16	0/16	1/16	0/15
Compositae negative	65	0/65	0/65	1/32

have not found sensitivity to chicory without concomitant reactions to other Compositae species. Another two patients had leg ulcers with positive patch tests to balsam of Peru, colophony and wood tars. Balsam of Peru contains a sesquiterpene, the allergenic farnesol (Hjorth 1961, Rudzki & Kielak 1972), which is a precursor of sesquiterpene lactones (Hendrickson 1959). The last patient in this group had unexplained positive reactions to Compositae.

Five patients with a positive patch test to a Compositae in the standard series were not tested with other Compositae. In spite of a careful history the relevance of the positive patch tests was questionable. Two had positive reactions to balsams.

The positive patch tests to balsams in Compositae-sensitive patients were found almost exclusively among those with an unexpected positive reaction (Table 10). Since our patients with aimed patch tests, and therefore with relevant positive reactions to Compositae, did not react to balsams (Table 11), we suggest that cross-sensitivity from balsams to Compositae is not reciprocal. The question whether these concomitant reactions are true cross-sensitivities and whether they are reciprocal needs further investigation in guinea pig experiments.

The frequency of irritant reactions and late reactions warrants further work on standardization of the test material. In acetone as a vehicle the oleoresins caused no irritant reactions and no late reactions. But since acetone evaporates and leaves an unknown concentration of test material, it is an undesirable vehicle. When petrolatum was used, the concentration of allergen seemed to be too high, as estimated by the late and irritant reactions observed (Tables 4-7). The risk of active sensitization is considerable, especially when patch testing with the whole series of 24 species in pet. (Table 5 & 6). Severe reactions were observed in a patient retested with the 24 species (Table

7). The duration of this active sensitization, and the consequences for the patients, is as yet unknown. Since patch-test sensitizations may be of short duration (White & Baer 1950) these patients will be reviewed in a follow-up study.

Alantolactone in our experience cannot be used to screen for Compositae sensitivity. Hjorth (1970a, b) found that alantolactone 1 % in petrolatum caused late reactions in nine out of 178 patients and negative reactions in two patients sensitive to *Chrysanthemum*. To avoid active sensitization, the patch test concentration of alantolactone should not exceed 0.1 % in petrolatum. In our series (Table 4) it appears that a rise in concentration from 0.1 % pet. to 1 % pet. did not increase its value as a screening agent. In this series we saw no false positive reactions and no late reactions to alantolactone. Bleumink et al. (1976) patch-tested six persons with contact dermatitis from *Chrysanthemum* using different sesquiterpene lactones. All reacted to alantolactone 0.3 % in alcohol. Schulz et al. (1975) found negative reactions to alantolactone 1 % in alcohol in three out of five *Chrysanthemum*-sensitive patients, while all had positive patch tests to the sesquiterpene lactone parthenolide, the major allergen in *Parthenium hysterophorus* (Lonkar et al. 1976) and *Chrysanthemum parthenium*. In guinea pig experiments Schulz et al. (1975) found, that primary sensitization with *Chrysanthemum indicum* gave cross-reactions to parthenolide in 10 out of 15 animals and to alantolactone in only two out of 15. Primary sensitization with parthenolide gave cross-reactions to *Chrysanthemum* leaf in 15 out of 20 and to alantolactone in 11 out of 20. Twenty guinea pigs primarily sensitized with alantolactone had negative reactions to *Chrysanthemum indicum* (leaf) and parthenolide. By thin-layer chromatography neither parthenolide nor alantolactone could be detected in *Chrysanthemum indicum*,

which contains several other allergenic sesquiterpene lactones (Hausen & Schulz 1976).

In a preliminary study at this department, Bergh (1975) found that five out of six Compositae-sensitive patients had positive reactions to *Ambrosia artemisifolia* (short ragweed), which appeared promising as a screening test for Compositae sensitivity.

Our present results revealed that only 13 out of 21 Compositae-sensitive patients had positive reactions to *Ambrosia artemisifolia*. None of the 24 species has given positive reactions in all Compositae-sensitive patients, and none has given negative reactions throughout. Thus, no single species can be used reliably as a screening agent.

Table 12. Relevance of positive patch tests to Compositae oleoresins

Preliminary diagnosis	Aimed patch testing	Standard patch testing Further patch-tested and positive to several Compositae species
<i>Hand eczema</i> 12 patients	F. Atopic. Amateur gardener F. Atopic. Florist F. Florist. F. Housewife. Positive also to chicory salad (leaf) F. Sandwich maker. Positive also to chicory salad (leaf) F. Florist F. Dermatitis of face. Relevance to actual eczema? M. Amateur gardener M. Atopic. Amateur gardener M. Florist	F. Positive also to lettuce and chicory salad (leaf) F. Cleaner. Not relevant to actual eczema
<i>Universal dermatitis</i> 2 patients	M. Botanist	F. Atopic dermatitis. Recurrence during employment in a green- grocer's shop. Positive also to chicory salad (leaf)
<i>Leg ulcer and stasis dermatitis</i> 2 patients		F. Amateur gardener. Dermatitis of forearms after gardening. Positive to balsam of Peru, colophony, wood tars M. Positive to balsam of Peru, colophony, wood tars
<i>Photo dermatosis</i> *) 6 patients	M. Atopic dermatitis. Flared in light-exposed areas during summer M. Gardener. Seasonal dermatitis of light-exposed areas M. Railroad worker. Seasonal dermatitis of light-exposed areas M. Seasonal dermatitis of light-exposed areas F. Seasonal dermatitis of light-exposed areas	M. Atopic. Farmer. Seasonal dermatitis of light-exposed areas

*) Hjorth et al. 1976.

Table 13. Relevance of positive patch tests to Compositae oleoresins

Positive to a Compositae species included in the standard series.
Not further patch-tested. Not relevant to actual dermatitis.

M. Dermatitis of forearms and legs.

Positive to balsam of Peru, wood tars and trichlorocarbaniide

F. Stasis eczema

F. Dermatitis of scalp, neck, ears

Positive to own hair spray and wood tars

F. Stasis eczema

F. Folliculitis of scalp

Using a mix of oleoresins from different Compositae species reduces the risk of active sensitization and also the frequency of irritant reactions. Table 10 shows that a screening test with two mixes containing eight and 12 different species respectively could have detected 14 out of 16 sensitive patients. Further work will show which species should be used in a mixture to make it reliable and safe for screening purposes.

Relevance of positive reactions

Analysis of the history and patch-test findings showed that the majority of positive reactions were relevant to a Compositae dermatitis, some to balsam sensitivity and only four out of 27 were not relevant (Table 12 & 13).

Site of allergen

Too much emphasis has been laid upon the occurrence of lipid soluble oleoresins in pollens (Shelmire 1939). Both wind-pollinated Compositae species (such as *Ambrosia spp.*) and insect-pollinated (such as *Chrysanthemum spp.*) cause dermatitis. The site of the allergens in the Compositae plants have been studied by Rodriques et al. (1976) who found trichomes containing sesquiterpene lactones on the leaf surfaces, phyllaries and achenes of *Parthenium hysterophorus*, species of *Ambrosia*, *Iva* and *Helenium*. Hausen (1976) has found iden-

tical oleoresins in the surface trichomes as in the pollens of some Compositae.

Treatment

Compositae-sensitive patients cannot avoid the allergens, which are almost ubiquitous in the summer months. Not only may direct contact with the plants cause eczema, but airborne contact with dried parts of the plants may also result in dermatitis of exposed areas (Hjorth et al. 1976). Hausen (1976) found that extracts of fresh plants are identical to extracts of dry plants (*Chrysanthemum indicum*, *Arnica montana* and *Achillea millefolium*) kept for years with no regard to preservation.

Oral hyposensitization with extracts of the plants as described by Kligman (1958) in his study of poison ivy dermatitis is theoretically and practically possible. Mitchell & Dupuis (1971) gave alantolactone by mouth in increasing dosages to three sensitive patients and stated that the early results of such hyposensitization appeared promising, as shown by quantitative patch testing, although further investigations are needed. Storrs et al. (1976) treated four Compositae-sensitive patients; two of them believed that their dermatitis was "somewhat better" while taking oleoresin-filled capsules.

For oral hyposensitization, extracts of common allergenic Compositae species from

the patients' environment should be used, since these species in all probability are the primary sensitizers. Hollister-Stier Inc. market eight mixtures of different Compositae species for oral hyposensitization. Controlled studies of the effect and side effects of this therapy are to the authors' knowledge not available. Oral hyposensitization with poison ivy certainly causes a variety of unpleasant side effects (Kligman 1958).

The theoretical possibility for oral hyposensitization with the specific allergens in sensitive patients is supported by the opinion that allergy to *Chrysanthemum* does not exist in Japan, where *Chrysanthemum* leaves are eaten in salad (Hausen 1976). Red Indians eat poison ivy and do not get dermatitis from it (Kligman 1958).

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