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ALLERGIC REACTION PATTERNS IN RELATION TO AGE, SEX, SEASON, EOSINOPHILIA AND SOME GENETIC MARKER SYSTEMS

By

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MATERIAL AND METHODS

A. The Material

The present investigation is based on data which were collected during the years 1958 to 1964. They concern 4685 subjects tested at the Department of Clinical Chemistry, Danderyds Hospital, Sweden. The subjects had been submitted to tests from different departments of the hospital, mostly the oto-rhinolaryngological department, and on different indications, viz: 1) clinically manifested allergy; 2) suspicion of allergy; 3) clinical symptoms where allergy could not be excluded. The sample is thus a mixture of people with and without allergic reactions, but with a much higher incidence of allergy than the general population.

With age divided on 11 classes the distribution of the total material as to age and sex is shown in Table 1. Women are overrepresented in the material, and the age distribution is different for males and females. Compared with the age distribution in the general Swedish population ages below 10 years and above 50 years are underrepresented, all ages in between are in excess.

B. Methods

Tests for allergic reactions have been performed by the intradermal technique and each test has included 38 to 45 allergens. A total of 48 different allergen-extracts have been used, most of them commercial (Vitrum). The tests have been rather evenly distributed over the year, as can be seen from Table 2, but there is a small surplus in March, September and October.

TABLE I
Age and Sex of 4640 Subjects Tested for Allergic Reactions.

Age	Men		Women		General swedish Pop.	
	Number	%	Number	%	% men	% women
< 10	210	9.7	82	3.3	14.2	13.4
10-14	338	15.6	219	8.8	7.1	6.7
15-19	269	12.4	299	12.1	8.1	7.8
20-24	184	8.5	251	10.1	8.2	7.7
25-29	167	7.7	241	9.7	6.4	6.0
30-34	132	6.1	227	9.2	11.9	11.6
35-39	146	6.8	275	11.1		
40-44	180	8.3	257	10.4		
45-49	166	7.7	198	8.0	13.8	13.6
50-54	135	6.2	191	7.7		
> 54	234	10.8	239	9.6	30.3	33.2
Total	2161		2479			

Contingency χ^2 for heterogeneity between male and female age distributions: $\chi^2 = 176.6$; to degrees of freedom, $P < 0.001$.

Allergic reactions have been classified from ocular inspection as:

$$\begin{array}{ccccccccccccc} & \text{0} & \text{1} & \text{2} & \text{3} & \text{4} & \text{5} & \text{6} & \text{7} & & \text{8} & & \text{9} \\ - & (+) & + & + & (+) & ++ & ++ & (+) & +++ & +++ & + & \left\{ \begin{array}{l} ++++ \\ ++++ \end{array} \right. & > +++ & +++ \end{array}$$

At least 75 per cent of the classifications have been performed by two of the authors (AH and GW).

Degree number 1 is very weak and may be classified as an uncertain positive reaction. The maximal individual degree of allergic reaction (IMAX) among 4685 tested persons is shown in Fig. 1. About 25 per cent of the subjects show no allergic reaction and a further group of 8 per cent only an uncertain reaction. Thus about two thirds of the subjects can be taken as established allergics.

Differential blood counts for evaluation of frequency of eosinophilic leukocytes have been performed on 4413 of the subjects (94 per cent). The percentages (EP-values) have been given as integers and high percentages have been pooled as shown in Table 3.

The blood typing for ABO and Rh has been performed by standard methods. 1326 subjects have been tested for ABO, where four types, A, B, AB, and O were distinguished. For Rh only positive or negative reaction with anti-D was

TABLE 2
Distribution of Tests on Months of the Years. In the Analyses the Months have
been Pooled into Six Pairs as shown by the Brackets.

Month	Jan.	Febr.	March	April	May	June	July	Aug.	Sept	Oct.	Nov.	Dec.	Total
Number of tests	385	391	421	368	346	382	380	345	438	471	404	347	4678
%	8.2	8.4	9.0	7.9	7.4	8.2	8.1	7.4	9.4	10.1	8.6	7.4	
	16.6		16.9		15.6		15.5		19.5		16.0		

TABLE 3
Distribution of Percentage of Eosinophilic Leukocytes (EP) among 4413 Subjects.
In the Analyses Values have been Pooled into 4 or 11 Classes as shown by the
Brackets.

EP	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	>18*	Total
Number	92	540	679	583	540	428	321	266	225	176	139	92	69	61	38	42	32	17	19	54	4413
%	2.1	12.2	15.4	13.2	12.2	9.7	7.3	6.0	5.1	4.0	3.2	2.1	1.6	1.4	0.9	1.0	0.7	0.4	0.4	1.2	

* median value 22.

registered, and the sample included 1275 subjects. These distributions are shown in Table 4.

The secretor character was tested on 533 subjects by agglutination reactions of saliva samples. The samples were boiled and centrifugated whereafter the supernatant was added to anti-A, -B, or -H test-sera, according to the blood type of the subject. The mixture was tested for agglutination ability by adding blood cells in dilution 1/50.

TABLE 4
Distribution of Blood Types in the ABO and Rh Systems.

	A	B	AB	O	Total	Rh+	Rh—	Total
Number	655	126	58	487	1326	1063	212	1275
%	49.4	9.5	4.4	36.7		83.3	16.6	
District average % (Beckman 1959)	48.3	10.5	5.0	36.2		84.7	16.6	

χ^2 for deviation from average:

$$\chi^2 = 2.76; 3 \text{ d.f.}$$

$$P \text{ 0.5-0.3}$$

$$\chi^2 = 1.62; 1 \text{ d.f.}$$

$$P \text{ 0.3-0.2}$$

TABLE 5
Distribution Among 533 Subjects Tested for the Secretor Character.

	Secretors	non-Secretors	Total
Number	431	102	533
%	80.9	19.1	
Swedish average % (Nerell 1963)	77.9	22.1	

χ^2 for deviation from average: $\chi^2 = 2.17; 1 \text{ d.f.}; P \text{ 0.2-0.1.}$

The saliva from secretor individuals contains antigen which reacts with the serum antibody and inhibits the subsequent agglutination of blood cells. Non-secretors are thus characterized by agglutination in this test. The distribution of this character is shown in Table 5.

Ability to taste phenylthiocarbamide (PTC) was tested on 1124 subjects. These were classified as tasters or non-tasters according to their ability to taste

PTC in diluted solutions. Six different concentrations were used and the threshold was placed at the point of minimum frequency, which was found to be between the dilutions 0.0625 per cent and 0.0156 per cent. The distribution of test results and of tasters and non-tasters is shown in Table 6. For part of this material an association has been found between the taster character and protein bound iodine (Widström & Henschen 1963).

TABLE 6
Distribution among 1124 Subjects tested for their Ability to Taste Phenylthiocarbamide (PTC) in Diluted Solutions.

	No taste reaction	Taste reaction at dilution					
	0.25%	0.0625%	0.0156%	0.00391%	0.000975%	0.0005%	
Number	151	121	85	76	196	383	112
	non-tasters 357			tasters 767		Total 1124	
	31.8%			68.2%			
Swedish average	30 %			70 %			

χ^2 for deviation from Swedish average: $\chi^2 = 1.66$; 1 d.f.; P 0.2-0.1

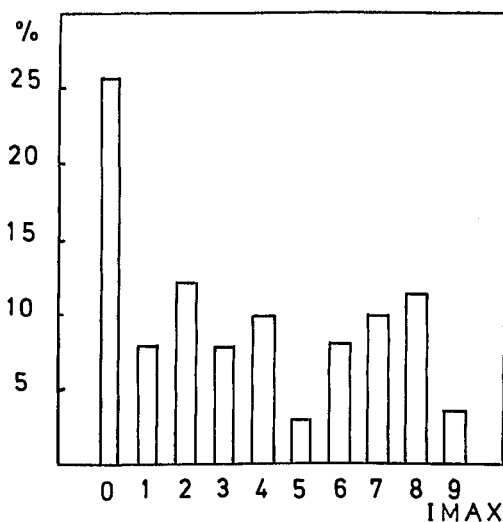


Fig. 1.

Distribution of maximal individual degree of allergic reaction (IMAX) among 4685 subjects tested with 38-45 allergens.

TABLE 7
Width of the Allergic Spectrum. Observed and Expected Number of Subjects with Different Number of Allergic Reactions > 1 , > 3 , > 5 . The Expected Numbers are Calculated from the Geometric Distribution $P(n) = N \cdot a^k(n-1)$; where n is the Number of Reactions.

Number of reactions	Subjects with reactions > 1			Subjects with reactions > 3			Subjects with reactions > 5		
	obs.	%	exp.	obs.	%	exp.	obs.	%	exp.
1	518	16.74	463.4	490	22.73	490.3	474	30.48	556.9
2	407	13.15	394.3	348	16.15	382.6	386	24.82	361.1
3	330	10.67	335.6	246	11.42	298.6	237	15.24	234.3
4	281	9.08	285.6	223	10.95	233.0	180	11.58	152.0
5	203	6.56	243.1	183	8.49	181.8	110	7.07	98.6
6	206	6.66	206.9	161	7.47	141.9	62	3.99	64.0
7	161	5.20	176.0	108	5.01	110.7	34	2.19	41.5
8	155	5.01	149.8	94	4.36	86.4	27	1.74	26.9
9	116	3.75	127.5	78	3.62	67.4	17	1.09	17.5
10	120	3.88	108.5	56	2.60	52.6	12	0.77	11.3
11	101	3.26	92.3	46	2.13	41.0	7		
12	79	2.55	78.6	47	2.18	32.0	2		
13	70	2.26	66.9	25	1.16	25.0	2		
14	65	2.10	56.9	14	0.65	19.5	1		
15	39	1.26	48.4	12	0.56	15.2	3		
16	43	1.39	41.2	5			0		

17	36	1.16	33.2	4	0
18	37	1.20	29.9	4	1
19	23	0.74	25.4	4	
20	19	0.61	21.6	1	
21	19	0.61	18.4	3	
22	15			1	
23	9			1	
24	10			1	
25	5				
26	2				
27	7				
28	5				
29	1				
30	3				
31-35	3				
36-40	3				
41-45	3				
Total (N)	3094			2155	1555
a	0.1498			0.2275	0.3580
k	0.8510			0.7803	0.6487
χ^2	23.63 d.f. 18			27.93* d.f. 12	22.04* d.f. 7

* $P < 0.01$

For the genetic systems comparisons with available average frequencies for Sweden or the Stockholm area have been made. In no case has significant discrepancies between the present material and these averages been found.

All informations concerning the subjects: age, sex, date of test, percentage of eosinophilic leukocytes (EP), ABO- and Rh-blood type, secretor and taster reaction and reaction to allergens No 1-48 were punched on cards for data processing. The analyses have been performed at UMDAC, the data central at the University of Umeå.

ANALYSIS OF TEST RESULTS

A. Distribution of Reaction Patterns

Two aspects of the severity of allergic conditions have been considered:

- 1) the maximal individual degree of reaction for all allergens included in the test, IMAX;
- 2) the width of the reaction spectrum, measured as number of reactions >1 , >3 , or >5 for each patient.

Fig. 1 shows that the distribution of IMAX-values is bimodal with maxima at degree 2 and 8 and a minimum at degree 5. This may have some biological cause or simply be due to the subjective assessment of reaction values. The highest IMAX-value, 9, is reached by 158 patients, which is 3.4 per cent of the total material and 5.1 per cent of the 3094 established allergics. The distributions of patients with increasing numbers of allergic reactions >1 , >3 , >5 are given in Table 7. The distributions are approximately geometric, i.e. the expected frequency of a certain number of reactions, n , can be described by the formula $P = a \cdot k^{(n-1)}$; where a is the probability of one reaction and k the probability of one additional reaction. The best estimates of a and k are obtained from the regression of the logarithm of the frequency on number of reactions (Fig. 2). Only frequencies greater than 0.5 per cent have been included. These estimates are given in Table 7 together with the expected frequencies and χ^2 -tests for deviations from expectations. As can be seen the deviations give significant χ^2 -values in two cases. The greatest discrepancies are confined to the frequency of one or a few reactions. The re-

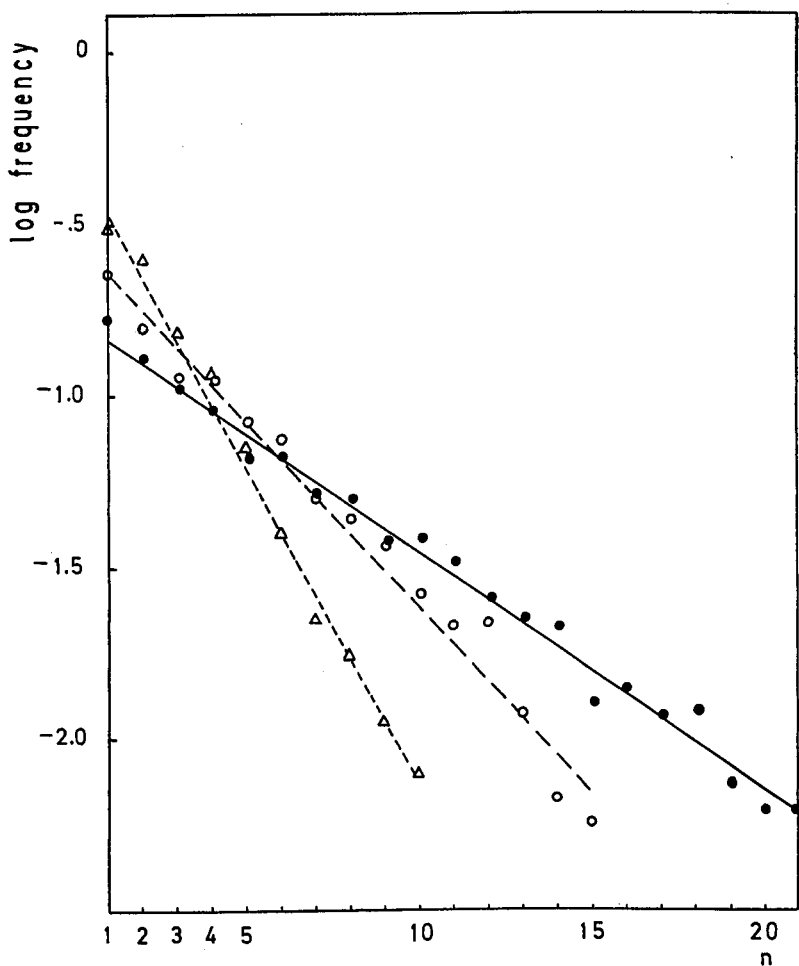


Fig. 2.

Number of reactions > 1 (●); > 3 (○); > 5 (△) plotted against the logarithm of their frequency. Regression lines are estimated from observed frequencies > 0.5 per cent (log frequency > -2.301). Regression equations:

$$\begin{aligned} Y &= -0.825 - 0.070 (n-1); \text{——— reactions } > 1; \\ Y &= -0.643 - 0.108 (n-1); \text{--- reactions } > 3; \\ Y &= -0.446 - 0.188 (n-1); \text{--- reactions } > 5. \end{aligned}$$

TABLE 8

List of Allergens used in the Tests, Frequencies of Reactions and Estimated Mean and Standard Deviation of the Underlying Normally Distributed Liability for Allergic Condition.

No.	Type of allergen	Accumulated % of reactions			Number of tests	Mean M	Stand. dev. σ
		= 0 (X)	≤ 2 (Y)	≤ 4 (Z)			
1	Dog, hair and dander	90.31	95.39	97.62	4673	-7.8	6.0
2	Horse "	62.52	76.01	87.25	4672	-1.6	4.9
3	Cat "	81.21	88.47	93.93	4673	-5.4	6.1
4	Cow "	57.94	80.19	93.09	4670	-0.6	3.1
5	Feather	92.86	98.68	99.78	4667	-4.2	2.9
6	Wool	81.71	92.25	98.51	4669	-2.9	3.3
7	Mold	80.85	94.02	98.35	4637	-2.8	3.2
8	Housedust	73.39	87.68	96.74	4663	-2.1	3.3
9	Yeast	94.97	99.26	99.96	4634	-3.8	2.3
10	Egg yolk, boiled	94.70	99.24	99.84	4645	-4.0	2.5
11	Egg yolk, unboiled	89.47	96.59	99.09	4646	-4.5	3.5
12	Egg white, boiled	90.81	97.89	99.40	4646	-3.8	2.9
13	Egg white, unboiled	90.66	97.52	98.90	4647	-4.1	3.1
14	Milk, boiled	95.23	99.52	99.97	4635	-3.9	2.3
15	Milk, unboiled	93.54	98.52	99.77	4643	-4.6	3.0
16	Fish	93.71	97.83	99.27	4643	-6.8	4.4
17	Meat	96.23	99.33	99.81	4639	-5.1	2.9
18	Shellfish	90.30	96.30	99.38	4640	-4.5	3.5
19	Oats	93.82	98.87	99.85	4613	-4.4	2.8
20	Barley	90.95	97.66	99.65	4618	-4.0	3.0
21	Maize	94.72	99.53	99.91	4618	-3.3	2.1
22	Rye	92.62	98.36	99.66	4620	-4.2	2.9
23	Weat	89.25	96.31	99.02	4615	-4.6	3.7
24	Orris-root	89.37	96.95	99.44	1966	-3.9	3.1
25	Spices	94.87	99.11	99.89	4621	-4.5	2.8
26	Cacao	86.79	98.33	99.55	1968	-2.2	3.1
27	Orange	93.29	99.04	99.96	1967	-3.2	2.1
28	Hazelnut	81.46	88.51	94.53	4639	-5.3	5.8
29	Cottoncake	90.76	98.02	99.55	4630	-4.2	3.2
30	Phleum, pollen	68.71	78.23	84.43	4675	-3.8	7.8
31	Lycopodium powder	90.48	97.41	99.06	4666	-5.3	4.1
32	Foliferous trees, pollen	69.09	77.54	83.55	4675	-4.2	8.4
33	Phragmites, pollen	68.81	80.50	90.58	4671	-2.4	4.9
34	Vegetables	88.44	97.18	99.74	4619	-3.0	2.5
35	Chrysantemum, pollen	72.09	83.06	92.67	4675	-2.8	4.7
36	Anti-catarrh vaccine	81.39	94.68	99.11	4627	-2.4	2.7
37	Solidago, pollen	92.02	97.28	99.06	4600	-6.0	4.3

TABLE 8 (continued)

No.	Type of allergen	Accumulated % of reactions			Number of tests	Mean M	Stand. dev. σ
		= 0 (X)	≤ 2 (Y)	≤ 4 (Z)			
38	Honeycomb	86.91	94.80	98.51	3637	-4.3	3.8
39	Taraxacum, pollen	72.46	81.54	90.74	3152	-3.4	5.7
40	Horsehair	96.84	98.84	99.54	2692	-9.1	4.9
41	Excelsior, upholst material	95.12	98.88	99.81	2687	-5.4	3.2
42	Kapok	95.24	99.00	99.82	2688	-5.4	3.2
43	Stafylococc. anatoxine	86.35	95.17	99.26	2666	-3.4	3.1
44	Stafylococc. bact.	89.08	96.73	99.62	2665	-3.5	2.8
45	Whoping-cough vaccine	97.46	99.81	99.99	2167	-4.2	2.1
46	Coniferous trees, pollen	95.08	98.04	99.45	2701	-7.5	4.5
47	Artemisia, pollen	74.47	81.31	88.93	2702	-4.9	7.4
48	Brassica, pollen	69.27	79.01	91.71	2700	-2.5	5.0

sults indicate that the allergic reactions can be considered as random events, usually not occurring in clusters. The allergens used are sufficiently different to cause specific and independent reactions. The probability of one additional reaction is given by k and is thus 85 per cent for reactions >1 , 78 per cent for reactions >3 , and 65 per cent for reactions >5 .

B. Reaction Patterns for Specific Allergens

Allergens of different kinds vary both as to the frequency with which they induce positive reactions and as to the degree of reaction they produce. In Table 8 the 48 allergens used in the tests are tabulated, together with the percentage of negative tests and the accumulated percentage of reactions ≤ 2 and ≤ 4 . The distributions are in accordance with an underlying normally distributed liability for allergic reactions with a threshold value above which positive reactions occur. The underlying normal distribution has its specific mean value and standard deviation for each allergen, and these can be estimated from the percentual distribution according to a method devised by *Falconer* (1960). The place of the mean (M), stated as units to

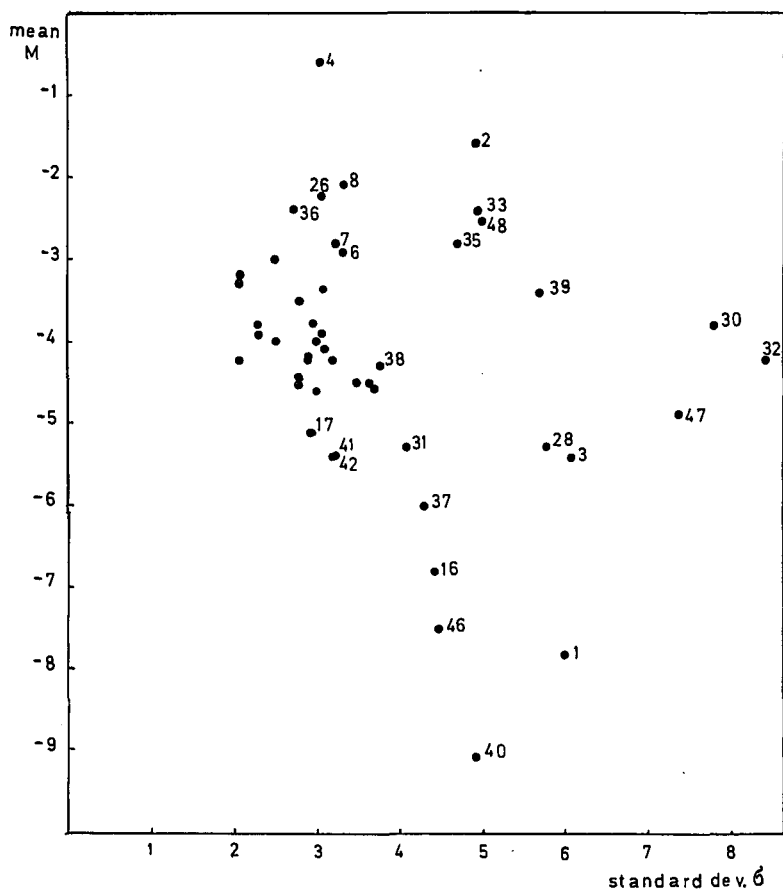


Fig. 3.

Mean, measured as units below the threshold value, plotted against σ , the standard deviation of the underlying normal distribution for allergic liability, for each of the 48 allergens used in the tests. Scale unit: degree of allergic reaction. Not all allergens have been numbered on the figure. For further identification see Table 8.

the left of the threshold point, and the standard deviation (σ) appear in the last columns of the table. The unit of measurement is degree of reaction. Two estimates of σ were obtained, one from the difference Y-X (see Table 8) and the other from Z-Y. In the table the average of these two estimates is

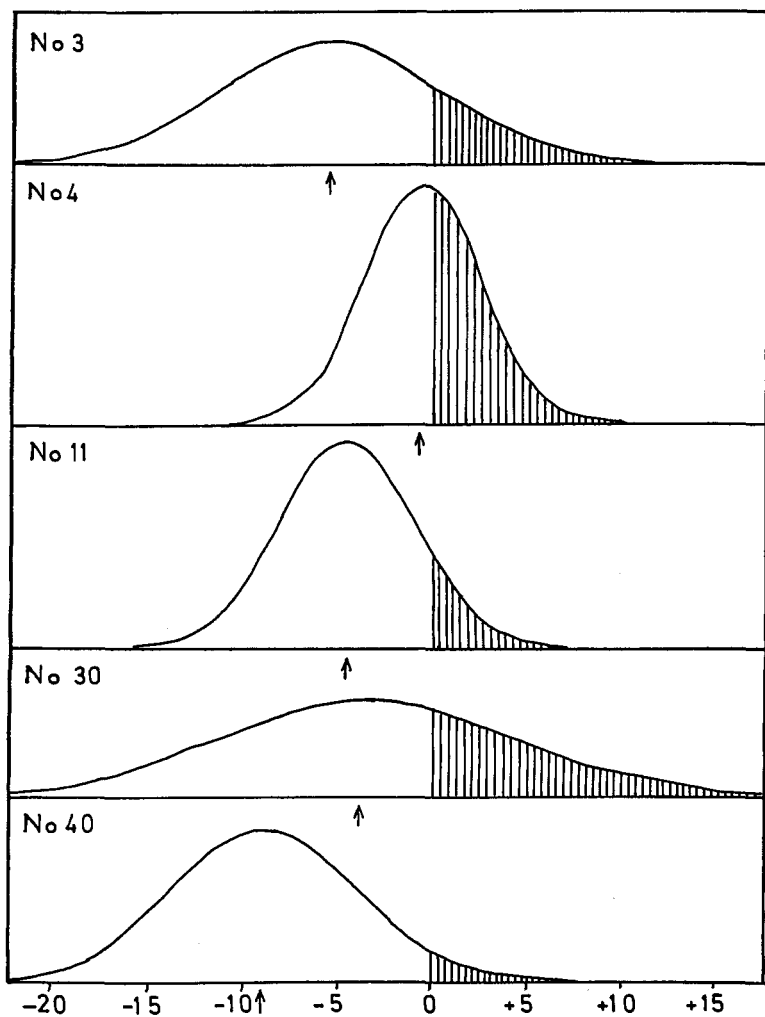


Fig. 4.

Some examples of normal distributions on the underlying scale of liability to allergic conditions. Threshold point at zero. Scale unit: degree of allergic reaction. Arrows indicate the mean of the distributions. For identification of the allergens see Table 8.

stated, except in eight cases where very few testvalues exceeded 2 and the estimate from Z-Y was clearly inconsistent.

In Fig. 3 the value of the mean, M , is plotted against the standard deviation, σ , for each allergen, and in Fig. 4 some examples of distributions of underlying liability for allergic conditions are shown. Neither the mean nor the variance is uniform for the set of allergens used in the tests, but a main group of rather weak allergens is found with mean values between -3 and -5 units and a standard deviation between 2 and 4 units. The allergens which fall outside this group are mostly animal danders and pollens, which are generally distinguished by their higher standard deviations.

TABLE 9
Analysis of Variance for Average Maximal Individual Allergic Reaction (AMAX).

Source of variation	d.f.	MS	F	P
Age	10	18.594	29.87	< 0.001
Sex	1	22.638	36.35	< 0.001
EP	10	7.164	11.51	< 0.001
Age-Sex	10	1.424	2.29	< 0.025
Age-EP	100	1.286	2.07	< 0.001
Sex-EP	10	0.440	—	
Residual	99	0.622		
Total	240			

The factors which interact to give the underlying distributions are unknown, but can be considered as partly genetic, partly environmental. The proportion of the variance which is due to genetic factors equals the heritability of the trait. This cannot be estimated from the present material, only from knowledge of the proportion of affected subjects among relatives to the probands. However, such estimates are based on the assumption of an underlying normal distribution, and since these distributions clearly are not uniform it follows that heritabilities of allergic conditions are likely to differ depending

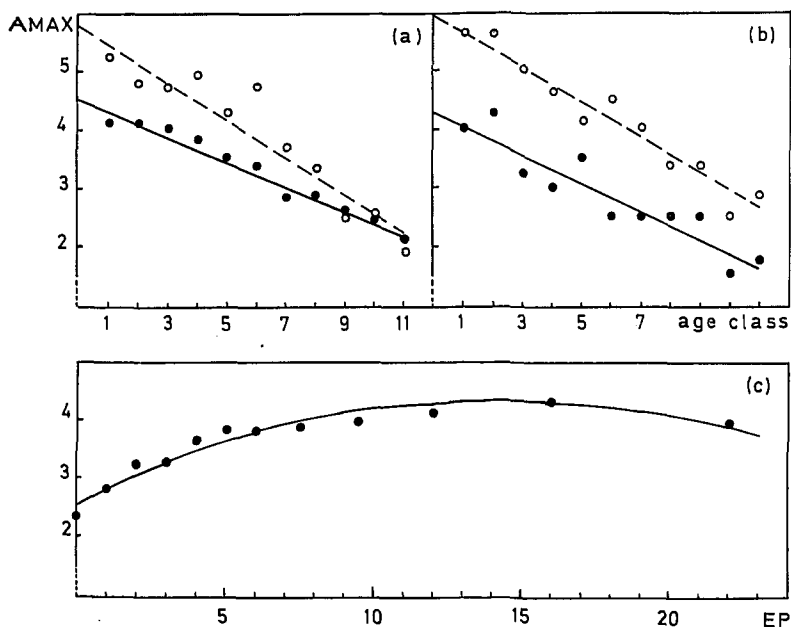


Fig. 5.

Relationship between average maximal degree of allergic reaction (AMAX), age, sex, and eosinophilic percentage (EP).

a) Regression of AMAX on age. ●—● females, $b = -0.21$; ○—○ males, $b = -0.32$. t -value for difference between regression slopes: 2.73; d.f. 18; $P < 0.05$.

b) Regression of AMAX on age. ●—● EP = 1, $b = -0.24$; ○—○ EP > 9, $b = -0.31$. t -value for difference between regression slopes: 2.62; d.f. 18; $P < 0.05$.

c) Regression of AMAX on EP. Estimated regression equation:

$$Y = 2.658 + 0.235x - 0.008x^2.$$

on which allergen is responsible for the reaction. It may be that some allergic conditions have a much higher familial predisposition than others.

C. Average Maximal Degree of Allergic Reaction (AMAX) in Different Combinations of Age, Sex and EP-Values

When age was divided into 11 classes as shown in Table 1 and EP-values likewise into 11 classes (all percentages > 13

TABLE 10

Analyses of Variance for $\ln(EP + 1)$, the Percentage of Eosinophilic Leukocytes after Logarithmic Transformation.

A. Sex as main, age as subgroup classification.

Source of variation	d.f.	MS	F	P
Between sexes	1	6.717	2.42	> 0.05
Between ages within sexes	20	2.782	7.40	< 0.001
Within age and sex	4375	0.376		
Total	4396			

B. Age as main, sex as subgroup classification, separation of age classes 1+2 versus the others.

Source of variation	d.f.	MS	F	P
Between ages	10	5.746	15.28	< 0.001
Between age class 1+2	1	1.086		> 0.05
Between others	8	0.396		> 0.05
1+2 versus others	1	53.208	141.5	< 0.001
Between sexes with ages	11	0.445	1.18	> 0.05
Within age and sex	4375	0.376		
Total	4396			

pooled in one class, otherwise as in Table 4). 242 combinations of age, sex and EP-values were obtained. The combinations included an average number of 18.2 subjects, with a maximum of 52 and a minimum of 0 (one combination). For each combination an average value of maximal individual degree of allergic reaction (AMAX) was computed and the missing combination was given an estimated value. These 242 AMAX-values were found to be approximately normally distributed, and an analysis of variance was employed with the AMAX-values as variates to test for influence of age, sex, and EP. The varying reliability of the variates was ignored since this is not supposed to bias the results, only to increase the residual variance. The resulting analysis of variance is

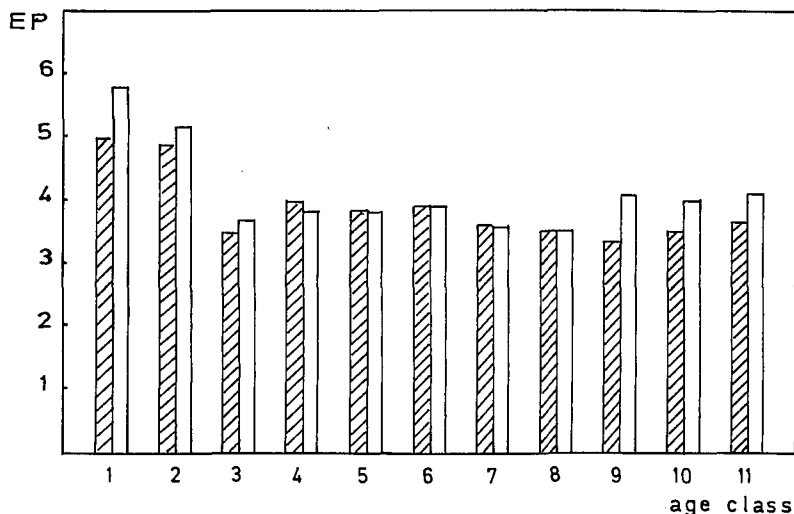


Fig. 6.

Average eosinophilic percentage (EP) after age- and sex-classification. Striped bars: females; white bars: males.

shown in Table 9. There is a significant influence of all the main factors. Males have a higher AMAX-value than females (3.88 versus 3.27). The AMAX-values decrease with increasing age (Fig. 5 a and b) and increase with increasing EP (Fig. 5 c).

Two of the interactions are significant, age-sex and age-EP. Fig. 5 a shows that the regression of AMAX on age is different in males and females. Males tend to have higher AMAX-values than females in age classes up to 45 years but not beyond this age. The interaction age-EP is revealed as an increased influence of age on AMAX at higher EP-values, which can be seen in Fig. 5 b where AMAX is plotted against age for 538 subjects with EP-value 1 and for 422 subjects with EP-values > 9 .

D. EP-Values in Relation to Age and Sex

The relation between EP, age and sex was analysed also without consideration of allergic reactions. The distribution

of the EP-values could be normalized by logarithmic transformation, and this was taken advantage of in an analysis of variance of hierarchical design, including 4397 subjects distributed on sex and 11 age classes. The EP-values were grouped in 12 classes according to Table 3 and the mid-values of these were transformed to $\ln(EP + 1)$. The result of this analysis is shown in Table 10. Both used as main- and as sub-group classification age was found to have a significant influence on EP, whereas sex was of no significance. From the averages for age classes (Fig. 6) it is clearly seen that the differentiation is between the two first age classes (up to 15 years) and the others, which was also confirmed by the statistic analysis. There is also a tendency for males to have higher EP-values at low and high ages. The high EP-values in ages below 15 years may be only a consequence of the higher frequency of strong allergic reactions in the low ages. But there is no corresponding abrupt change in AMAX at the age of 15 (Fig. 5 a), and therefore it seems as if the relation between allergic reactions and EP is changed at puberty.

E. Heterogeneity Tests

The results obtained by analysis of variance for EP-values and average maximal degree of allergic reaction (AMAX) can be confirmed by frequency distributions of EP and individual allergic reactions at various classifications. Contingency χ^2 , based on observed numbers, was employed to test for heterogeneity of IMAX-frequencies among classes of age, sex, EP-value and month of test.

As a consequence of the sampling the present material can be considered as a mixture of two populations, one with and one without allergic conditions. The test for heterogeneity was therefore split in two parts: 1) a comparison between subjects with and without allergic reactions: class 0 versus classes > 0 ; 2) comparisons among subjects with different intensity or number of allergic reactions. The indications of allergic reactions have been set at four different levels, corresponding to those stated in section 2A: 1) at least one reaction > 0 ,

TABLE 11 a

Contingency χ^2 and Percentual Frequencies of IMAX-Values in Different Classes of Age, Sex, EP and Month of Test. Age Classes, EP and Months of Test as in Tables 1, 2, 4. N = Number of Observations.

Age	IMAX-values										N
	0	1	2	3	4	5	6	7	8	9	
1	12.7	7.6	7.6	3.8	4.1	1.4	12.0	20.3	23.7	6.9	291
2	14.6	7.1	8.6	4.1	6.6	3.4	10.9	18.2	21.6	4.8	560
3	22.9	6.7	8.5	5.4	8.3	2.6	9.2	12.8	17.1	6.5	568
4	18.3	5.7	11.7	6.2	10.8	4.4	8.9	13.1	15.4	5.5	436
5	23.0	6.8	10.2	10.0	11.6	2.4	8.7	10.0	14.3	2.9	412
6	24.3	7.7	11.9	6.1	12.1	5.0	8.3	9.7	11.9	3.0	362
7	28.9	10.6	12.9	11.0	9.8	2.6	6.8	6.3	8.5	2.6	426
8	32.0	8.0	11.0	10.5	11.4	3.7	10.3	5.7	5.0	2.3	437
9	32.0	9.3	16.9	11.5	11.2	2.7	6.3	5.5	4.4	0.3	366
10	33.8	9.1	19.9	10.9	12.4	2.4	4.2	2.7	3.6	0.9	331
11	42.5	10.7	16.6	9.3	10.3	2.1	4.4	2.5	1.0	0.4	475
Total %	25.9	8.1	12.1	7.9	9.8	3.0	8.2	9.9	11.7	3.4	4664

Contingency χ^2 : 0 versus > 0 : $\chi^2_{10} = 178^{**}$; among classes > 0 : $\chi^2_{80} = 552^{**}$

Sex											
Males	23.7	7.0	10.1	6.5	8.8	2.8	9.5	12.4	15.0	4.2	2194
Females	27.8	9.1	13.8	9.2	10.7	3.2	7.2	7.6	8.8	2.6	2486
Total %	25.9	8.1	12.0	7.9	9.8	3.0	8.3	9.8	11.7	3.4	4680

Contingency χ^2 : 0 versus > 0 : $\chi^2_1 = 9.77^*$ among classes > 0 : $\chi^2_8 = 112^{**}$

EP											
1	29.2	8.9	13.2	8.5	10.2	2.4	7.3	8.5	9.1	2.6	2432
2	21.1	7.4	11.2	7.3	10.0	3.9	8.5	10.8	16.0	3.9	1241
3	18.4	6.1	10.8	7.2	7.6	3.6	12.2	13.9	14.3	5.9	474
4	17.1	4.9	9.9	7.2	9.1	4.9	12.2	14.4	15.6	4.6	263
Total %	25.1	7.9	12.2	7.9	9.8	3.1	8.5	10.1	12.0	3.4	4410

Contingency χ^2 : 0 versus > 0 : $\chi^2_3 = 53.1^{**}$ among classes > 0 : $\chi^2_{24} = 103^{**}$

TABLE 11 a (continued)

Month of test	IMAX-values										
	0	1	2	3	4	5	6	7	8	9	N
1-2	23.8	9.1	13.8	9.3	12.5	4.0	7.5	7.1	9.7	3.2	776
3-4	28.8	8.8	13.5	9.7	11.0	2.2	6.7	8.6	8.0	2.7	787
5-6	25.3	7.4	13.5	8.8	7.6	2.2	8.0	10.3	12.6	4.4	728
7-8	21.0	9.9	10.1	5.4	8.4	2.2	8.4	11.7	18.0	4.8	724
9-10	25.6	5.4	10.4	7.3	9.2	2.7	11.3	12.5	12.5	3.2	907
11-12	30.0	8.5	11.6	7.3	10.1	4.7	7.2	8.5	10.0	2.1	752
Total %	25.8	8.1	12.1	7.9	9.8	3.6	8.3	9.8	11.7	3.4	4674

Contingency $\chi^2_6 = 21.3^{**}$ 0 versus > 0 ; among classes > 0 : $\chi^2_{40} = 139^{**}$

* $P < 0.01$; ** $P < 0.001$

(IMAX); 2) at least one reaction > 1 , ($IN > 1$); 3) at least one reaction > 3 , ($IN > 3$); 4) at least one reaction > 5 , ($IN > 5$). Further, IMAX classifies the individuals according to their maximal *intensity* of reaction, $IN > 1$, $IN > 3$, and $IN > 5$ according to the *number* of reactions above respective indication value.

The distributions and the results of the contingency tests are summarized in Table 11 a-d. There is heterogeneity for age, sex, EP and month of test between non-allergics and subjects with allergic reactions, using any of the four criteria. High frequencies of allergic reactions are found in low age, among males, among subjects with high EP-values and during the months July-August.

The comparisons among subjects with varying intensity of reaction, Table 11 a, show that the high intensities are mainly found at low ages, and that their frequency gradually grows less as age increases. The high intensities are also more common among males than females, allergic reactions greater than 5 are found among 41.1 per cent of the males but only among 26.2 per cent of the females. High intensities of allergic reactions are more common among persons with high EP-values, but there is far from perfect agreement; even among

TABLE 11 b

Contingency χ^2 and Percentual Frequencies of $IN > 1$ Values in Different Classes of Age, Sex, EP and Month of Test.

Age	Number of allergic reactions > 1					N		
	0	1	2-5	6-10	> 10			
1	20.3	7.2	27.5	24.4	20.6	291	Contingency χ^2 : 0 versus > 0 : among classes > 0 : $\chi^2_{10} = 201^{***}$ $\chi^2_{30} = 197^{***}$	
2	21.8	10.2	23.4	24.5	20.2	560		
3	29.6	7.0	25.7	19.2	18.5	568		
4	24.1	11.0	28.7	17.4	18.8	436		
5	29.9	10.7	25.2	20.4	13.8	412		
6	32.0	12.4	28.5	14.9	12.2	362		
7	39.4	9.4	27.7	15.0	8.5	426		
8	40.0	10.8	27.2	13.3	8.7	437		
9	41.3	13.1	25.9	11.2	8.5	366		
10	42.9	17.2	24.8	9.1	6.0	331		
11	53.2	14.7	23.1	6.7	2.1	475		
Total %	33.9	11.1	26.0	16.2	12.8	4664		
Sex								
Males	30.7	9.8	25.7	18.3	15.5	2194	$\chi^2_1 = 19.5^{***}$	$\chi^2_3 = 35.1^{***}$
Females	36.8	12.2	26.3	14.4	10.3	2486		
Total %	34.0	11.0	26.0	16.2	12.8	4680		
EP								
1	38.1	11.6	25.6	14.3	10.4	2432	$\chi^2_3 = 69.9^{***}$ $\chi^2_9 = 33.0^{***}$	
2	28.5	11.3	26.5	18.4	15.3	1241		
3	24.5	7.8	30.2	21.1	16.4	474		
4	22.0	11.8	27.4	19.8	19.0	263		
Total %	33.0	11.1	26.5	16.5	12.9	4410		
Month of test								
1-2	33.0	13.9	25.6	14.9	12.5	776	$\chi^2_5 = 19.2^{**}$ $\chi^2_{15} = 15.9$	
3-4	37.6	11.7	25.2	14.1	11.4	787		
5-6	32.7	10.8	27.5	17.3	11.7	728		
7-8	30.9	10.9	26.7	18.1	13.4	724		
9-10	31.0	10.1	27.0	17.8	14.1	907		
11-12	38.6	9.0	24.2	14.9	13.3	752		
Total %	33.9	11.1	26.0	16.2	12.8	4674		

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

TABLE 11c

Contingency χ^2 and Percentual Frequencies of $IN > 3$ Values in Different Classes of Age, Sex, EP and Month of Test.

Age	Number of allergic reactions > 3					N
	0	1	2-4	5-6	> 6	
1	31.6	8.2	25.1	13.1	22.0	291
2	34.5	9.3	25.3	12.0	18.9	560
3	43.5	9.1	20.6	10.4	16.4	568
4	42.0	12.2	21.8	7.3	16.7	436
5	50.0	10.2	20.2	9.2	10.4	412
6	50.0	12.1	19.1	9.1	9.7	362
7	63.4	10.8	15.5	4.0	6.3	426
8	61.5	13.7	13.3	6.2	5.3	437
9	69.7	9.8	11.7	3.3	5.5	366
10	73.7	8.5	10.3	4.2	3.3	331
11	79.1	10.5	7.6	1.3	1.5	475
Total %	53.9	10.4	17.5	7.4	10.8	4664
Sex						
Males	47.3	10.5	19.4	9.1	13.7	2194
Females	59.8	10.5	15.7	5.8	8.2	2486
Total %	53.9	10.5	17.5	7.3	10.8	4680
EP						
1	59.9	9.9	15.4	6.5	8.3	2432
2	47.0	11.8	19.4	8.4	13.4	1241
3	42.4	9.1	23.6	10.3	14.6	474
4	39.2	11.4	22.4	10.3	16.7	263
Total %	53.2	10.4	17.8	7.7	10.9	4410
Month of test						
1-2	56.1	12.5	15.7	5.9	9.8	776
3-4	60.7	11.8	13.5	4.7	9.3	787
5-6	54.9	9.6	17.9	7.4	10.2	728
7-8	46.4	9.2	21.7	10.1	12.6	724
9-10	48.6	9.7	19.4	9.5	12.8	907
11-12	57.4	9.8	16.6	6.4	9.7	752
Total %	53.9	10.5	17.5	7.3	10.8	4674

Contingency χ^2 :
 0 versus > 0 : among classes > 0 :
 $\chi^2_{10} = 434^{***}$ $\chi^2_{30} = 134^{***}$

$\chi^2_3 = 106^{***}$ $\chi^2_9 = 17.3^*$

$\chi^2_6 = 46.9^{***}$ $\chi^2_{15} = 32.4^{**}$

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

TABLE 11 d

Contingency χ^2 and Percentual Frequencies of $IN > 5$ Values in Different Classes of Age, Sex, EP and Month of Test.

Age	Number of allergic reactions > 5				N		
	0	1	2-3	> 3			
1	37.1	15.1	26.8	21.0	291	Contingency χ^2 : 0 versus > 0: among classes > 0: $\chi^2_{10} = 584^{***}$ $\chi^2_{20} = 54.5^{***}$	
2	44.5	13.9	23.6	18.0	560		
3	54.4	11.8	17.6	16.2	568		
4	57.1	13.8	14.2	14.9	436		
5	64.1	10.4	14.8	10.7	412		
6	67.1	9.7	14.9	8.3	362		
7	75.8	9.4	8.9	5.9	426		
8	76.7	9.6	9.1	4.6	437		
9	83.6	6.5	7.4	2.5	366		
10	88.5	4.5	5.1	1.8	331		
11	91.6	4.8	2.5	1.1	475		
Total %	66.8	10.1	13.3	9.8	4664		
Sex							
Males	58.9	12.0	16.8	12.3	2194	$\chi^2_1 = 116^{***}$	$\chi^2_2 = 1.78$
Females	73.7	8.5	10.3	7.5	2486		
Total %	66.8	10.1	13.3	9.8	4680		
EP							
1	72.5	8.8	11.7	7.0	2432	$\chi^2_3 = 112^{***}$ $\chi^2_6 = 8.78$	
2	60.8	11.0	15.5	12.7	1241		
3	53.6	13.1	18.1	15.2	474		
4	53.2	14.1	17.5	15.2	263		
Total %	66.0	10.2	13.8	10.0	4410		
Month of test							
1-2	72.6	8.5	11.5	7.5	776	$\chi^2_5 = 88.2^{***}$ $\chi^2_{10} = 2.07$	
3-4	74.0	8.0	10.4	7.6	787		
5-6	64.7	10.6	13.7	11.0	728		
7-8	57.1	13.1	16.4	13.4	724		
9-10	60.5	12.2	15.8	11.5	907		
11-12	72.2	8.1	11.8	7.8	752		
Total %	66.8	10.1	13.3	9.8	4674		

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

subjects with the highest EP-values there are 17 per cent without allergic reactions, and all combinations of intensity of allergic reaction and EP-value are present in the material.

TABLE 12
Contingency χ^2 and Percentual Frequencies of EP-Values in Different Age Classes, Sexes and Months of the Year. N = Number of Observations.

Age	EP-values				N			
	0-4	5-8	8-12	> 12				
1	34.5	32.0	21.4	12.1	281	Contingency χ^2 : low 9P-value (< 5) among classes versus high of high EP $\chi^2_{10} = 126^{***}$ $\chi^2_{20} = 48.2^{***}$		
2	40.4	33.5	15.4	10.7	544			
3	60.7	26.0	8.4	4.9	549			
4	55.2	29.5	11.4	3.9	413			
5	58.5	29.7	8.2	3.6	390			
6	56.2	28.7	10.1	5.0	338			
7	59.5	25.6	8.8	6.0	398			
8	63.6	24.3	7.8	4.3	412			
9	58.8	27.4	7.9	5.9	340			
10	60.7	26.6	9.1	3.6	308			
11	57.0	26.1	11.3	5.6	426			
Total %	55.1	28.1	10.8	6.0	4399			
Sex								
Males	52.1	29.8	11.8	6.3	2083	$\chi^2_1 = 15.16^{***}$	$\chi^2_2 = 0.36$	
Females	57.9	26.6	9.8	5.6	2327			
Total %	55.2	28.1	10.7	6.0	4410			
Month of test								
1-2	57.1	27.2	10.9	4.8	725	$\chi^2_5 = 14.32^*$	$\chi^2_{10} = 5.73$	
3-4	59.9	23.9	10.5	5.7	733			
5-6	55.7	28.0	10.3	6.0	686			
7-8	51.0	29.4	12.6	7.0	684			
9-10	53.0	30.3	10.3	6.7	856			
11-12	54.3	29.9	10.0	5.8	722			
Total %	55.2	28.1	10.7	6.0	4406			

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

The trend is much the same when the width of the allergic spectrum is used as criteria. For allergic reactions > 1 (Table 11 b) high numbers (> 10) are most common at low age, among males and among subjects with high EP-values, but there is no seasonal heterogeneity. When the criteria of allergic reaction is more stringent, allergic reactions > 3 in Table 11 c and > 5 in Table 11 d, the tendency is similar, but the heterogeneity among varying numbers of reactions decreases and becomes insignificant for sex, EP and month of test.

Tests for frequency heterogeneity of EP-values among different age classes, sexes and among different months of the year were also performed. Since an EP-value below 5 per cent can be considered as normal, this class was tested against higher EP-values, and in a second test three different classes of high EP-values were compared. The observed frequencies and their contingency χ^2 are stated in Table 12.

There is heterogeneity among age classes in both comparisons and a marked change is seen to occur between age class 2 and 3, which confirms the findings in the previous section. An influence of sex is also found, but this is limited to the lowest EP-class versus the others. There are more women than men with low EP-values. The months of the year show a slight heterogeneity in the same direction as the allergic reactions, viz. a minimum of low EP-values in July–August.

So far the heterogeneity tests have not taken into consideration the type of the allergen. In order to elucidate if the heterogeneities were confined to any special type of allergen, contingency χ^2 were also calculated for frequencies of maximal reaction within some special groups of allergens and a few specific allergens. Four groups were considered: animal dander, including 6 allergens (No:s 1–6), pollen, including ten allergens (No:s 30, 32, 33, 35, 37–39, 46–48), egg-milk with 6 allergens (No:s 10–15), and cereals with 5 allergens (No:s 19–23). Further, the allergens mold (No 7), housedust (No 8), hazelnut (No 28), anticatarrh vaccine (No 36), and stafylococc. anatoxine (No 43) were chosen, because they all had more than 10 per cent positive reactions.

TABLE 13

Contingency χ^2 , Degrees of Freedom (df), Number of observations (n), and Significance of Heterogeneities among Age, Sex, and EP Classes and among Months of the Year for Related Groups of Allergens and Specific Allergens.

	Animal dander	Pollen	Egg-milk	Cereals	Mold	House- dust	Hazel- nut	Anti- cat. v.	Staf. anatox
Age	χ^2	155***	362***	45.6***	109***	20.77*	242***	13.22	16.06
	df	10	10	10	10	10	10	10	10
	n	4645	4666	4615	4590	4617	4619	4607	2653
	χ^2	280***	200***	101***	61.9***	44.2**	54.2***	4.54	4.32
	df	20	20	20	10	20	20	10	10
Sex	n	2574	2137	988	1004	883	858	858	362
	χ^2	20.4***	45.1***	0.61	9.69**	0.03	2.18	0.04	0.64
	df	1	1	1	1	1	1	1	1
	n	4661	4682	4631	4606	4633	4663	4623	2665
	χ^2	41.0***	72.9***	13.98***	31.9***	1.98	4.43	4.24	0.66
EP	df	2	2	2	2	2	2	2	2
	n	2126	2142	990	1008	889	905	861	364
	χ^2	82.4***	51.1***	41.4***	43.9***	39.0***	19.06***	2.80	6.01
	df	3	3	3	3	3	3	3	3
	n	4398	4412	4368	4345	4369	4398	4371	2477
Month	χ^2	63.7***	26.0***	19.55**	22.45**	22.2**	8.63	6.35	5.21
	df	6	6	6	6	6	6	6	3
	n	2042	2061	944	972	851	858	818	332
	χ^2	6.02	39.3***	3.84	3.92	5.81	8.31	12.18*	10.34
	df	5	5	5	5	5	5	5	5
	n	4656	4676	4626	4601	4628	4658	4630	2658
	χ^2	45.2***	78.7***	9.48	25.3**	30.8***	5.06	22.0*	10.22
	df	10	10	10	10	10	10	10	5
	n	2125	2141	990	1006	888	905	860	364

In order to divide the observations so that a sufficient number of observations were included into the different classes, the degrees of allergic reaction were pooled into three or four groups, the first including degree 0 (degrees 0 and 1 for animal dander and housedust). Contingency χ^2 , degrees of freedom, number of observations and significance of the heterogeneity are given in Table 13.

Since animal dander and pollen are strong allergens and often contribute the maximal individual testvalue, these two groups confirm most of the findings for IMAX (see Table 11 a). The other allergens show some conspicuous discrepancies from this measurement. Concerning sex no heterogeneity is found for mold, housedust, anticat. vacc. and staf. anatoxine. The seasonal heterogeneity is confined to reactions > 0 for animal dander, cereals and mold, and is totally absent for egg-milk, housedust, and staf. anatoxine. Anticat. vaccine and staf. anatoxine differ from the others in showing no heterogeneity among age, sex, and EP classes. The situation revealed by the different allergens is thus more complex than what was indicated by IMAX alone.

F. Association with Genetic Markers

Contingency χ^2 has also been computed for the distribution on alternative phenotypic classes in the genetic marker systems ABO, Rh, Secretor and PTC-tasting reaction.

In the ABO system the four phenotypic classes were pooled into two, with and without antigen A ($A+AB$ versus $B+O$), because of the low numbers of B and AB in some combinations. The distribution on type O and the non-O types (O versus $A+B+AB$) was also tested but was found to be less informative.

Table 14 shows the results of tests including the four measurements of general allergy as well as the allergen groups and specific allergens used in the preceding section. EP values were also tested for association with the genetic systems.

There are a few significant χ^2 values, scattered over all systems. The most pronounced heterogeneity is found for the

TABLE 14

Contingency χ^2 Based on Observed Numbers in Alternative Phenotypic Classes of the Genetic Marker Systems ABO, Rh, Secretor, and PTC-Tasting Ability. Numbers in Parenthesis are Degrees of Freedom (df) if these Deviate from what is Stated at the Top of the Column. n = Number of Observations.

		ABO, $n=1325$ A+AB versus B+O		Rh, $n=1275$ + versus -		Secretor, $n=533$ + versus -		PTC-taste, $n=1125$ + versus -	
		0->0 1 df	among>0 2 df	0->0 1 df	among>0 2 df	0->0 1 df	among>0 2 df	among>0 2 df	0->0 1 df
IMAX	χ^2	1.24	2.30	0.69	1.46	0.04	0.61	2.11	1.46
	n		1163		1121		451		776
IN > 1	χ^2	3.06	4.44 (3)	0.01	4.95 (3)	0.46	1.54 (3)	1.40	0.60 (3)
	n		1005		971		365		677
IN > 3	χ^2	1.25	2.04 (3)	0.77	1.21 (3)	0.26	0.68 (3)	0.27	1.85 (3)
	n		582		558		221		485
IN > 5	χ^2	2.89	0.50	0.32	1.39	0.48	2.42	1.24	0.44
	n		374		357		156		356
Animal dander	χ^2	6.95**	0.22	0.002	1.76	0.06	0.05	0.19	2.74
	n		743		720		256		416
Pollen	χ^2	0.02	2.38	2.40	1.42	0.55	3.26	0.37	2.29
	n		615		591		237		484
Egg-milk	χ^2	1.23	3.01	0.001	8.81*	0.47	0.01 (1)	0.61	0.29 (1)
	n		390		374		112		175
Cereals	χ^2	1.20	0.17	3.67	0.20 (1)	0.81	4.36* (1)	0.08	0.14 (1)
	n		409		395		133		159
Mold	χ^2	1.18	0.51	0.14	0.78 (1)	0.54	0.41 (1)	3.14	5.11* (1)
	n		419		405		121		118
House- dust	χ^2	0.30	0.74	1.21	1.10	0.17	2.37 (1)	0.01	1.88
	n		351		340		139		210
Hazelnut	χ^2	0.44	3.46	0.22	6.62*	2.99	0.88	1.27	1.36
	n		292		280		129		171
Anticat. vaccine	χ^2	0.67	0.001	0.96	1.02 (1)	0.04	0.39 (1)	0.46	0.08 (1)
	n		413		403		134		122
Staf. anatox	χ^2	-	-	-	-	-	-	0.66	2.11 (1)
	n							894	174
EP	χ^2		1.20 (3)		4.73 (3)		3.55 (3)		2.03 (3)
	n		1267		1220		355		1050

* $P < 0.05$; ** $P < 0.01$

allergen group animal dander and concerns the ABO system. It is found that persons with allergic reactions against this group of allergens more often belong to blood type A or AB than do non-allergics (56.9 per cent against 49.3 per cent among those which show no reaction and 53.2 per cent in the general population).

The Rh system has two significant χ^2 values, for the egg-milk group and for hazelnut. Both concern the allergic classes > 0 and is caused by a very low frequency of Rh⁻ in the allergic degrees 3-4, 6.1 per cent and 7.7 per cent as compared to 16.6 per cent in the total material. Since the numbers of subjects in these combinations are small (< 100) the importance of this result is dubious. The remaining two significant χ^2 values, concerning the secretor system for cereal allergens and the taster character for mold, are probably spurious. The table includes more than one hundred χ^2 tests and by pure chance some of these ought to reach significance values at the 0.05 level. The only important association thus seems to be the one between the ABO system and the animal dander allergen group.

This was further confirmed by calculation of contingency χ^2 for the separate allergens within this group. Three allergens, dog, horse, and cow, gave significant χ^2 -values, whereas no heterogeneity was found for cat, sheep-wool and feather.

G. Measurements of Relationship among Allergens

In Fig. 3 all allergens are characterized by their mean value, M , and standard deviation, σ . Pollen and animal dander allergens are widely scattered over the area, but are all characterized by rather high values of σ . None of these two parameters, however, seem to reflect the taxonomic relationship among the allergens. For instance the composites, No:s 35, 37, 39, and 47 are widely separated, whereas Brassica and Phragmites (No:s 33 and 48) are very close to each other.

Similarity of reaction could be measured in many ways between pairs of allergens. If the reactions are classified as negative (0) and positive (> 0) only, concordance between two

TABLE

Correlations between Positive Reactions with Allergens of Animal and Plant Origin.
Lower Part: Number of Observations with

	Dog	Cat	Horse	Cow	Sheep-wool	Feather
Dog		.54	.49	.45	.31	.38
Cat	303		.43	.37	.26	.26
Horse	368	700		.57	.42	.31
Cow	369	676	1307		.53	.41
Sheep-wool	220	370	678	752		.38
Feather	109	168	223	271	198	
Chrysanthemum	235	429	930	950	575	196
Solidago						
Taraxacum						
Artemisia						
Phleum	269	525	1025	916	530	188
Phragmites						
Brassica						
Foliferous trees	275	542	1031	916	563	186
Coniferous trees	34	62	111	105	84	37
Lycopodium powder						
Honeycomb						

allergens can be calculated. *Total* concordance is defined as the proportion of identical reactions, either both positive (> 0 ; > 0) or both negative (0 ; 0). *Positive* concordance is the proportion of identical positive reactions (> 0 ; > 0) among all tests showing at least one positive reaction: (0 ; > 0) + (> 0 ; > 0) + (> 0 ; 0). None of these measurements proved satisfactory. They were not consistent with known taxonomic relationship, but were mainly influenced by the proportion of positive tests for the allergens in question.

Because of the great number of negative tests (degree 0) for each allergen the usual crossproduct correlation, which assumes a normal distribution of the variates, could not be

Upper Part: Correlation Coefficients with Significant Values ($P < 0.01$) Italicized. Positive Reactions for both Allergens (> 0 ; > 0).

Chrysanthemum	Solidago	Taraxacum	Artemisia	Phleum	Phragmites	Brassica	Foliferous trees	Coniferous trees	Lycopodium powder	Honeycomb
.06				.10			.07	.15		
.08				.11			.23	.27		
.11				.15			.17	.10		
.16				.09			.16	.28		
.27				.01			.11	.45		
.20				.09			.17	.02		
	.51	.61	.64	.20	.30	.52	.14	.19	.16	.49
278		.45	.42	.24	.30	.26	.20	.38	.25	.58
540	152		.69	.14	.22	.36	.13	.30	.11	.42
494	146	529		.00	.15	.36	.17	.37	.01	.41
811	245	633	448		.58	.14	.15	.02	.04	.13
900	253	607	431	1071		.32	.15	.10	.02	.25
528	146	611	562	556	530		-.04	.34	.03	.33
826	258	653	460	1015	1033	540		.31	.22	.12
96	51	102	108	99	97	113	111		.06	.47
266	121	148	110	293	304	121	293	43		.11
363	180	164	132	317	368	134	327	51	136	

used. If, however, an underlying normally distributed liability for allergic reactions is assumed, the positive reactions constitute the upper portion of this distribution. Excluding all the zero reactions, which cannot be further classified, leaves the (> 0 ; > 0) group as a truncated bivariate normal distribution. It was therefore assumed that a correlation coefficient based only on the (> 0 ; > 0) group should be the most adequate measurement of the similarity between two allergens. The less of the total distribution that lies below the threshold, the better can the correlation between two variables be estimated from the remaining portion. Strong allergens therefore should give the most reliable correlation estimates.

Table 15 gives the resulting correlation coefficients for some allergens including pollen and animal dander. With a few exceptions the correlation is higher within taxonomic families than between members of different families, orders or phyla. Honeycomb has a high correlation with the composites, coniferous trees and Brassica, but low with the mostly windpollinated grasses and foliferous trees. Lycopodium powder which is of chryptogamic origin shows low correlations with all the pollen allergens. In the animal dander group the highest correlations are found between dog-cat and among horse-cow-sheep, as expected. But also the correlation dog-horse is high and correlations with the feather allergen are not remarkably lower than those among allergens of mammalian origin. The correlations between allergens of plant and animal origin are low, but in many cases significantly positive, and on the whole not less than those between Lycopodium powder and pollen. It seems as if correlation within the (> 0 ; > 0) group is associated with taxonomic relationship if comparisons are made within very homogeneous groups of allergens. As soon as allergens of more disparate origins are included in the comparison, other as yet unknown factors are decisive for the similarity of allergic response.

DISCUSSION

The investigation gives a clear picture of the wellknown influence of age and sex on the occurrence and strength of allergic conditions. The association between allergy and a high percentage of eosinophilic leukocytes is also obvious but not without exceptions. Age and sex have a somewhat different influence on allergic reaction and on EP, as can be seen from Figs. 5 and 6. Whereas there is a gradual change of AMAX with age and the sexes differ up to the age of 45, the most pronounced change in EP is at puberty and the sexes differ below puberty and above 40 years of age.

Many of the allergens used in the tests are aero-allergens. Since it is known that the clinical manifestation of allergy is

influenced by the environmental richness in allergens, it is to be expected that those allergic conditions which are due to allergens with seasonal occurrence should show a cyclic variation during the year. This is confirmed by the heterogeneous distribution of allergic reactions in different months. It is specially pronounced for pollen allergens, with a maximum frequency of allergics in July–August and a corresponding increase of the high degrees of allergic reactions during the summer season. Food allergens, housedust and drug allergens do not show such a pronounced variation among different months.

Non-genetic factors such as age and exposure thus play a great role in the clinical manifestation of allergy. The question of a possible association with genetic marker systems was investigated, choosing those systems for which associations had been found with various diseases. This part of the investigation was mainly negative, only one significant association being found, that between some animal dander allergens and the ABO-system. There is a higher incidence of allergics among blood-type A+AB than among non-A types. This association is of about the same magnitude as that found between blood-type A and gastric cancer or between blood-type O and duodenal ulcer, and like these no explanation can yet be given.

In 1967 Johansson found a strong association between a new immunoglobulin and allergic asthma, and this was later (Johansson et al. 1968) confirmed also for other kinds of allergic diseases. Oprée, Krause & Stockberg (1972) have studied the level of this serum immunoglobulin, IgE, in a random population and in members of atopic families. They found a multimodal distribution of IgE levels and could relate this to the occurrence of two alleles and three genotypes, AA, Aa, and aa. The aa homozygotes have the highest levels of IgE and are persons subjected to allergic conditions. The heterozygotes have intermediate IgE levels and are either healthy (5/6) or have allergic conditions with a late manifestation (1/6). The AA individuals have no atopic disposition. This

investigation shows that there is a common genetic control of IgE level and atopic disposition, and confirms the old hypothesis of Wiener et al. (1936) concerning the genetics of allergy. The frequencies of the genotypes found by Oprée et al. were 76 per cent AA, 22 per cent Aa, 2 per cent aa, in a random sample of 50 individuals. Similiar frequencies have been found by Bazaral et al. (1971) in a smaller sample.

How can the assumption of a common genetic condition for allergy be consistent with the specificity of the allergens? As has been shown there are differences both as to means and standard deviations and in their relation to age, sex, EP and seasons. Allergens also show a varying degree of similarity of reaction, which in many cases is unpredictable from their type.

Liability to allergic reaction to an allergen with fluctuating occurrence, local and seasonal, is bound to be more varying than for instance to a commonly occurring food allergen. The variation in liability due to genetic causes may be equal for both allergens, but the former has many more environmental variables, which contribute to the total variance in liability. This can explain the throughout higher variances for pollen and animal dander allergens which were found in this investigation, and are illustrated in Fig. 3. The strength of the allergen, as given by its mean value in the same figure, is probably dependent on chemical structure and number of allergic determinants, and shows no relation to variance. Similarities in reaction for two allergens can be due both to common allergic determinants and to common environmental variables, and correlated responses are therefore predictable from taxonomic relationship only within uniform groups of allergens, such as pollen.

SUMMARY

A group of 4685 persons were tested by intradermal allergy tests for 38-45 different allergens, including extracts from animal dander, pollen, dust, food and drugs. Allergic reactions were classified on a scale of ten degrees by ocular inspection. In most cases also the percentage of eosinophils (EP) was

determined. About 1200 subjects were tested for ABO and Rh blood group and PTC taste response (ability to taste phenylthiocarbamide), and a smaller group for the secretor character.

Reaction patterns were studied for maximal individual degree of allergic reaction and number of allergic reactions greater than degree 1, 3, and 5. The distribution of subjects with increasing numbers of positive reactions indicates independence among the allergens used.

Mean and standard deviation for liability to allergic reaction against the specific allergens were estimated. Pollen and animal dander had higher standard deviations than the other allergens.

Analysis of variance was performed on average maximal degree of reaction for influence of age, sex and EP, and on EP values for influence of age and sex. Contingency χ^2 on observed numbers was used to test for heterogeneity among age- sex- and EP-classes and for seasonal fluctuations. Generally a marked heterogeneity was found. Low age, male sex, high EP and summer season were associated with high frequency of allergics and high degrees of allergic reactions. The specific allergens, however, varied as to their dependence on these factors.

Only one association with the genetic marker systems was found, viz. between animal dander allergy and the ABO system.

Pollen and animal dander allergens were analyzed for correlated responses and it was found that the correlation was highest between allergens from species belonging to the same taxonomic family, but that also unpredictable high correlations occurred.

It is concluded that allergic conditions are under genetic control, but that random events are involved and of varying importance for different allergens.

ACKNOWLEDGEMENT

This investigation has been supported by a research grant from Stockholms Läns Landsting.

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