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STUDIES IN BRONCHIAL ASTHMA

I.

*Examination of Patients with Bronchial Asthma.
Occurrence of Asthma without and with Specific Allergy as
the Cause of the Disease*

By

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INTRODUCTION

Bronchial asthma is now considered to be an allergic complaint. However, there are many cases where it is not possible to find any specific allergy.

In the present work, consisting of 4 chapters, the author has investigated a Swedish asthma material concerning the occurrence of asthma without and with specific allergy respectively. These two main groups have been compared with reference to age when taken ill, sedimentation rate, and the role of infections as a primary cause for the onset of asthma.

The present work includes 748 asthma patients from Stockholm, all at least 18 years old.

Definition of Bronchial Asthma.

In its typical form, bronchial asthma is an illness characterized by recurring attacks of paroxysmal difficulty in breathing, above all prolonged expiration, combined with wheezing respiration, coughing and the coughing up of a

glue expectoration, after which the patient can go for a longer or shorter time quite free of distress—until a fresh attack of the same kind occurs. It is, however, only in certain cases that this condition with a limited period of distress occurs; other patients suffer more lengthy periods.

It is also well-known that bronchial asthma is not a unitary illness as far as etiology is concerned. It is of course still considered with the allergic complaints, but it is only in a limited number of cases that one can prove any definite allergic genesis with our present methods of diagnosis, and in many cases one cannot find any specific allergen.

As bronchial asthma has such a varied etiology and clinical course an attempt has been made to systematize the illness into different groups.

A Literary Survey of Different Types of Asthma.

Salter (1868) was one of the first persons to classify bronchial asthma according to more modern views. Those cases in which the causes operated directly on the air passages were called *intrinsic*; those in which the causes operated indirectly to produce symptoms were called *extrinsic*.

Rackemann (1918, 1951) whose classification of asthma has become one of the best known in American literature, uses the conception of intrinsic and extrinsic in the following way:

With *extrinsic* asthma, the cause is allergic “unless proven otherwise” and comes from an external source. The allergen is usually dust, sometimes food-stuffs or drugs. It occurs mainly in patients who have had asthma before 30 years of age. Rackemann points out that more than 75 % of all asthma belongs to this group.

With *intrinsic* asthma, however, the patient bears the cause within himself, and it is not allergic “unless proven otherwise”. The level of distress with asthma does not depend upon season or environment. Skin tests are most often negative. It occurs as a rule in patients, who get asthma after 40 years of age.

Cohen (1944) and *Criep* (1945) have similar views, and *Vaughan* and *Black* (1948) consider that *Rackemann's* classification is "helpful". In their opinion, there are very few cases of purely intrinsic asthma.

Walker (1918) divides his cases into *sensitive* and *non-sensitive* according to skin tests.

Larsen and *Bell* (1922) classify cases into those where *sensitivity* can be proved with certainty, and those where *sensitivity* cannot be proved with certainty, *Peshkin* (1926) distinguishes between *protein sensitive*, *non-protein sensitive* and *para-asthma*.

Kämmerer (1956) has a classification embracing *allergic* asthma, *toxic* asthma, *unspecific reflex* asthma, *constitutional psychopathic* asthma and also *mixed forms*.

Ramirez (1938) divides asthma into *allergic exudative* and *non-allergic spastic*, *Coke* (1939) into *allergic*, *infective* and *mixed allergic-infective*, *Coca*, *Thommen* and *Walzer* (1941) into *immunologic* and *non-immunologic*.

Urbach and *Gottlieb* (1946) have an extensive classification with the following main groups: *allergic* asthma, asthma due to *bronchial irritation*, *psychogenic* asthma, *pathergic* asthma and asthma of *unknown* origin.

Cooke (1947) makes a distinction between *non-infective* and *infective* asthma, *Tuft* (1949) between *allergic* and *non-allergic* asthma.

Hansen (1943) classifies asthma according to clinical course into *paroxysmal* asthma and *non-paroxysmal* asthma.

Unger (1945) and *Hansel* (1953) have considered the best method to be a classification of asthma according to clinical condition into *paroxysmal* and *chronic* asthma and *Kobro* (1941), *Lederer* (1921), *Tuscherer* (1930) and *Engel* (1931) have a similar classification. *Diener* (1938) uses the conception *spastic* and *catarrhal* asthma.

Gay (1937) has introduced a very detailed classification, of which the main groups consist of asthma *in children* and asthma *in adults*. *Berresford* (1945) also divides asthma ac-

cording to condition into *mild, moderate, severe* and *very severe asthma*.

Swineford (1954) is opposed to all these different classifications of asthma. He considers that asthma is a syndrome, and it is therefore more correct to call illnesses with wheezing respiration, *asthma*, and indicate the type in question by adding a modifying term, e.g. asthma, atopic; asthma, cardiac; asthma, chron. emphysema. *Brown* and *Halpin* (1954) have similar views.

The abundance of different terms and conceptions makes a survey of relevant literature difficult. A closer analysis of the great number of asthma classifications shows, however, that for the most part, they say the same thing using different names. The greater proportion of them are based on etiology. It is possible to distinguish between two large main groups, namely the first when the cause of the asthma is known allergens of different kinds (extrinsic, allergic, sensitive, non-infective asthma) and the second, when the releasing cause is unknown or is not considered to be of allergic nature (intrinsic, non-allergic, non-sensitive, infective). A great many of the above-mentioned classifications are based on clinical course instead of etiology.

A common trait is that there is very little information as to the basis of the classification, the size, age-groups, sex-groups etc. in the material examined.

A Survey of Literature Dealing with the Frequency of Different Types of Asthma.

It is, of course, interesting to know to what extent the type of bronchial asthma occurs where there is evidence of known allergens as the cause, in relation to the cases where no such cause has been able to be found. Perusal of literature on this subject gives the following information:

Walker (1917) examined 150 non-classified asthmatic patients, and found 55 % sensitive and 45 % non-sensitive. It should be noted that the author has also included in the

first-mentioned group such cases as have shown positive skin reactions to bacterial proteins. It is not possible to decide from available material how many of these cases have been included. Walker also has another method of distinguishing between sensitive patients (i.e. in his opinion skin positive) and non-sensitive (i.e. skin negative), namely, the age of the patient when the complaint started. Apparently, no patient whose asthma made its appearance after 40 year of age, had a positive skin reaction.

Larsen and Bell (1922) found amongst 100 children that 44 % were sensitivity determined, 12 % were sensitive types but with negative reactions, 33 % chronic bronchitis, and 11 % not sufficiently tested to be classified.

Woldrich (1930) found with the help of anamnesis and skin tests that 25 % was caused by dust allergens, 63 % by bacterial allergens, and 12 % by pollens, climatic factors and food-stuffs.

Diener (1938) found that out of 1008 asthma patients 231 (22.9 %) belonged to the spastic group and 777 (77.1 %) to the catarrhal asthma group. The classification was made with the help of prehistories amplified by a set of questions. The spastic group corresponded, for the most part, to the cases where specific allergens were evident.

Cooke (1947) found in a group of patients from all age-groups that the cause in 50 % of cases was inhalants, food-stuffs, or drug allergens, in 35 % infections, and in 15-20 % both infective and non-infective.

Abderhalden (1950) says that bronchial asthma which starts before 30 years of age is as a rule allergic, and that which starts after 40 years of age non-allergic. *Davidson* (1953) has similar theories, and also *Rackemann* (1951) who states that more than 75 % of all asthma is extrinsic. In earlier works (1918) he gives, however, quite different figures, namely 28 % extrinsic, 53 % intrinsic and 19 % unclassified in 150 cases of bronchial asthma.

Harley (1952) found about 20 % extrinsic asthma in an investigation. *Hansel* (1953) states that inhalation, food-

stuffs and "drug" allergens are the predominating causes of asthma.

Hollman and *Krause* (1953) have found in a not clearly defined number of cases that only 10-20 % of asthma cases are brought out by specific allergens. In the majority of cases the cause is infectious, either due to the sensitizing of bacteria living in the body as saprophytes, usually in connection with influenza, tonsillitis or the common cold (40-50 %) or after protracted bronchitis (about 35 %).

Diaz and *Arjona* (1953) found a clear sensitizing in 24.7 % of 4069 cases.

According to *Williams* (1954) infections play the most important part in children from 0-4 years of age, allergic and psychological causes from 4-14 years, allergic in 15-25 years, after which infectious and psychological factors increase in importance.

Colldahl (1956) found indication for specific hyposensitization in about 25 % in a series of 387 asthma patients. According to *Bruun* (1956) asthma in most cases (probably all) is an allergic condition.

DISCUSSION

There are proportionally few works, which deal with the type of asthma, where there is evidence of specific allergy as compared with the type, where there is no evidence of specific allergy; as a rule, all types of bronchial asthma are united in one group and are dealt with as one unit. It ought, however, to be of great interest to investigate these two main groups singly to find out if one can establish any important differences between them.

There are great possibilities of being able to cure or improve those cases where there is evidence of specific allergy by specific hyposensitization, and we already have a great deal of knowledge of the mechanism of this type of asthma.

The position of the type of asthma, where no specific cause has been successfully proven is somewhat different. Know-

ledge of this type of asthma is still incomplete, and this tends to make the treatment unsure and tentative. This type of asthma often follows a chronic course with complications of different kinds. It is therefore of the utmost importance to attempt a greater understanding of it. The main point of this work is to make a comparative investigation, using unitary and similarly examined clinical asthma material, of the cases where certain allergy has been proven, and cases where allergic factors have not been found. In order that the investigation should be as significant as possible, one must first of all divide the cases into two such groups. In what follows, the author therefore begins by giving an account of the investigations, with whose help this division has been made possible, and also the results.

THE AUTHOR'S RESEARCH

The Composition of the Available Material with Respect to Number and Type of Patients and Classification by Sex and Age.

All the patients accounted for in this work have been nursed at the Medical Clinic II, St. Görans Hospital, or at its Out-patient allergy clinic through the years 1949 to 1953. All patients included in the investigation were at least 18 years old. The majority of patients lived in Stockholm, but many had moved there from other parts of the country.

Hospitalized Patients.

The results have been primarily obtained by examination of the patients who have been hospitalized. The number of adult patients, who could be included, was 400, of whom 148 were men and 252 were women. The cases where the diaries were defective or where patients have had another kind of lung or heart-complaint which has made it difficult to decide how many of the symptoms could be attributed to asthma, have not been included.

The period of hospitalization of the individual case has as a rule been at least two weeks. For some it has lasted for several weeks. Many of the patients have been hospitalized on more than one occasion during the above-stated period. The data given below concern, however, the first period of hospitalization for all patients.

The distress caused by the complaint has varied considerably from status asthmaticus to very slight or complete freedom from distress, and in the latter case, the patients have been admitted for investigation rather than for nursing. The data, which form the basis of this investigation are in the first place hospital records. The patients have been carefully examined in different ways. Thus a detailed prehistory has been the source of information for heredity, course of the complaint, complications, causal factors according to the patients, and earlier treatment. The object of the physical examination, amplified by laboratory tests and an X-ray of the lungs, sinus, teeth, heart and, in certain cases, gall bladder, and a special examination by otologists and dentists, is among other things to reveal possible foci or other significant diseases. Further all patients have been skin tested. Provocation tests have been carried out in many cases.

Out-Patients.

To increase the material and get a broader sampling than would have been the case with an entirely hospitalized group, the study has been expanded by including out-patients of St. Görans Hospital 1949-1952. Altogether this group comprises 348 newly registered asthma patients, of whom 140 are men and 208 are women, all of whom are also at least 18 years old. Information concerning these patients has been obtained from out-patient records, which have been set out in a similar way to those of the hospitalized patients, although in some cases they are much shorter.

Out-patients will be discussed in special tables.

In order to complete the investigation and complement it, the author made a follow-up during 1955-1957 by sending out questionnaires of the kind shown in Fig. 1.

400 of these circulated among the hospitalized patients. 331 (82.7 %) have returned their questionnaires with such complete answers that it was possible to edit them. 38 questionnaires (9.5 %) have been returned unanswered, with the information that the patient has died. Finally 31 patients (7.8 %) were not traced.

348 questionnaires were circulated among the out-patients. The corresponding figures were 275 (79.0 %), 6 (1.7 %), and 67 (19.3 %).

In the following pages an account will be given of the authors classification of different types of asthma. Before this, however, there is an account of the methods with the help of which it has been possible to make such a classification, namely skin tests and provocation tests.

SKIN TESTS

A Short Survey of the Literature.

Ever since skin-testing was used for the first time by *Blackley* (1873) but above all since it was improved and further developed by *Cooke* (1911) among others, who was the first to use intracutaneous (i.c.) tests for general allergy diagnosis, *Schloss* (1912) who was most interested in i.c. testing with food-extracts and *Walker* (1917) who used scratch tests for allergic conditions in general, it has been one of the most important aids in diagnosis of allergic diseases.

FIGURE 1

Questionnaire for the Follow-up Investigation.

Name	Date of birth
Telephone	
Is there anyone in your family who has had, or has:	
asthma?	urticaria?
eczema?	
vasomotor rhinitis?	

Did you have as a child:

asthma? eczema? vasomotor rhinitis? urticaria?

When did you first get asthma?

What do you think was the reason for your first asthmatic attack?

Does your asthma get worse in the presence of some kinds of flowers or plants?

Which kinds?

Foods, which?

Dust?

Animals, which?

Colds?

Do you catch colds easily?

By infection?

By a chill?

How do your colds start?

Have you had a nose operation?

When?

Where?

Why?

Do you think your asthma started the first time after bronchitis or cold?

Does the asthma get worse when you are worried or nervous?

Have you had an operation on your gall bladder?

When?

Which years were you confined to the hospital on account of your asthma?

Answer the Questions below either yes or no.

Since you were last in St. Görans Hospital, have you been able to work normally?

Do you think that you have recovered?

If so, give the date.

Do you think that your condition has improved considerably, by which we mean that although you still may have some distress, you can still carry out your work?

Do you think there is no improvement?

Do you have to take medical aid every day?

If so, do you have to have adrenal injections?

Every modern textbook contains detailed accounts of the theoretical foundations of skin tests and their practical application. It will only be mentioned here that nowadays there are two different methods mainly used, the cutaneous method which is applied with a scarificator, and the intracutaneous

method. With both these, the readings are taken after 15-30 minutes. The cutaneous method is considered by many to be less sensitive than the i.c. method and therefore less dangerous. In many cases, one first makes a cutaneous test. The reactions which are doubtful or negative are further investigated using i.c. tests.

The Authors Method.

Only i.c. tests have been taken at St. Görans Hospital with altogether 41 standard extracts, which are shown in Figure 2. Apart from this, tests have been carried out with other allergens in cases where other hypersensitivity was suspected.

FIGURE 2

Table indicating Standard Extract used in I.c. Testing at St. Görans Hospital, Stockholm.

Name:	Skin test i.c.
Ward:	
Control	
Sheep wool	
Feathers	
Dust 2410 Radhe	
Dust 1996 Wistedt	
Dust 136 Carlsson	
Dust 2442 Riksdagsdamm	
Histamine (1: 10,000)	
Fish	
Meat	
Vegetables	
Dog hair	
Cat hair	
Horse hair	
Cattle hair	
Boiled milk	
Unboiled milk	
Boiled egg yolk	
Unboiled egg yolk	
Unboiled egg white	

Vegetable sulphur
 Crustaceous animals
 Cocoa
 Wheat
 Rye
 Barley
 Oats
 Corn (hominy)
 Timothy (grass) pollen
 Tree pollen
 Daisy pollen
 Reed pollen
 Oranges
 Hazel nuts
 Fungi
 Household dust
 Cotton seed
 Violet root
 Spices
 Birch pollen
 Pine pollen
 Cat hair
 Conc. dust "Vitrum"

The technique which has been used is in short as follows: About 0.1 ml of each extract is injected intracutaneously on the back. Control tests have been made with sterile extracting fluid (physiologic saline mixed with 0.5 % phenol) and with histamine in a dilution of 1:10,000. The results have been read after 20 minutes by measurement of the size of the weals with a ruler. If the weal, when the diameter is measured in two diametrically opposite directions, has reached a size of at least 20 mm it is classified +, if at least 30 mm, ++, if at least 40 mm, +++, if at least 50 mm, +++++, etc. The advantage of this technique is that one gets the exact measurement in each case. By measuring the size of the histamine weal at the same time one gets in each case an idea of the tendency of the skin reaction. Antigen dilutions of a concentration of 10^{-3} have been used for skin tests. The main part of the extracts have been produced by Vitrum the me-

dical supplies firm. All the autodust extracts have, however, been prepared at the allergy laboratory of St. Görans Hospital.

RESULTS OF THE AUTHOR'S SKIN TESTS

Hospitalized Patients (tables 1-4).

Out of these, 5 men and 14 women have been tested on an occasion other than the time of hospitalization, but with the same technique as just described.

From table 1, it appears that out of 148 male patients, 82 (55.4 %) were completely negative and 66 (44.6 %) positive, and out of the 252 women, 172 (68.3 %) were negative and 80 (31.7 %) positive.

TABLE 1

Results of I.c. Tests carried out on 400 Patients with Bronchial Asthma, nursed at St. Görans Hospital, Medical Department II.

	Number of patients		
	♂	♀	♂ + ♀
Positive i.c. tests	66	80	146
Negative i.c. tests	82	172	254
Total	148	252	400

In table 2, the results of the tests have been placed in relation to the age of the patients at the time of the test. The patients with positive reactions have been divided in the table into groups with positive reactions to inhalation allergens on the one hand, and food-stuff allergens on the other. A special column indicates the cases with positive reactions to both food-stuff and inhalation allergens. Males and females have been plotted in separate tables. From these, it appears that the majority of positive reactions are caused by inhalation allergens. In fact, 40 men and 52 women reacted to them, while only 1 man and 8 women showed a reaction solely to food-stuffs. Apart from this, 25 men and 20 women showed

TABLE 2 A

Results of I.c. Tests carried out on Patients with Bronchial Asthma, nursed at St. Görans Hospital, Medical Department II.

Males = 148.

Patients' age at time of testing	Number of patients in different age-groups with completely negative reactions	Number of patients in different age-groups who showed positive i.c. reactions to:			Total	% positive i.c. reactions
		Inhalants alone	Food-stuff allergens alone	Both inhalants and food-stuff allergens		
18-24	0	5	0	7	12	100
25-34	5	6	0	9	20	75
35-44	14	10	0	4	28	50
45-54	23	12	0	2	37	37.8
55-64	27	7	0	3	37	27.0
≥ 65	13	0	1	0	14	7.1
Total	82	40	1	25	148	

TABLE 2 B

Results of I.c. Tests carried out on Patients with Bronchial Asthma, nursed at St. Görans Hospital, Medical Department II.

Females = 252.

Patients' age at time of testing	Number of patients in different age-groups with completely negative reactions	Number of patients in different age-groups who showed positive i.c. reactions to:			Total	% positive i.c. reactions
		Inhalants alone	Food-stuff allergens alone	Both inhalants and food-stuff allergens		
18-24	4	6	0	3	13	69.2
25-34	14	9	2	5	30	53.3
35-44	33	18	0	5	56	41.1
45-54	50	11	0	4	65	23.1
55-64	40	8	6	1	55	27.3
≥ 65	31	0	0	2	33	6.1
Total	172	52	8	20	252	

TABLE 3

Frequency of Positive Skin Reactions among 66 Male and 80 Female Patients, nursed at St. Görans Hospital, Medical Department II.

1. Inhalants (dust, pollen, animal epitelis).

	♂	♀	♂ + ♀
Dust	44	35	79
Horse hair	32	26	58
Cow hair	25	26	51
Dog hair	26	21	47
Cat hair	16	12	28
Tree pollen	26	25	51
Timothy grass	28	24	52
Daisy	13	16	29
Sheep wool	15	16	31
Cotton seed	13	8	21
Reeds	5	5	10
Vegetable sulphur	4	3	7
Fungi	4	6	10
Violet root	4	0	4
Mite (cheese)	4	1	5
Pine	2	4	6
Feathers	2	2	4
Kapock	1	1	2
Radix glycyrrhiza	0	1	1
Fol. digitalis	0	1	1
Total	264	233	497

positive reactions both to inhalants and food-stuff allergens. It also appears from the tables, that the number of positively-reacting patients lessens with increasing age.

In tables 3-4 the allergens used for the tests are set down in tabular form to show the frequency of positive skin reactions to various allergens. As will be seen, in the first place, the individual patient with a positive skin test has a number of positive reactions. Among the 66 men there were actually 337 of these altogether, and among the 80 women there were 282.

TABLE 4
*Frequency of Positive Skin Reactions among 66 Male and 80 Female Patients,
 nursed at St. Görans Hospital, Medical Department II.*

2. Food-stuff allergens.

	♂	♀	♂ + ♀
Hazelnuts	9	6	15
Wheat	9	5	14
Rye	5	1	6
Milk	5	6	11
Crustaceous animals	7	7	14
Egg white	5	2	7
Egg yolk	2	6	8
Spices	5	2	7
Barley	5	1	6
Oats	3	3	6
Meat	4	2	6
Flax-seed	3	0	3
Cocoa	4	2	6
Vegetables	2	2	4
Corn (hominy)	2	1	3
Fennel-seed	2	0	2
Aniseed	1	0	1
Tomato	0	1	1
Liver preparation	0	1	1
Oranges	0	1	1
Total	73	49	122

In the second place, there is a considerable predominance of inhalation allergens and in the third place, the greatest part among these is played by dust, animal epithelials and pollen. Among the food allergens, however, there is nothing which has a marked frequency.

Out-patients (tables 5-8).

Amongst the 140 men, the records have been incomplete in 8 cases and amongst the 208 women in 11 cases to such an extent that it has not been possible to draw any conclusions

regarding the skin tests carried out on them. In all the remaining cases, the skin tests have been carried out with the same technique used for the hospitalized patients.

From table 5, it appears that out of the remaining 132 men, 76 (57.5 %) were completely negative and 56 (42.5 %) positive; and of the 197 women, 119 (60.4 %) negative and 78 (39.6 %) positive.

In table 6, the results of the tests have been put in relation to the age of the patient when the test was carried out. The patients found to be positive, have been divided into different columns, in the same way as has been described with the hospitalized patients. From the tables, it appears that, in the same way as with the hospitalized patients, it is inhalants which have caused the positive reactions in the majority of cases. 31 men and 47 women actually showed only this type of reaction. 3 men and 6 women showed only food-stuff reactions. 22 men and 25 women had positive skin reactions both for inhalants and food allergens. It also appears from the tables that the number of negatively reacting patients increases with increased age in the patient at the time of testing.

In tables 7-8, the different allergens used for the tests have been set out in tabular form to indicate the frequency of positive skin reactions. The position is similar to that among the hospitalized patients, i.e. firstly, that the individual patient has a number of positive reactions (altogether 488 skin reactions in 134 patients); secondly that inhalation allergens

TABLE 5
*Results of I.c. Tests carried out on 384 Patients with Bronchial Asthma,
nursed at St. Görans Hospital Out-patients Allergy Department.*

	Number of patients		
	♂	♀	♂ + ♀
Positive i.c. tests	56	78	134
Negative i.c. tests	76	119	195
Details concerning skin tests lacking ...	8	11	19
Total	140	208	348

TABLE 6 A

Results of I.c. Tests carried out on Patients with Bronchial Asthma, nursed at St. Görans Hospital Out-Patients Allergy Department.

Males = 140 from whom 8 test results are missing.

Patients' age at time of testing	Number of patients in different age-groups with completely negative reactions	Number of patients in different age-groups who showed positive i.c. reactions to:			Total	0/10 positive i.c. reactions
		Inhalants alone	Food-stuff allergens alone	Both inhalants and food-stuff allergens		
18-24	0	5	0	7	12	100
25-34	7	12	1	6	26	73.1
35-44	14	6	0	5	25	44
45-54	22	5	0	3	30	26.7
55-64	20	2	2	1	25	20
≥ 65	13	1	0	0	14	7.1
Total	76	31	3	22	132	

TABLE 6 B

Results of I.c. Tests carried out on Patients with Bronchial Asthma, nursed at St. Görans Hospital Out-Patients Allergy Department.

Females = 208 from whom 11 test results are missing.

Patients' age at time of testing	Number of patients in different age-groups with completely negative reactions	Number of patients in different age-groups who showed positive i.c. reactions to:			Total	0/10 positive i.c. reactions
		Inhalants alone	Food-stuff allergens alone	Both inhalants and food-stuff allergens		
18-24	3	4	0	4	11	72.7
25-34	18	9	1	5	33	45.4
35-44	41	15	0	3	59	30.5
45-54	38	10	4	6	58	34.5
55-64	15	7	0	4	26	42.3
≥ 65	4	2	1	3	10	60
Total	119	47	6	25	197	

TABLE 7

Frequency of Positive Skin Reactions among 56 Male and 78 Female Patients, nursed at St. Görans Hospital Out-Patients Allergy Department.

1. Inhalants (dust, pollen, animal epitels).

	♂	♀	♂ + ♀
Dust	35	35	70
Horse hair	26	18	44
Cow hair	16	15	31
Dog hair	11	19	30
Cat hair	10	14	24
Tree pollen	14	12	26
Timothy grass	16	17	33
Daisy	11	13	24
Sheep wool	7	4	11
Cotton seed	1	2	3
Reeds	2	3	5
Vegetable sulphur	5	2	7
Fungi	7	9	16
Violet root	1	2	3
Mite (cheese)	1	0	1
Pine	4	3	7
Feathers	5	6	11
Kapock	3	5	8
Tobacco	5	4	9
Rabbit hair	3	0	3
Painter's spray fluid	1	0	1
Fol. sennae	0	1	1
Gum. arabic.	1	0	1
Menstruation extract	2	1	3
Total	187	185	372

predominate; and thirdly that dust, animal epitels, and pollen are the most important.

PROVOCATION TESTS

Introduction.

A positive skin reaction need not mean the allergen in question is the cause of the patient's actual allergic distress. To find out whether or not this is so, the skin testing must

TABLE 8

Frequency of Positive Skin Reactions among 56 Male and 78 Female Patients, nursed at St. Görans Hospital Out-Patients Allergy Department.

2. Food-stuff allergens.

	♂	♀	♂ + ♀
Hazelnuts	6	4	10
Wheat	7	7	14
Rye	5	6	11
Milk	4	5	9
Crustaceous animals	11	7	18
Egg white	6	6	12
Egg yolk	7	6	13
Spices	2	6	8
Oats	1	0	1
Meat	2	1	3
Cocoa	1	1	2
Vegetables	2	2	4
Aniseed	1	0	1
Tomato	0	1	1
Rape	1	0	1
Tea	2	1	3
Fish	0	2	2
Oranges	0	1	1
Mustard	1	0	1
Banana	0	1	1
Total	59	57	116

be amplified by further investigations. One way is further to examine the anamnesis with the help of skin test, another is to try to bring about the allergic symptoms which the patient is seeking, by different kinds of provocation tests, or to try to establish the symptom in question by elimination.

Provocation tests are described in a number of modern handbooks concerned with allergic complaints.

It is, however, surprising to see how differently the value of these tests are considered.

When there is a question of suspected food-stuff allergy, one tries to provoke distress by introducing the suspected food-

stuff, or food-stuffs, in small ingested amounts. There are also more laboratory-like methods, for example, by examination of leucocyte or thrombocyte variations. A decrease in the number of leucocytes or thrombocytes, after the consumption of a suspected food-stuff, in relation to the number before the meal, is considered to be enough to assume that an allergy to the food-stuff in question is present. In the case of suspected hypersensitivity to inhalation allergens, it is possible to try to induce distress by exposure to the suspected allergen, or by introducing it by drops into the conjunctiva and the nose or by sniffing. The kind of provocation test which ought to be most suitable for use in asthma is the inhalation test, by which the suspected allergen comes into direct contact with the bronchial mucosa. In such cases, the antigen is inhaled with the aid of artificial methods, normally in greater concentration than under natural conditions. This may be the reason why provocation tests can prove positive while exposure tests are negative. With the latter, the patient is exposed to the effect of the antigen under normal conditions.

Manifest and Latent Allergy.

With the help of exposure and above all provocation tests it is therefore possible to decide whether a positive skin reaction is an expression of manifest allergy (i.e. the antigen which causes a positive skin reaction has also etiological significance for the patient's illness) or latent allergy (i.e. an allergic condition characterized by skin allergy but where this has no clinical significance). (*Salén and Juhlin-Dannfelt 1935*).

Survey of Literature concerning Inhalation Tests.

Peipers (1931) found that inhalation of house dust extract which had given positive skin reactions could cause asthmatic symptoms.

Flood (1931) found in a group of 55 patients with chronic asthma that 8 (14 %) gave positive skin reactions to common

air-borne fungi. Typical asthmatic attacks were produced in 1 of these patients by spraying the nose and throat with a filtrate of *Mucor plumbeus*, one of the fungi, to which the patient gave a positive skin test.

Stevens (1934) considered inhalation tests to be of great value, when they were combined with i.c. tests, in estimating over-sensitivity in the bronchial mucosa. 11 out of the 45 patients had completely negative skin reactions to the 90 allergens, which were used. All inhalation tests with this group were also negative. Of 34 other patients, who had positive skin reactions to one or more of the 90 allergens, 25 inhalation tests on 15 patients were found to be positive: 7 times, when the extract in question gave a strong positive skin reaction, 6 times with a fairly strong reaction, twice with a weak reaction, and 10 times with a negative skin reaction.

Harris (1941) let asthma patients, who reacted positively to alternaria spores by dermal testing, partly inhale and partly sniff these. 12 patients had typical anamnesis for over-sensitivity to mould and of these, 10 were caused distress. 10 others had uncharacteristic anamnesis. Out of these, only 1 was caused distress.

Pennington (1941) exposed patients, who showed positive skin reaction to moulds, by spraying the nasal passage and pharynx with extract of the moulds. 22 of the 61 patients were caused distress.

Unger (1945) considers that inhalation tests are dangerous.

Urbach and *Gottlieb* (1946) on the other hand suggest that they have been able to show bronchial oversensitivity to pollen, dust, animal hair and other substances by this method.

Feinberg (1946) states concerning inhalation tests: "In bronchial allergy when skin reactions are negative or when the significance of positive reactions is doubtful, a direct bronchial test with the inhalant allergen may be tried This is an excellent method except that it is too complicated and too expensive for routine use".

Salén (1948) has pointed out the difficulty of interpretation of the provocation tests. Experience from dust and flour

allergy shows that it can take several days after a dust-sensitive patient has returned to his home before distress arises. The reason for this can be, however, that as mentioned above the intensity of the exposure is considerably less in natural circumstances than in provocation tests.

Christensen and *Sonne* (1948) carried out different kinds of inhalation tests on 7 asthma patients with positive skin reactions to house dust. In only 1 case did asthmatic distress occur 6 hours later. The author's conclusion was that provocation tests are valueless.

Nilsby (1949) came to the same conclusion after an investigation of oversensitivity to moulds in 23 asthma patients.

Juhlin-Dannfelt (1950) published the results of 165 provocation tests of which the majority were carried out by sniffing. Every provocation test corresponded to a very strongly positive skin reaction. He found that not less than 2/5 of the patients had latent allergy.

Arner (1949) measured in 2 cases the relative oxygen saturation in the blood and was able to show that provocation tests could be successfully carried out by inhalation of the suspected allergen extract.

Damgaard (1951) carried out provocation tests on 141 asthmatic children by inhalation of different allergen extracts in different concentrations, which gave positive skin reactions. About 43 % of the inhalation tests proved positive.

Schiller and *Lowell* (1948, 1952) carried out provocation tests on asthma patients by inhalation of dust and pollen extract in different dilutions. Reduction of at least 10 % in vital capacity or obvious slowing in expiratory rate were considered evidence of sensitivity. Out of 75 patients, 57 reacted to one or more allergens. Only the allergens which gave positive skin reactions gave positive provocation tests. On the other hand, there were positive skin reactions without pulmonary reactions in the inhalation experiments.

Colldahl (1952) found provocation tests valuable also in the case of weak or even negative skin reactions. He also

found that it is possible to perform provocation tests on patients with rough breathing sounds. 44 asthma patients were examined with altogether 169 provocation tests by determination of washing-out time for nitrogen during inhalation of oxygen. 43 % of these were positive with positive skin reaction to the allergen in question, and 16 % with negative skin reaction.

Author's own Provocation Tests; Indications and Methods.

Provocation tests have been carried out on all of the author's hospitalized cases showing positive skin tests, where it was impossible to state with absolute certainty that a causal connection between the testing and the clinical distress could be ruled out. However, in doubtful cases where the allergen in question had been suspected, and as a rule even in the cases with an obvious connection and in which specific treatment has been considered, provocation tests have been carried out.

As far as the out-patient cases are concerned, provocation tests have not been carried out as extensively as with the hospitalized patients, but specific treatment has only been given on the strength of skin tests and anamnesis. This applies particularly to the patients who were entered when the out-patients clinic first commenced operation.

All the provocation tests described in this work have been carried out by inhalation of different antigen extracts, through a spray driven by compressed air, except in the suspected cases of hypersensitivity to food-stuffs, where the allergen in question was introduced per os. This, however, only concerned a few cases.

The provocation tests were performed on patients with normal breathing sounds before the test. Adrenalin or other similar symptomatic drugs had not been given in the previous 12 hours. Before the experiment had commenced the patient's lungs were carefully auscultated and any abnormalities recorded. After this, the patient had first to inhale the extracting fluid (physiologic saline mixed with 0.5 % phenol). As

a rule no reaction occurred from this. After an interval of 10 minutes, the patient then inhaled the antigen solution in question in a dilute state, after which the strength was successively increased if no reaction took place with the first inhalation. The patient inhaled 1 ml of each antigen dilution, which took about 10 minutes, after which the patient was allowed to rest for 10 minutes before the next inhalation. After each, the condition of the patient was noted. If no distress occurred and if there was no change in respiratory-sounds, the patient had to inhale gradually strengthened antigen solutions until the maximum concentration was reached. If not even this caused distress, the provocation test was considered to be negative. An important detail which should be mentioned is that the patient has not been allowed to know in advance what is being done, in order to avoid all psychical influences or autosuggestions.

RESULTS OF THE AUTHOR'S PROVOCATION TESTS

Hospitalized Patients.

As has been mentioned earlier in connection with the skin tests, 82 of the 148 men and 171 of the 252 women had completely negative skin reactions when intracutaneous testing took place. In these cases, no provocation tests were carried out. The remaining 66 men and 81 women showed positive skin reactions to one or more allergens. In the case of 11 men and 42 women it has been possible to dismiss these reactions as not indicating asthma only with the help of anamnesis and clinical progress. There thus remain 55 men and 38 women. In all these cases one or more provocation tests have been carried out. If these were positive and the anamnesis corresponded, manifest allergy for the allergen in question was considered to be present, after which the patient has normally been given specific hyposensitization. This type of asthma was found in 37 men and 28 women. In the remaining 18 men and 10 women, provocation-tests have been made, but have turned out negative, and in these cases therefore, no proof of

manifest allergy has been present. Therefore no specific treatment has been given in these cases.

Out-Patients.

As has been mentioned above, provocation tests have not been carried out to as great an extent amongst out-patients as amongst the hospitalized patients, but the specific therapy has been started only with the help of anamnesis and skin tests. This treatment has been considered indicated in 38 men and 30 women out of the 348 out-patients. The remaining 102 men and 178 women have thus not received any such therapy, either because the skin tests have been negative or because latent allergy was considered to be present.

The Author's Classification of the Cases with Regard to Proved Specific Allergy on the One Hand and without Proved Allergy on the Other. The Conceptions Exogenous and Endogenous Asthma.

From the previous description it appears that out of 400 hospitalized patients, 37 men and 28 women had positive skin reactions and positive reactions to provocation tests with regard to one or more allergens. Of the 348 out-patients, a similar connection was considered to be present in the cases of 38 men and 30 women. These 133 patients will be called *exogenous* asthma patients.

All the other patients, i.e. the 335 hospitalized and the 280 out-patients, have thus either been completely negative to skin tests, or have had positive skin reactions with no corresponding clinical significance regarding asthmatic trouble. These will be called *endogenous* asthma patients.

Further Observations concerning the Classification of Exogenous and Endogenous Asthma respectively.

In the available material, thus, only 17.9 % had exogenous asthma and 82.1 % endogenous asthma. A more detailed examination of the classification of the different types

shows the following existing position. Of a total of 748 patients, there were 288 (38.5 %) men and 460 (61.5 %) women, i.e. a considerable predominance of women. With the *exogenous* group, however, there was a clear predominance of men. Out of the 133 exogenous cases, there were actually 75 (56.4 %) men and 58 (43.6 %) women. The predominance of the women thus occurs in the *endogenous* group, i.e. 615 cases. Of these, there were only 213 (34.6 %) men but 402 (65.4 %) women. In other words, 75 (26 %) of the 288 men, but only 58 (12.6 %) of the 460 women had exogenous asthma.

Account of the Allergens for Which Manifest Allergy was present.

Thus only about 18 % of the patients can be treated by hyposensitization or elimination. For the remaining patients it is necessary to find other treatments. As can be seen from table 9, where the allergens for which manifest allergy was present are set down, it was almost without exception inhalation allergens that caused the asthma, firstly dust, secondly pollen of different kinds and animal epithelials. It also appears that some patients were manifestly oversensitive to more than one allergen.

In this connection, it may be appropriate to stress further the importance of carrying out a proper investigation. Out of the 748 patients accounted for here, not less than 280 had a total of 1107 positive i.c. reactions, but out of these, only 195 were shown to have clinical significance in a total of 133 patients. Thus 147 patients had 912 positive skin reactions without corresponding clinical manifestation. These figures give further support to the importance of not deciding on a specific hyposensitization with the help of only a skin test.

ACCOUNT OF TOTAL MATERIAL

The discoveries made, i.e. that positive skin tests occur mainly in the younger age-groups and decrease with age, is illustrated in figure 3.

TABLE 9
*The Allergens for which Manifest Asthma was present in
 75 Men and 58 Women.*

	Number of positive reactions:	
	♂	♀
Dust	48	28
Horse hair	7	3
Cow hair	3	1
Timothy grass	17	14
Daisy	2	5
Dog hair	5	8
Cat hair	5	3
Tree pollen	8	16
Wheat	7	1
Rye	5	0
Sheep wool	1	2
Tobacco	0	1
Radix glycyrrhiza	0	1
Fol. digitalis	0	1
Fol. sennae	0	1
Fish	0	1
Painter's sprayfluid	1	0
Total	109	86

The fact, that positive skin reactions occur without having clinical significance for the actual allergic complaint, is illustrated by figures 4 and 5, where the most important allergens which gave positive provocation test results are set down at the same time as the number of positive skin test reactions to the allergen in question has been accounted for.

SUMMARY

A survey of the literature shows that there are a number of classifications of bronchial asthma most of which are done by the help of etiology but some by the clinical course of the complaint. With regard to etiology, two large main groups can be distinguished, namely, one where specific allergens of

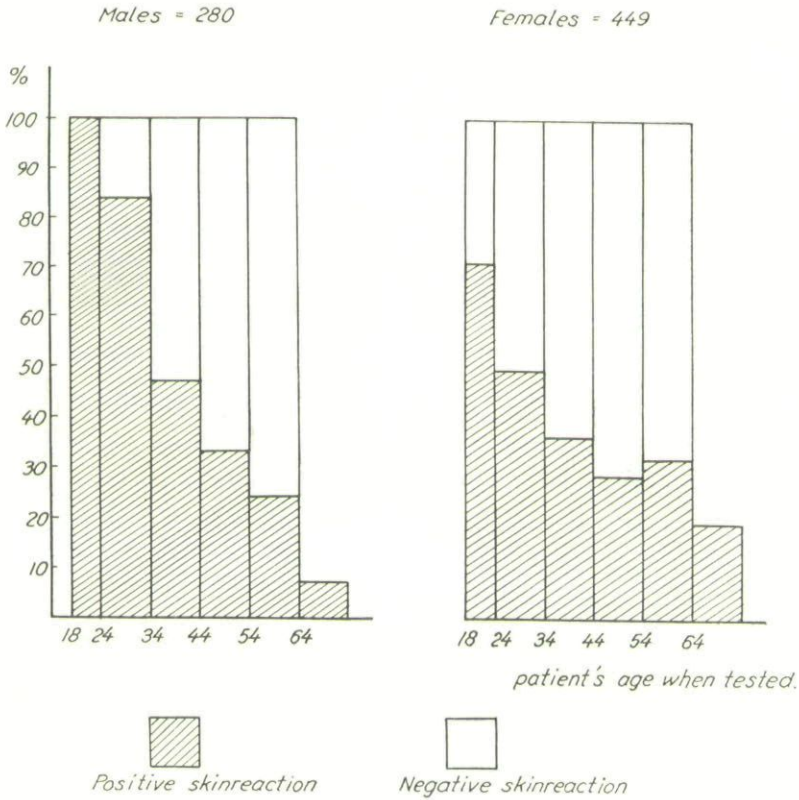


Fig. 3.

Cases in per cent with positive and negative skin reactions in i.c. tested patients in age groups when tested (details concerning skin test lacking in 19 cases).

different kinds are the cause of the asthma and the other where no such causes have been found.

In the present work, the classification has been made with regard to the etiology in *exogenous* and *endogenous* asthma respectively, depending on whether specific allergens have been distinguishable as the cause of the asthma or not. From available literary data it appears that in different investigations, exogenous asthma was found to be present from 20–75 %. In this investigation, which concerned 748 adult patients, this type of asthma could be proved with the help

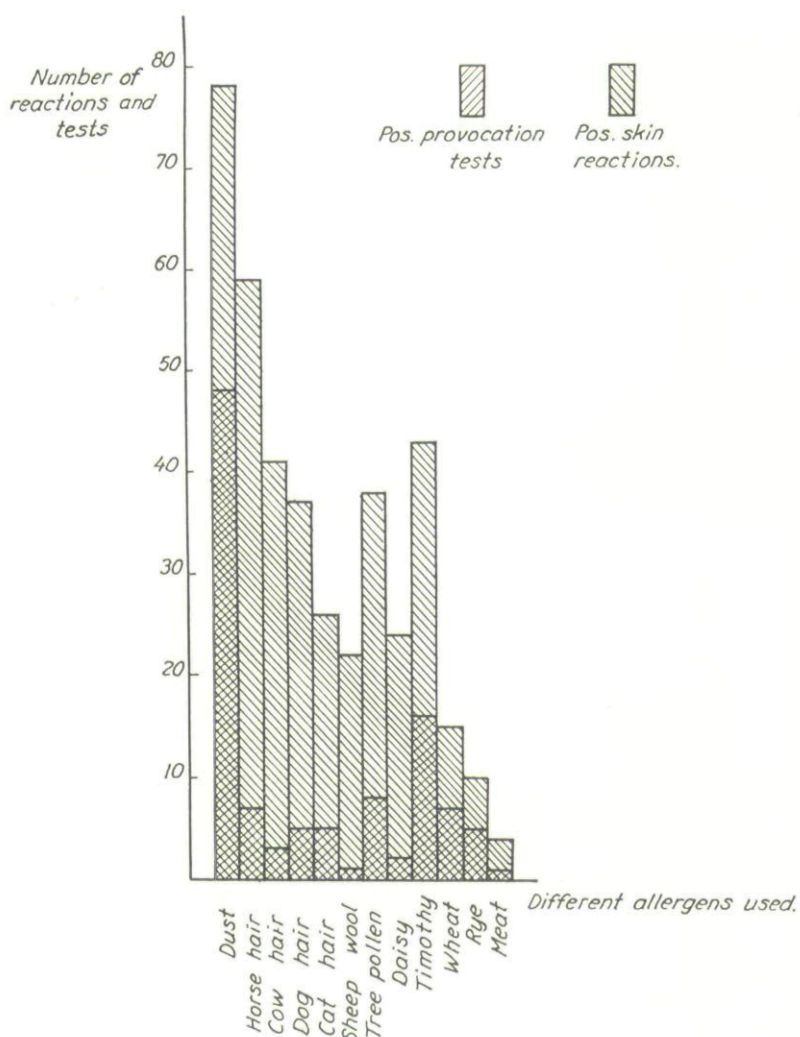


Fig. 4.

Number of positive provocation tests in comparison with the respective number of positive skin reactions to the most usual allergens.

Males

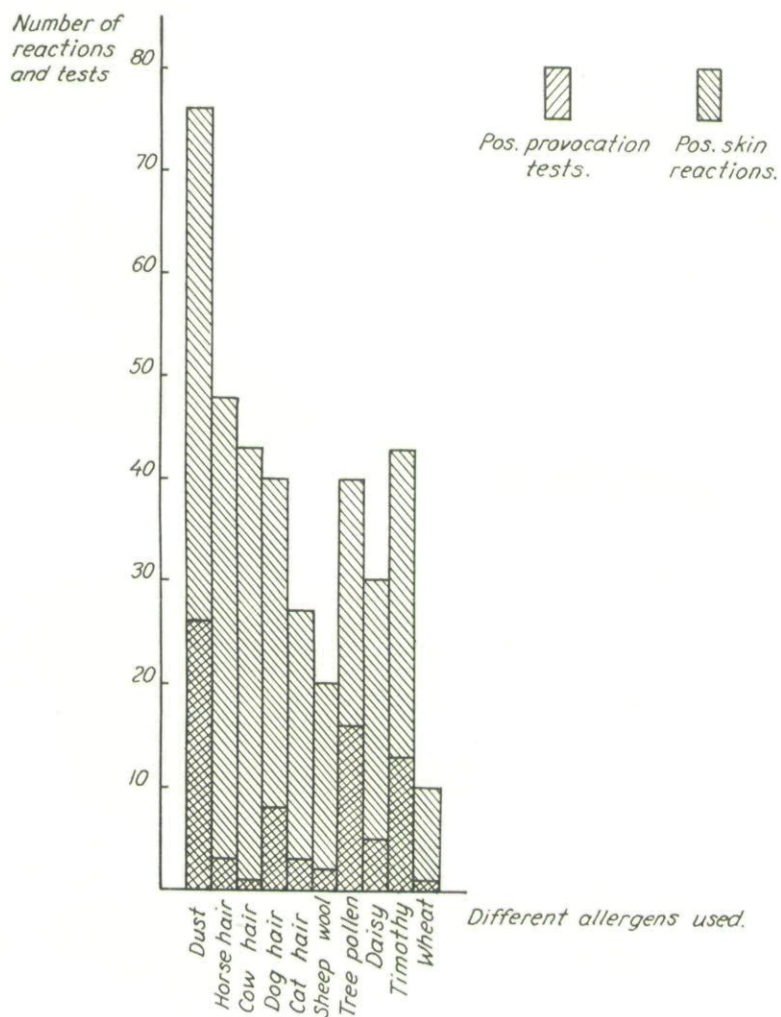


Fig. 5.

Number of positive provocation tests in comparison with the respective number of positive skin reactions to the most usual allergens.

Females

of anamnesis, skin tests and provocation tests, only in 133 (17.9 %) cases. The investigation also suggested that women predominated in the total material, and that the majority of the exogenous group were men.

The investigations also showed the significance of different kinds of case-examination. Skin tests by themselves are not sufficient to decide whether the positive skin allergens also have significance for the actual allergic complaint (= manifest allergy) or if they are just an expression of a skin allergy without clinical significance (= latent allergy).

Among the asthma patients included herein, more than 80 % suffered from the type of asthma, for which it has not been possible to prove any specific allergen as the cause and in which case it is therefore necessary to find methods of treatment other than specific hyposensitization. In order that these may be successful, it is of importance to know as much as possible about the nature of the complaint. The intention in the following is to try to contribute to such knowledge by investigating the age when asthma commences, sedimentation rate reaction, and causes to the start of the complaint.

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