Acta Dermatovener (Stockholm) 51: 123–128, 1971

ALLERGIC DISEASES AMONG RELATIVES OF PATIENTS WITH ALLERGIC CONTACT DERMATITIS

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Abstract. Siblings, parents, and children of patients suffering from allergic contact dermatitis have been patch-tested with commonly occurring contact allergens, and investigated with respect to present or previous allergic contact dermatitis and atopic diseases. A control group composed of randomly selected twins (one from each pair), and the husbands and wives of the patients have been similarly tested and investigated. The frequency of persons reacting positively to the patch tests was higher among the relatives of the probands than among the controls. These results support the hypothesis that genetic constitution may be of importance for the development of delayed hypersensitivity reactions. The rate of positive reactors was higher among women than among men. This difference may be explained by the effects of sex-chromosome-linked, or sex-controlled factors, or the degree of penetrance may differ between the two sexes. The frequency of atopics was somewhat higher among the relatives of the probands than among the controls. The incidence of atopics was higher among the persons with only positive tests than among either those with positive patch tests and previous or current allergic contact dermatitis or among the probands. There may, thus, be some connection between the development of atopy and delayed hypersensitivity reactions. However, there is no evident explanation for such a connection.

Ever since the work of Chase (2) it has been generally accepted that the genetic constitution of experimental animals is of importance for their ability to show contact sensitivity. Chase was able to establish two strains of guinea pigs which differed significantly in their degree of sensitivity to 2,4-dinitrochlorobenzene despite the same sensitizing procedure and the same environmental conditions. These findings have been confirmed in many studies using different antigens (11). However, it is more questionable whether hereditary factors also operate in the development of human allergic contact dermatitis.

We have, in earlier preliminary reports (4, 5), shown that the frequency of atopic diseases (asthma, hay fever, atopic dermatitis) and positive patch test reactors is high among relatives of patients suffering from allergic contact dermatitis. Since our reports appeared, Walker, Smith & Maibach (14) have published their results of sensitizing volunteer parents and children to 2,4-dinitrochlorobenzene and *p*-nitrosodimethylaniline. They found that children whose parents could be sensitized to these two substances became sensitized to a higher degree than children of parents who could not be sensitized. They conclude that their findings support the hypothesis that genetic factors play a role in susceptibility to human allergic contact dermatitis.

In the present work we have extended our series of relatives of patients with allergic contact dermatitis who have been patch tested, and investigated with regard to current and previous contact dermatitis and atopic diseases. In addition, a control group has been similarly tested and investigated.

METHODS

Patch test. Patch testing was performed with 23 substances known to be common contact allergens in Sweden (10). They were used in the following concentrations: 1) potassium bichromate, 0.5% in water; 2) *p*-phenylenediamine, 2% in petrolatum; 3) balsam of Peru, 25% in petrolatum; 4) cobaltous chloride, 2% in water; 5) wood tars, 5% in petrolatum; 6) nickel sulphate, 5% in water; 7) Vioform® + Sterosan®, 3 + 3% in petrolatum; 8) tetramethylthiuramdisulphide, 2% in petrolatum; 9) formaldehyde, 2% in water; 10) coal tars, 5% in petrolatum; 11) benzocaine, 5% in petrolatum; 12) *n*-phenyl-*n*-cyclohexyl-*p*-phenylenediamine ("Bayer 4010"), 2% in

Table I. *The substance considered relevant to the dermatitis of the probands*

Substance	No. of probands ♀	♂
Chromium	5	31
Nickel	16	3
Cobalt	4	3
Formaldehyde	7	0
p-Phenylene-diamine	5	1
Tetramethylthiuramdisulphide	5	1
Turpentine	1	5
Balsam of Peru	2	0
N-Phenyl-*N*-cyclohexyl-*p*-phenylenediamine ("Bayer 4010")	0	2
Neomycine	1	0
Primrose	1	0
Mercaptobenzothiazole	1	0
Total number of probands	48	46

petrolatum; 13) diphenyl-*p*-phenylenediamine, 2% in petrolatum; 14) neomycine sulphate, 40% in petrolatum; 15) primrose, leaf.; 16) mercaptobenzothiazole, 2% in petrolatum; 17) turpentine, 10% in peanut oil; 18) procaine HCl, 1% in water; 19) lanolin, as is; 20) methyl-ethyl-propyl-*p*-oxibenzoate, 5% in petrolatum; 21) perfume "A", 5% in petrolatum; 22) perfume "B", 5% in petrolatum; 23) perfume "C", 5% in petrolatum.

The substances were applied to the skin of the back of the patients in two vertical rows with circular occlusive patches. These were removed after 48 hours, and the readings were recorded 24 hours later. Positive reactions comprised erythema and infiltration with or without papules and vesicles.

Selection of probands. The probands were consecutive patients with allergic contact dermatitis, admitted to the skin clinic, Karolinska Hospital, Stockholm. The diagnosis was based upon the history of the disease and the results of the patch test. Altogether 94 probands (48 women and 46 men) are included in the investigation. The age varied between 16 and 79 years. Table I shows the substances which we considered the cause of the dermatitis of the probands.

Investigation of relatives. The parents of the probands, as well as siblings, and children older than 10 years were questioned about past or current allergic contact dermatitis and atopic diseases (atopic dermatitis, asthma and hay fever) and they were all examined for the presence of these diseases. In many cases the diagnoses were verified by hospital records. Patch testing was performed on all.

Controls group. The controls included wives and husbands of the probands and a group composed of randomly selected twins—one from each pair— whom we recently have observed (6).

All controls were investigated and patch tested in exactly the same way as the probands and their relatives.

Statistical methods. For statistical comparisons of the incidence of positive patch tests, allergic contact dermatitis, or atopy in two different groups, the observed numbers were arranged in fourfold tables. The independence or homogeneity was tested by χ^2 method or by use of Fisher's (3) exact treatment of 2×2 tables.

For homogeneity tests involving more than two groups the observed data were arranged in $2 \times n$ tables and χ^2 values were calculated.

RESULTS

In Table II are shown the results of the investigation of the relatives to the probands and the controls. No significant heterogenity was found either between the male groups or between the female groups of relatives. Therefore, it was considered appropriate to assemble all female relatives in one group and all male relatives in another as shown in Table III. The controls are also summarized in one female and one male group in Table III since here too there was no significant hetereogeneity among the female and the male groups.

The frequency of positive reactors is signifi-

Table II. *The results of patch testing different groups of relatives of probands and of controls*

	Total	Pos. reaction *n*	%
Male, relatives of			
♂ probands			
Brothers	60	15	25
Sons	36	3	8
Fathers	14	1	7
♀ probands			
Brothers	44	11	25
Sons	24	7	29
Fathers	18	2	11
Female, relatives of			
♂ probands			
Sisters	63	16	25
Daughters	28	10	36
Mothers	15	5	33
♀ probands			
Sisters	60	20	33
Daughters	19	1	5
Mothers	23	10	43
Male controls			
Unrelated twins	33	5	12
Husbands of female probands	19	4	21
Female controls			
Unrelated twins	68	15	22
Wives of male probands	36	4	11

cantly higher among the *female* ($0.05 > p > 0.025$) than among the male relatives and also significantly higher than in the female control group (18.3 %) ($0.05 > p > 0.025$). The corresponding frequency of the male controls is not significantly different either from that of the female controls.

In Table III are also recorded the frequencies of current dermatitis which appeared in a significantly higher frequency among female than among male relatives ($0.025 > p > 0.01$). The difference between the female relatives and the female controls is also statistically significant ($0.05 > p > 0.025$). The frequency of contact dermatitis among male controls is not statistically different from that of the female controls or that of the male relatives.

Also the percentages of individuals refusing testing are shown in Table III.

Table IV shows the occurrence of positive reactors in different age groups of the relatives of the probands and the controls. The frequencies of reactors are lower in the younger than in the older age groups, though the differences are not statistically significant.

Among the controls the lower age groups are small or absent.

Table V shows the occurrence of individuals among the positive reactors who actually had or previously had had allergic contact dermatitis. The control group and the group of relatives within each sex do not differ significantly with regard to the frequency of those with contact dermatitis. However, the frequency is significantly higher among the *females* than among the males ($0.005 > p > 0.001$).

Table III. *Summarized results of patch testing, occurrence of current allergic contact dermatitis, and rates of individuals refusing testing*

		Pos. reaction		Current dermatitis		Refusing testing	
	Total	*n*	%	*n*	%	*n*	%
Relatives of probands							
♂	196	39	19.9	8	4.1	48	19.8
♀	208	62	29.8	23	11.1	42	16.8
Controls							
♂	52	8	15.4	1	1.9	23	30.7
♀	104	19	18.3	4	3.8	32	23.5

Table IV. *Age distribution of the relatives of the probands and the controls and the frequency of positive reactors in age groups*

	Age groups						
	10–19	20–29	30–39	40–49	50–59	60–69	70+
Relatives of probands							
Male							
Number tested	25	37	24	30	45	23	12
% pos.	16	16	13	23	22	35	8
Female							
Number tested	16	39	28	38	49	26	12
% pos.	19	21	32	37	29	31	50
Controls							
Male							
Number tested	—	1	5	19	19	6	2
% pos.	—	—	—	11	26	—	50
Female							
Number tested	—	2	5	37	38	18	6
% pos.	—	—	—	14	21	28	17

The occurrence of atopic diseases among the probands, their relatives and the controls are shown in Table VI. The frequency of atopics is higher among the relatives than among the controls and also than among the probands. However, the differences are not statistically significant. A significant heterogeneity of the frequencies of atopics was found between the six different groups of female relatives ($0.01 > p > 0.005$). The frequency of atopics was especially high among the daughters of the male probands. In this group, 12 of 28 tested, that is 41 %, were classified as atopics. This group caused the bulk of the heterogeneity. A homogeneity test, where the daughters of the male probands are excluded gives $\chi^2 = 3.79$ (d.f. = 4).

In Table VI it can be seen that the atopics are similarly distributed among positive and negative patch test reactors within each of four groups: female relatives, male relatives, female controls and male controls, respectively. It was seen in the same table that the frequency of atopics was low among the probands. Therefore, it was considered of interest to study the frequency of atopics in the two groups: 1) positive reactors with previous or present allergic contact dermatitis, 2) positive reactors only. The results of this comparison are

Table V. *The occurrence of individuals with current or previous allergic contact dermatitis among those who reacted positively at the patch tests*

	Pos. reaction	Contact dermatitis	
	n	*n*	%
Male			
Relatives	39	18	46
Controls	8	3	38
Total	47	21	45
Female			
Relatives	62	41	66
Controls	19	17	89
Total	81	58	72

shown in Table VII where all positive reactors among the relatives and the controls have been included. The difference found is statistically significant ($0.05 > p > 0.025$), which means that the frequency of atopics is high among reactors without dermatitis.

DISCUSSION

Studies of prevalence rates of allergic contact dermatitis in human populations are few. In connection with mass health examinations in Sweden, Hellgren (8) estimated the incidence of contact dermatitis to be 3.5% among men and 6.1% among women. The rates of individuals with current contact dermatitis in the control group of the present study were similar to those found by Hellgren. Agrup (1), who investigated certain communities in Sweden with regard to hand eczema, also found a higher incidence of contact dermatitis among women than among men.

In the control group about every sixth individual reacted positively to patch testing. We have not found any comparable investigation in the literature, however, of patch testing of groups of individuals selected because of skin diseases other than allergic contact dermatitis which show that the delayed sensitivity reaction is fairly common (1, 13).

One could speculate on the possibility that the test concentrations of the antigens are too high and, therefore, that part of the reactions are not allergic but primary irritant reactions. However, that seems improbable as the distribution of the frequency of the positive reactions to the different antigens follows the same distribution as has been found among antigens which are the cause of allergic contact dermatitis in Sweden (10).

It is quite possible that contact dermatitis is developed under extreme exposure to allergens while milder exposure may result in latent allergy revealable only by the patch tests. According to Lowney (9) if a very low degree of sensitivity is induced the intensity of sensitivity remains fixed near that level regardless of further sensitizing exposures. In that way the latent allergy would be a protection against a manifest allergic contact dermatitis. There was a higher frequency of positive reactors and individuals with current dermatitis in the female control group than in that of the males. This difference might be an underestimation because of the somewhat higher rate of males refusing testing. It seems likely that those who had skin diseases were more willing to take part in the investigation than those without skin diseases. The results of testing the relatives of the probands also shows the same difference between females and males.

On the whole the frequency of positive reactors was higher among the relatives of the probands than among the controls. The rates of individuals refusing testing were larger in the control groups than in the groups of relatives. Therefore, the difference in rates of positive reactors between

Table VI. *The incidence of atopic diseases among positive and negative patch test reactors*

	Patch test	Total	Atopy	
			n	%
Male				
Probands	Pos.	46	3	6.5
Relatives of probands	Pos.	39	5	12.8
	Neg.	157	22	14.0
	Total	196	27	13.8
Controls	Pos.	8	1	12.3
	Neg.	44	5	11.4
	Total	52	6	11.5
Female				
Probands	Pos.	48	4	8.3
Relatives of probands	Pos.	62	12	19.4
	Neg.	146	29	19.9
	Total	208	41	19.7
Controls	Pos.	19	3	15.8
	Neg.	85	9	10.9
	Total	104	12	11.5

the relatives and the controls might have been underestimated. We also observed as did Agrup (1) and Fregert et al. (7) that the frequencies of positive reactors among the relatives of the probands are lower in the younger than in the older age groups. However, among the controls lower age groups were small or absent. This may be another source of underestimating the differences between the controls and the relatives of the probands.

The higher frequency of positive reactors among relatives of individuals with allergic contact dermatitis as compared with the controls indicates that the genetic constitution may be of importance for the development of delayed hypersensitivity reactions. The present results are thus in agreement with other investigations on man (14), and on experimental animals (11). The manifestation of the delayed hypersensitivity reactions must however be influenced very much by environmental factors. In an earlier study the distributions of concordant and discordant monozygotic twin pairs were found to be very similar to each other (6). It must be stressed, however, that the twin study was restricted to a relatively small material of randomly selected twin pairs.

The higher rate of positive reactors among women than among men may indicate that sex-chromosome-linked or sex-controlled factors are involved in the determination of any genetic constitution which may be necessary for the development of the delayed hypersensitivity reaction. Of course one cannot exclude the possibility that this difference between males and females may be due to environmental factors. Different habits, for example wearing of nickel-plated zipfasteners, suspenders, clasps on necklaces, or earclips, may cause women, in daily life, to be exposed to allergenic substances to a higher degree than men. The higher rate of contact dermatitis among women than among men with positive patch tests (Table VI) may also have the same cause.

The frequency of atopic diseases in the control groups shows a good correlation with the morbidity rate in other similar investigations (12). Among the relatives of the probands the overall frequency of atopics was somewhat, though not significantly, higher than among the controls. Among the daughters of the male probands there was a very high incidence of atopics causing a heterogeneity between the different groups of female relatives. These results suggest that there may exist some kind of connection between the delayed hypersensitivity reaction and the atopy.

Table VII. *The frequency of atopics compared in the two groups: previous or current dermatitis and only positive patch test*

	Total	Atopy	
		n	%
Previous and/or current contact dermatitis	79	8	10.1
Positive reaction only	49	13	26.5

The frequency of atopics was found to be higher among relatives and controls with positive patch tests only than among relatives and controls with previous and/or current contact dermatitis. The frequency of atopics of the latter group was very similar to that among the probands. Also these results suggest that there may be a connection between the two types of disease. However, this connection seems to mean that the development of allergic contact dermatitis and atopy is competitive in some way.

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Received August 17, 1970

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