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ANALYSIS OF SKIN-TEST RESULTS AND CASE-HISTORY DATA FOR ASTHMATIC CHILDREN USING A COMPUTERIZED PUNCHED-CARD METHOD

By

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The basic mechanisms of the course of bronchial asthma is initiated by the bronchospasm resulting from the liberation of histamine and other active substances; the release of biologically active substances is induced by the reaction of an antigen (allergen) which penetrates into the organism and the specific antibody formed against it, IgE (12). It is clear from a consideration of the very high number of foreign substances involved, together with the individual immune response (3) and bronchial activity (16), which vary with the age, that very many factors must be taken into account in the recognition and evaluation of the clinical picture. Many such relations have been put forward in the allergological literature (9, 11, 24, 25), but in most cases it is a matter of a supposed conclusion of general validity, deduced from a few, but obvious connections. It therefore seemed necessary for us to try to establish the really essential, confirmable relations from among the many factors affecting the condition of asthmatic children, by using principles of modern statistical evaluation (4, 6).

MATERIALS AND METHODS

After the collection of the case-history data, the course of the processing consists of the following steps: The data are first filed in coding records on the basis

of a given coding instruction. They are transferred to punched-cards, and the numerical formation of the desired statistical relations is achieved with the aid of "tables".

The histories of the asthmatic children obtained by means of a questionnaire comprising 48 main and 40 sub-questions. The data for 205 asthmatic children were evaluated, and 120 different types of comparison were made.

Skin-tests were performed intracutaneously, and the obtained reaction referred to an allergen extract of 100 Noon unit (NU)/ml, that is a dilution of 10^4 ; only ++ and +++ positivities were evaluated, by the standard procedure given in the literature. The extracts were obtained from the Institut Pasteur.

The severity of the asthmatic clinical picture was estimated on the basis of the annual number of attacks, according to the scheme of *Engström & Kraepelien* (7), 4 grades being distinguished. Three degrees of severity were distinguished in the evaluation of the status asthmaticus: wheezing without severe complaints; a state which can be relieved with drugs at home, and a state requiring admission to hospital or urgent medical intervention. Within the clinic, the status asthmaticus was classified in the more serious category in the case of rest dyspnoea, a weakened respiration resulting from the prolonged inflation of the lung, and a Tiffeneau quotient below 50 per cent.

RESULTS

During ablactation, children of an allergic disposition frequently react with disease symptoms merely on the intake of foreign proteins. This "preasthma" may be followed later by real bronchial asthma. Our data-processing indicates that in the

TABLE 1

Relation Between the Time of the Beginning of the Asthma and the Symptoms Appearing in Connection with the Ablactation..

Beginning of asthma	Symptoms on ablactation		
	Eczema	Bronchitis	Symptom-free
Infancy	4	12**	31
1-3 years	10*	5	81
4-6 years	4	5	28
7-10 years	2	1	15
Above 10 years	0	0	7
Totals	20	23	162

** $p < 0.001$ $t = 12.540$.

* $p < 0.03$ $t = 6.549$.

majority of cases reacting with bronchitis on ablactation the clinical picture is gradually transformed from infancy on into asthma in later childhood (Table 1), while in the case of eczema the asthma symptoms appear later, at the age of 2-3 years, that is on the improvement of the eczema. With symptom-free ablactation the time of the beginning of the bronchial asthma is significantly later.

The lengthening of the duration of the lactation period does not affect the development of the allergic symptoms; only the time of the appearance of the symptoms can be delayed. At the same time, the allergic symptoms arising on ablactation in infancy are of prognostic value: there were respiratory or dermal symptoms in infancy in 40 per cent of the more serious asthmatic cases (Table 2), whereas among the milder asthmatic cases the proportion was only 20 per cent.

The bronchial asthma frequently develops after a fairly serious respiratory infection accompanied by fever; these cases are most often accompanied later too by dyspnoea with fever, whereas those beginning without fever continue without fever (Table 3); this difference is very significant. In the latter disease-group, however, there are substantially more severe cases.

TABLE 2

Relation Between the Frequency of the Dyspnoea and the Symptoms Appearing in Connection with the Ablactation.

Frequency of the dyspnoea (yearly number of attacks)	Symptoms on ablactation				Symptom-free
	Eczema	Bronchitis	Enteritis	Number of cases with symptoms	
0-5	3	3	1	31*	26
6-10	12	8	4		47
11-24	11	7	4	41*	25
Above 24	13	5	1		30
Totals	39	23	10	72	128

The eczema data include the numbers of cases appearing before ablactation.

* $p < 0.05$ $t = 3.994$.

TABLE 3
*Relations Between the Appearance of the First and Frequencies of the Later
 Asthmatic Attacks.*

Disease accom- panying the first asthmatic attack	Appearance and frequency of the further asthmatic attacks					Totals
	Pyretic	Apyretic	5	Annual number of dyspnoeal attacks	25+	
				6-10	11-24	
Pyretic pneumonia	23	23	7	16	14	48
Pyretic bronchitis	26	14	18	10	12	41
Other pyretic states	14	10	3	11	6	25
Apyretic dyspnoea	8**	75**	10*	33	17	85
Totals	74	122	38	70	59	199

** $p < 0.0005$ $t = 43.859$.

* $p < 0.05$ $t = 5.161$.

TABLE 4

Relation Between the Severity and the Frequency of the Asthmatic Dyspnoea.

Severity	Annual number of dyspnoeic attacks				Totals
	< 5	6-10	11-24	25+	
II (only wheezing)	8	8 = 16*	1	4 = 5*	21
III (rest dyspnoea can be treated at home)	12	30	38	37	167
IV (a status asthmaticus necessitating admission to hospital)	10	24 = 34*	24	21 = 45*	79
Totals	30	62	13	12	67

* $p < 0.03$ $t = 7.293$.

The status asthmaticus which can be relieved only by medical intervention is significantly more common among the asthmatics who frequently suffer from dyspnoea (Table 4); the proportion of cases suffering from rare but severe asthmatic attack is low: only 12 per cent.

The positivity of the family history is substantially more frequent among the cases who suffer from more than 10 dyspnoeal attacks annually (Table 5), although even in this group it does not attain 50 per cent.

A recognized factor in the development of the asthma are the dwelling conditions, and primarily of the furniture and flooring. Our data indicate that the disease is manifested at

TABLE 5

Relation Between the Family History of the Asthmatic Patients and the Annual Number of Dyspnoeal Attacks.

Disease which has occurred in family	Annual number of dyspnoeic attacks				Totals
	< 5	6-10	11-24	25+	
Bronchial asthma	9	16 = 25*	20	22 = 42*	67
Other allergies	5	10 = 15	5	3 = 8	23
No allergy or asthma	19	46 = 65*	25	25 = 50*	115

* $p < 0.05$ $t = 6.248$.

TABLE 6

Relation Between the Nature of the House and the Beginning of the Asthma.

Beginning of the asthma	Nature of the house			Totals
	Higher than ground-floor, or cellared	Ground-floor (dry)	Ground-floor (damp)	
Under 1 year	6	24	8	38
1-3 years	22	48	25	95
4-6 years	13	18	5	36
Above 7 years	4	11	2	17
Totals	45	101	40	186

* $p < 0.05$ $t = 4.297$.

an early age more frequently among children living in rooms with earthen floors than in those living in healthy, up-to-date houses (Table 6).

If the social conditions of the asthmatic children are taken into consideration, it is found that in two-thirds of the cases of children of agricultural workers the clinical picture has a tendency to worsen, in contrast with the other social categories (Table 7); the reason may be the livestock, granary, decaying substances, etc. in the vicinity of the house.

Two important negatives were found during the statistical

TABLE 7

Relation Between the Tendency of the Asthmatic Clinical Picture and the Occupation of the Parent.

Tendency	Agricultural worker	Industrial worker	White-collar worker	Other	Totals
Improving	7	17	8	8	40
Unchanging	2	12	5	6	25
Deteriorating	21	31	10	12	74
Totals	30	60	23	26	139

* $p < 0.05$ $t = 4.317$.

processing of the histories: one of these was that neither a positive nor a negative correlation was found between the performance of tonsillectomy and the severity of the process; this can thus be regarded as an indifferent intervention. The scholastic results are quite good, even for cases suffering from more than 24 dyspnoeal attacks per year; thus, the intellectual capacity is little affected by asthma in childhood.

The nature of the individual susceptibility is today established with the help of skin-tests; nevertheless the evaluation of their clinical importance can be ascertained only by respiratory provocation test.

Skin-reactions positive to the various allergens were obtained in very variable proportions according to age: the proportion of inhalative grass-pollen and house-dust allergies (Fig. 1) increases very significantly, whereas the feather and inhalative fungus susceptibilities are slightly rarer under the age of 6 years than above 10 years. The proportion of skin-tests positive to bovine-hair extract also increases with age,

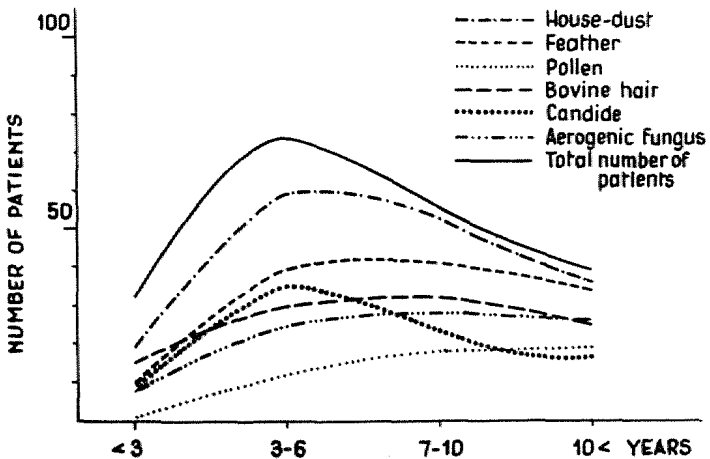


Fig. 1.

The frequency of inhalative grass-pollen and house-dust allergies.

TABLE 8

Relation Between the Candida Skin-Sensitiveness and the Time of the Beginning of the Asthma.

Skin-reaction to 100 NU/ml Candida extract	Beginning of asthma				Totals
	< 1 year	1-3 years	4-6 years	7 years+	
+++ and ++	16	23 = 39*	6	3 = 9*	48
Negative	16	27 = 43*	14	12 = 26*	69
Totals	32	50	20	15	117

* $p < 0.05$ $t = 4.838$.

but to a lower extent compared with the above. The proportion of Candida sensitization of infective origin, on the other hand, is practically unchanged. In those studied later too, Candida sensitization of an infective nature is significantly more frequent in asthmatic cases which began under the age of 3 years (Table 8).

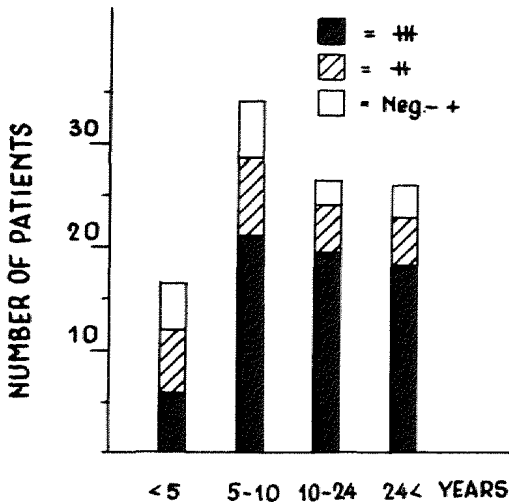


Fig. 2.

Incidence of house-dust allergy in various age groups.

TABLE 9

Relation Between the Effectiveness of High-Altitude Sanatorium Treatment and the Skin-Reaction Given to House-Dust.

Skin-reaction to 100 NU ic. Pasteur house-dust extract	Result of sanatorium treatment		Totals
	Symptom-free	No essential change	
> +++	36*	36*	72
++	6 }	15 }	21
Negative	3 } 9*	9 } 24*	12
Totals	45	60	105

* $p < 0.05$ $t = 4.772$.

The severe clinical picture accompanied by more than 10 dyspnoeal attacks annually (Fig. 2) is much more frequent among children who are very allergic to house-dust.

Patients who were very susceptible, and primarily to house-dust, were symptom-free much more frequently at the time of their stay in a sanatorium than were those patients allergic to other factors (Table 9).

One fact to emerge, which was unexpected and difficult to explain, was that cases allergic to feathers were significantly fewer among patients sleeping with eiderdowns, than those sleeping with other covers; it is true that practically every patient used a feather pillow (Table 10).

TABLE 10

Relation Between the Nature of the Bed-Cover and Feather Allergy.

Skin-reaction to 100 NU/ml ic. feather extract	Bed-cover		Totals
	Eiderdown	Other	
+++	18	103	121
++	20	20	40
Negative	14*	17*	31
Totals	52	140	192

* $p < 0.05$ $t = 6.117$.

TABLE 11

Relation Between the Time of the Occurrence of the Asthmatic Dyspnoea and Grass-Pollen Allergy.

Skin-reaction to 100 NU/ml ic grass-pollen extract	Occurrence of asthmatic attack				Totals
	Irregular	Morning	Afternoon	Evening	
++ and +++	2	0	3	41*	46
Negative	19	12	10	85*	126
Totals	21	12	13	126	172

* $p < 0.05$ $t = 4.326$.

Another fact, which was in contradiction with the literature view, was that the majority of patients allergic to pollen suffer from dyspnoea at night (Table 11). It is undoubtedly true that the liberation of pollens in the air is greatest by day (25). Thus, it must be assumed that these comparatively large bodies, which are caught already in the nose, induce the bronchospasm only after an incubation period and decomposition, while the rhinitis, as known, begins immediately.

Sensitizations by aerogenic fungi are significantly more frequent in the cases of rooms with earthen floors or isolated farmhouses than in a healthy town environment (Table 12). Patients allergic to aerogenic fungus report significantly more

TABLE 12

Relation Between Aerogenic Fungus Sensitization and the Situation of the House.

Skin-reaction to 1000 NU/ml fungus extract	Situation of house			Totals
	Isolated farmhouse	Village	Town	
+++ and ++	29*	28	3*	60
Negative	13*	39	11*	63
Totals	42	67	14	123

* $p < 0.03$ $t = 8.292$.

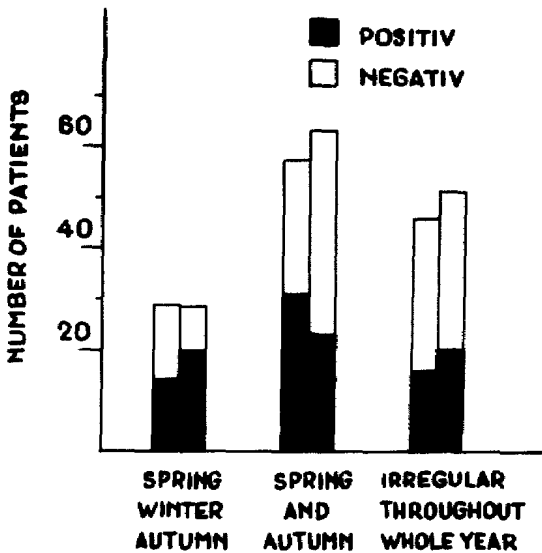


Fig. 3.

Patients allergic to aerogenic fungus, seasonality of their symptoms.

often on the spring-autumn seasonality of their symptoms (Fig. 3).

Meteorological observations (fog, wind and cold) made in the history, obviously because of their inaccuracy, did not give an evaluable relation with any other data.

DISCUSSION

According to our data the prolonged lactation postpone, but does not prevent the asthmatic disease; this agrees with the negative findings of *Bates et al.* (1) and *Eriksson-Lihr* (8); however it is striking that the early childhood preasthmatic diseases usually transform directly into typical asthma (13), and that the other allergic manifestations observed at a young age aggravates the course of the later asthma. On the other hand it is known (19) that significantly frequently children

allergic to bovine-hair had previously suffered from eczema in early childhood. All this supports the possibility that the antibody formed against the same bovine-protein determinant in early life reacts in later life only with the antigen entering by the inhalative route and these are the most serious cases of childhood asthma (17, 18, 19). Another relation found was that perhaps the *Candida* sensitization developing under the age of 3 years just as a result of the prolonged antibiotic treatment may be an important factor in the development of asthma in later childhood.

The asthmas beginning with fever are for the main part accompanied later too by pyretic dyspnoea, but at the same time milder than the average; in these cases the role of the infective allergy (10), or possibly a partial immune defect (14, 15, 23), is probable in the development of the clinical picture.

The more serious attacks of frequently dyspnoeic asthmatics can primarily be explained by the high IgE level (2), by the high degree of bronchial sensitivity (5), and by the lability of the beta adrenergic receptors (22). The latter are not immunological factors, but the development of the pathological state is most often brought about by an exogenous antigen, and thus by a factor acting on the pathway of the immune mechanism: the serious asthma occurs in a high proportion among those appreciably susceptible to house-dust. A relation between the effectiveness of the sanatorium treatment and the house-dust allergy had so far not been demonstrated statistically, but it is known that the living-conditions of the house-dust mite (20, 26) are unfavourable in high places, and this allergen therefore depends mainly on the altitude factor (21).

Earthen-floored and isolated farmhouses in general favour the development of the aerogenic fungus sensitization according to our data; this corresponds to the relation expected on the basis of the literature data (27). The seasonality (autumn-spring) of these asthma cases whose most important causing agent is *Mucor* and *Rhizopus* in Hungary, suggest the importance of indoor mould flora in the sensitization.

Only 25 of the 120 studied relations proved significant, but clearly even so a number of new conclusions became possible, and a positive or negative stand point could be taken with regard to other relations hitherto put forward in the literature. In the future we wish to use these data to follow the fates of the patients after the examination, and to evaluate the prognosis and the therapeutic susceptibility of childhood bronchial asthma, with the aid of a statistical prognosis model.

SUMMARY

The relations of the histories of 205 asthmatic children and the results of skin-tests were studied by the computer-processing of punched-cards. The possibilities of 120 types of relation were analyzed, and of these 25 proved significant. The evaluable relations were the following: Infants and young children, who suffer from prolonged respiratory inflammation or eczema after ablactation fall ill with asthma earlier and more seriously. In the event of relapses, the expiratory dyspnoea developing after the pyretic disease is accompanied by fever much more often, while those beginning without fever suffer dyspnoeal attacks without fever later too; the latter group, however, is considerably more serious. The sanatorium treatment of patients highly allergic to house-dust is much more effective than that of other allergic cases; the yearly number of dyspnoeal attacks at home, on the other hand, is significantly higher for those sensitive to house-dust than for other asthmatics. The proportion of pollen and fungus allergies increases considerably with age, whereas the percentage occurrence of *Candida* sensitization remains unchanged. The proportion of fungus susceptibility is higher among those living in earthen-floored and isolated farmhouses than among those in modern town-houses. Asthma cases showing a tendency of deteriorate are more frequent among children of agricultural workers than in the cases of other occupations.

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