

THE PREVALENCE OF DUST ALLERGY IN BRONCHIAL ASTHMA AND THE IMPORTANCE OF CARRYING OUT PROVOCATION TESTS, EVEN WHEN SKIN TESTS REVEAL NEGATIVE RESULTS

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The purpose of the allergological investigation of asthma patients is, *inter alia*, to find such allergens as can be of importance in producing or maintaining asthmatic complaints.

A thoroughly penetrated anamnesis—where it is a matter of finding out whether the patient himself has been able to ascertain or suspect a contact with some definite allergen as producing his asthma disorders—is in this connection a correct way of examining the patient.

Further, there is skin-testing, whereby it is possible to obtain certain information as to an eventual allergy. The method of testing the skin and appraising it varies in different quarters. In principle it is carried out by utilizing a standard skin test containing the most common allergens, in addition to which there is, in the individual case, a testing of other allergens to be examined. The skin test only yields information concerning the existence of a contingent skin allergy. In certain cases it may correspond to a sensitivity of a similar nature occurring in the bronchial mucous membrane. In order to ascertain whether this is the case, provocation tests of various kinds are employed.

Provocation by inhaling the suspected allergen is more increasingly being made use of, and it may no doubt be asserted that it is an erroneous expedient to begin a specific hypo-

sensitization without first convincing oneself of the fact that the allergen in question actually causes asthma in the patient. A determining factor as to whether the rather time-wasting provocation is to be carried out, or not, is as a rule what results from the first two examinations mentioned above, viz. anamnesis and skin tests. In relation to the large number of skin tests carried out, however, there is a relatively low number of provocation tests. The most substantial reasons for this are the following:—

(1) The patient reveals a negative standard skin test. This applies especially to elderly individuals. In these cases there are practically never any provocation experiments resorted to. A large group of patients belong to this category. As an example, mention may be made of an investigation by *Fagerberg* (1957) which comprised 748 adult asthma patients of the age of 18–70. Of these no less than 468 (65 %) had entirely negative skin tests, and in none of these cases did there seem to be any indication requiring provocation experiments.

(2) It has already been mentioned, by way of introduction, that a positive skin test reveals the existence of a skin allergy, but that it is by no means certain that the allergen in question also causes sensitivity of the bronchial mucous membrane. Such skin reactions of no clinical importance are in fact very common. In many cases it is possible to determine, by means of the anamnesis, if the allergens in question can be considered insignificant to the patient's asthma, and consequently if it is also unnecessary to make provocation experiments on these.

(3) Hence there remains a group of patients with positive skin reactions where provocation tests are carried out for the purpose of determining whether the allergen is of clinical importance or not. If claims are made that the anamnesis, skin tests, and provocation tests should correspond, there is finally a rather small group of patients that fulfil these requirements

(exogenous asthma). In the above investigation by the present writer the percentage of this was 17.8 %. *Colldahl* (1956) has, in other material examined in a similar way, found that there was an indication of specific hyposensitization in 25 % of 387 cases examined. Also other authors have found similar frequency figures with regard to exogenous asthma (*Diener* 1938, *Harley* 1952, *Hollman & Krause* 1953, *Jimenez-Diaz & Arjona* 1953). It should be pointed out, however, that many authors share *Rackemann's* opinion of more than 75 % of all asthma being exogenous i.g. *Bruun* (1956). In any case, endogenous asthma—where it has not been possible to indicate a specific allergen as a provocative cause—constitutes a large and significant group. Thus the latter comprises, on the one hand, such cases as have revealed an entirely negative skin test; on the other hand, such as where, it is true, the existence of positive skin reactions have been able to be proved, but where a meticulous evaluation of the positive reactions shows that these allergens are of no importance to the patient's asthma. In other words, it may be stated that there are a great many patients revealing erroneously positive skin reactions. It is then close at hand to question whether it is also possible to conceive the existence of erroneously negative skin reactions—in other words, whether exogenous asthma is manifest in spite of negative results of the skin test. When it pertains to drugs and food-stuffs, the question can no doubt be answered in the affirmative. The patient may be hypersensitive to some substance belonging to the groups mentioned above in spite of a negative skin test. The cause may be that the allergen was applied in too small a quantity, or that specific antibodies are lacking in the skin, but can be found in the shock-organ, or that it is metabolites of the substance in question that provokes the asthma. But also in the case of inhalation-allergens, which, as we know, are no doubt the most common releasing cause of asthma, certain authors have found that provocation tests were able to become positive in spite of negative skin tests. *Efron & Penfound* (1930) found a total absence of skin sensitivity in 4 (20 %) of clinically known

and nasal tested positive allergic cases. *Stevens* (1934) carried out 578 i.c. tests and an equal number of provocation tests by means of inhalation using 17 different allergens on 34 patients. He found positive provocation test ten times, in spite of a negative skin test. Dust was not to be found among the allergens tested. *Citron et al.* (1958) have recorded 2 asthma patients where the amnesia indicated hypersensitivity to timothy. The provocation tests were positive, but the skin tests negative. *Colldahl* (1952) examined 44 patients having asthma. He carried out a total of 169 provocation tests with, *inter alia*, auto-dust, pollen, and animal epiphelia, and in so doing he discovered that 16 % of the provocation tests turned out to be positive and 10 % dubiously positive, in spite of the skin reaction being negative to the allergen in question. *Ingestad* (1959) made 600 provocation tests using 14 different allergens on 85 patients with asthma. 13 % of the provocation tests were positive in spite of negative skin tests. The allergens used were *int. al.* dusts, moulds, pollens and epithelia.

INTRODUCTION

The Author's Investigations.

Various authors have claimed that inhalants—and then particularly dust—is of the greatest importance to the type of asthma where it is possible to indicate a provocative cause (exogenous asthma). It has also proved to be the case that dusts from various environments can contain different specific antigens and that several heterogenous dust extracts should therefore be found in a standard skin test. Furthermore, it has been observed that many asthma patients only react to dust from their own dwelling. This was pointed out by *Peipers* as early as 1931, and he too maintained that the dust extracts that are prepared from the homes of patients of asthma localities are the strongest.

Such cases as where other allergens than dust and mould have been of essential importance as a releasing factor of asthma have not been included in the present investigation.

As a matter of fact, the aim has been to investigate the two following matters of interest:—

(1) How often does it occur that auto-dust is a releasing factor of asthma?

(2) To what extent is the fact that provocation tests with auto-dust turn out positive in spite of negative skin tests?

To obtain an answer to these questions, each patient has— in addition to the customary anamnesis and standard skin test—also been skin-tested and provoked with auto-dust taken from the dwelling of each individual. Hence, these investigations have been carried out systematically, independent of the fact whether the skin tests turned out to be positive or negative.

At present, the material comprises 68 patients (32 male and 36 female). On account of its limited extent, it will be recorded as a unit. The distribution of age appear from Table I.

TABLE I
Patient's Age at Time of Examination.

Age in years	< 18	18-24	25-34	35-44	45-54	55-64	≥ 65
Number of patients	5	8	6	12	15	11	11

All the patients have been submitted to a thorough anamnesis according to a schedule employed by the present writer for many years. After a physical examination including, among other things, a focal investigation, the skin of the patients has been tested i.c. by means of a standard skin test, in which *int. al.* there were included 4-6 different dusts and 1-2 mould extracts. Antigen dilutions of a concentration amounting to 10^{-3} were used. The test was considered positive if this dilution gave rise to a wheal, where the sum of 2 diameters at right angles to each other had attained at least 20 mm. As already mentioned, i.c. tests were also carried out with an auto-dust extract independent of the fact whether the standard skin test turned out to be positive or negative. It was prepared from

the fine powder-dust obtained by vacuum-cleaning bed-clothes, chairs, textiles, and the like. The majority of the auto-dusts have been prepared at the allergy laboratory of St. Göran's Hospital Stockholm. Provocation tests were made by means of inhaling auto-dust according to the method described by *Arner* (1958) *Colldahl* (1952, 1955), *Fagerberg* (1957) *et al.* It should especially be pointed out that the patients had no knowledge of being the object of provocation experiments. The deduction as to whether the provocation tests turned out positive or not, was brought about by auscultation of the lungs and observing the general reaction of the patient. This investigation covered 90 provocation experiments.

The Results of the Present Investigation.

In Table II the 68 patients have been arranged with regard to how the provocation tests turned out. Furthermore it is evident what condition prevails with regard to the anamnesis, standard skin tests, and auto-dust tests. It appears from this table that the provocation tests with auto-dust turned out positive in 37 cases (55 %), positive without certainty in 6 (8 %), and negative in 25 (37 %). The cases of primary interest in this connection are the 37 patients with positive provocation tests. In the table the following conclusions are obvious:—

(1) No anamnestic information regarding hypersensitivity to dust could be obtained from 23 cases (62 %), whereas 14 (38 %) had observed that dust was a releasing factor.

(2) A negative standard skin test was applied to 17 cases (46 %), and a negative i.c. test for auto-dust to 10 (27 %). 8 patients (22 %) were given a negative standard test as well as one with auto-dust.

(3) Dust is a common releasing factor in bronchial asthma. This material revealed 37 cases (55 %) of that.

(4) In order to make sure of discovering all the cases having dust allergy, the investigation must not be concluded

TABLE 2

Results of Prehistory, Intracutaneous (i.c.) Tests and Provocation Tests by Inhaling Auto-Dust in 68 Asthma Patients.

		Provocation Tests with Auto-dust		
		Positive 37 (55 %)	Positive? 6 (9 %)	Negative 25 (36 %)
Asthma from dust in the prehistory of the patient	Pos.	14 (38 %)	2 (33 %)	6 (24 %)
	Neg.	23 (62 %)	4 (67 %)	19 (76 %)
Results of i.c. tests with commercial dust extracts	Pos.	20 (54 %)	1 (17 %)	9 (36 %)
	Neg.	17 (46 %)	5 (83 %)	16 (64 %)
Results of i.c. tests with auto-dust extracts	Pos.	27 (73 %)	1 (17 %)	9 (36 %)
	Neg.	10 (27 %)	5 (83 %)	16 (64 %)
I.c. tests with commercial dusts as well as auto-dusts	Neg.	8 (22 %)	4 (67 %)	12 (48 %)

until a provocation has also been carried out with auto-dust. This must be made even if the skin test for the dust in question should be negative. In 46 % of the cases of this material the fact that dust was a releasing cause of asthma would probably have been overlooked unless the directions given had been followed¹.

DISCUSSION

In a previous work (1958) the present writer has discussed the reasons why it is necessary to refer so many patients to the endogenous group, maintaining that, among other view-

¹ Lately, the present writer has also systematically begun investigating the prevalence of mould allergy. As a matter of fact, mould as well as dust is to be found everywhere in the environment of the asthma patients. Hitherto, however, hypersensitivity to moulds has not been regarded as occurring very frequently as a provocative cause of asthma. Among other reasons, this may depend on the fact that the anamnesis seldom offers any guidance and that skin tests with moulds often turn out negative, the investigation thus not being completed by applying provocation tests. So far, the present writer has examined the prevalence of mould allergy in 16 patients of the total 68. 7 (44 %) patients showed positive provocation tests, 6 of these in spite of negative skin tests for mould. Of the 7 patients 2 were also given positive provocation tests with auto-dust, whereas the remaining five were given negative.

points, this might depend on deficiencies in the technique of investigation and in the extracts of allergens. In this research, where the routine investigation included the testing of auto-dust in all the cases and of mould in a minor number of them, it appears as if this assumption should be justified to a certain extent. It has proved to be necessary to complete the investigation of each asthma patient-unless it is possible to indicate another releasing factor of real importance-by provocation with auto-dust and probably mould as well. This must be done independent of the fact whether the anamnesis and the skin tests turn out negative or positive. It is self-evident that also other allergens have to be tested in the same way if there should be any suspicion as to hypersensitivity with regard to them. That dusts and moulds themselves are the very allergens to be examined in the first place depends on the fact that dust is the most common provocative allergen in asthma, and furthermore on the fact that dusts as well as moulds are continually to be found in the patient's environment, exposing him to daily contact with them. Of course, it would be most correct to prepare auto-mould extracts too, but that is a laborious procedure, so for practical reasons one should use extracts of standard mould in which the most common varieties of mould are included. Indeed, it is a waste of time and also expense to carry out the investigations in the way denoted above. Nevertheless asthma is such a serious disease and of such torment to the patient that everything must be done to discover its eventual provocative causes and hereby enable to offer the individual afflicted an adequate treatment.

In a previous work (1958) the present writer has pointed out the fact that patients having exogenous asthma had fallen ill in 97.6 % of the cases prior to the age of 45 and only in 2.4 % of those subsequent to this age. Among the patients recorded there was, as a rule, an agreement between the anamnesis, skin tests, and provocation tests. It was also pointed out that the results were in good accordance with those attained by *Rackeman* (1950). The latter has indicated that, as a rule, patients afflicted with exogenous asthma fall ill

before the age of 30, whereas those having endogenous asthma are, as a rule, taken ill after 40.

In Table III the present writer has in the present investigation recorded the age of onset concerning 42 patients with positive provocation tests with regard to dusts and moulds. As a matter of fact, the skin tests of these cases were to a large extent negative. It appears from the Table that 83 % of the cases had fallen ill prior to the age of 45, and 17 % subsequent to this age. Exogenous asthma depending on hypersensitivity to dusts and moulds may thus arise even after 45.

TABLE 3
Age of Onset of Asthma in Relation to Age when Examined.

Patient's age at time of examination	Number of patients	Age of onset						
		< 18	18-24	25-34	35-44	45-54	55-64	≥ 65
< 18	5	5						
18-24	6	4	2					
25-34	5	3		2				
35-44	8			3	5			
45-54	8	1	2	1	3	1		
55-64	6	1			2		3	
≥ 65	4				1	3		
Total	42	14	4	6	11	4	3	

GENERAL SUMMARY

In this work, intended to be carried out on a large scale, 68 asthma patients have been examined. None of them had the type of asthma where animal epithelia, pollens, food-stuffs, or drugs were the releasing factor of major importance. All 68 of them have been examined by means of anamnesis, standard skin tests, i.e. auto-dust tests, and auto-dust provocations. 17 of them have also been provoked for moulds. The following conclusions were arrived at:—

(1) Auto-dust is a common releasing cause of asthma. In fact, 37 (55 %) patients of a total 68 had positive provoca-

tion tests. Of the provocation tests 46 % were positive where the standard skin was negative, and 27 % positive where the auto-dust skin test was negative. In 8 patients (22 %) there were negative standard as well as auto-dust skin tests.

(2) Also mould appears to be a provocative cause of asthma. Of 16 patients examined, 7 (44 %) had positive provocation tests for moulds. 6 (37 %) of these had negative i.c. tests for mould.

(3) In all asthma cases, where it has not been possible to point out any other allergen of essential importance, the investigation has to be completed by provocation tests with auto-dusts and moulds. No regard must be taken to a negative anamnesis and a negative skin test. Only when the provocation tests have been carried through may the investigation be regarded as completed.

(4) The age of onset is of no importance. Also elderly patients may have an asthma where dusts and moulds can be releasing factors.

REFERENCES

- Arner, B., Fürst, E. & Truedsson, E.*: Sv. läk. tidn. 51, 3689, 1958.
Bruun, E.: In *van Ufford*: The Therapy of Bronchial Asthma. H. E. Stenfert Kroese N.V., Leiden 1956, p. 15.
Citron, K. M., Frankland, A. W. & Sinclair, J. D.: Thorax 13, 229, 1958.
Colldahl, H.: In *van Ufford*: The Therapy of Bronchial Asthma. H. E. Stenfert Kroese N.V., Leiden 1956, p. 39.
Colldahl, H.: Acta Allergol. V, 133, 143 and 154, 1952.
Colldahl, H.: Sv. Läk. tidn. 50, 2001, 1953.
Diener, I.: Wien. Med. Wchnschr. 88, 1215, 1938.
Efron, B. G. & Penfound, W. T.: J. Allergy 2, 43, 1930.
Fagerberg, E.: Acta Allergol. XI, 293 and 327, 1957.
Fagerberg, E.: Studies in Bronchial Asthma. Appelbergs Boktryckeri, Uppsala 1958, p. 4.
Harley, D.: Fortschr. d. Allergielehre, III, 276, 1952.
Hollman, W. & Krause, W.: Ztschr. Inn. Med. 8, 243, 1953.
Ingestad, R.: Sv. Läk. tidn. 6, 360, 1959.
Jimenez-Diaz, C. & Arjona, E.: Acta Allergol., Suppl. III, 1953, p. 105.
Peipers, A.: Zschr. Immunitätsforsch. 71, 359, 1931.
Rackemann, F. M.: Postgraduate Med. 8, 134, 1950.
Stevens, F. A.: J. Allergy 5, 285, 1934.

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