

From the Medical Clinic, Lund, Sweden (Chief: Professor H. Malmros).

A STUDY OF PROVOCATION TESTS ON PATIENTS WITH BRONCHIAL ASTHMA

I. *The reliability of provocation tests performed under different conditions.*

By

HELGE COLLEDAHL

There exist in the literature of the subject very few extensive investigations where a larger number of exposure and provocation tests is examined. As is well known these tests are often used when a patient is examined for allergy, but different authors are of very different opinions as far as the result, value, and interpretation of the tests is concerned. Further, there exist different opinions concerning the possibility of performing provocation tests when the patients have not had entirely normal lung findings before the test.

Alexander (1927) in particular has emphasized the common occurrence of localized allergy. He states that "certain organs only are receptive to allergens, and unless the skin is so, no reactions can occur". On the other hand a positive skin reaction cannot without any further consideration be interpreted as diagnostic of a disease process. It only indicates a state of skin sensitivity. Rackemann (1931) aptly considers that dermal tests form a composite picture of the past, present and future sensitivities of the patient. It is now a well-known fact, resulting from the works of several investigators (Rackemann, Stevens, Salén, Juhlin-Dannfelt, Harris, Tuft), that before we can interpret a positive skin reaction as etio-

logically significant it must be correlated with the history. An allergic state with positive skin reactions which have no etiological significance for the disease of the patients even when under strong exposition has been called latent allergy by Salén and Juhlin-Dannfelt (1932-1935) and nonclinical allergy by Tuft (1943), in contrast to manifest allergy, where the skin test is etiologically significant. Salén and Juhlin-Dannfelt showed that in certain occupations latent allergy very often occurred. Colmes, Guild and Rackemann (1934-1935), studying the importance of occupational and environmental allergy, found that if normal persons are given sufficient exposure to substances of known allergenic potency the establishment of clinical hypersensitivity is not determined wholly by the frequency and degree of exposure or by the vulnerability of the shock organ alone. There still remains an unknown biological factor. To become skin-sensitive is a common property of human beings, according to these authors, while the capacity to express the sensitivity clinically is the property of those in whom operates an unknown biological factor.

According to Juhlin-Dannfelt (1950) experience with exposure and provocation tests has shown that among the patients giving a positive provocation test there is a quite considerable group of cases which under natural conditions of exposure have never shown any clinical evidence of the hypersensitiveness in question. This type of allergy, lying on the border between manifest and latent allergy, has been called semilatenent.

Tuft (1943) also states that some of the positive reactions by skin testing of an allergic patient may be clinically unimportant, yet they are normally immunologically specific, and should be so recognized, thus confirming the results of earlier investigators, among others Salén and Juhlin-Dannfelt. According to Tuft it is very important whenever possible to differentiate between all specific reactions into nonclinical positives and clinical positives. The term clinical positives would be reserved for those which are of proved clinical

significance, determined either by the history or by clinical tests or whenever possible by both.

Following the nomenclature used by Juhlin-Dannfelt (1950) exposure tests mean experiments in which a person is exposed to an allergen in a way similar to ordinary conditions. Provocation tests, on the other hand, cover experiments in which a person is exposed to an allergen in a way such as would not occur under ordinary conditions.

With the help of provocation and exposure tests it is possible to decide if a state of allergy is present in the absence of a positive skin test. But it is also possible to decide if a positive skin test is a sign of manifest or latent allergy (Juhlin-Dannfelt and others).

Juhlin-Dannfelt (1950) is of the opinion that provocation tests should be performed only with great caution in cases where the patients are not entirely free from discomfort, when, for instance, ronchi are heard by auscultation, since under such conditions unspecific reactions may occur. As most asthma patients, even after having stayed in hospital for some weeks, although subjectively symptom-free, have a rough breathing sound by auscultation, it is important to establish whether provocation tests can be performed on these patients with the same degree of reliability as on patients with a normal breathing sound.

Colldahl and Lundin (1952) showed that provocation tests could be performed on patients who had a rough breathing sound. In this investigation the washing-out time for nitrogen during oxygen breathing was determined after each inhalation period. This time did not change after the inhalation of Coca's solution or after the weaker solutions of the extract, which would have been the case if an unspecific reaction had occurred.

If the asthmatic breathing difficulties that occur in connection with the provocation test depend on unspecific reactions, a greater number of positive results can be expected to occur, if before the test the patients have a rough breathing sound.

TABLE I

Initials	Age	Sex	Number and outcome of inhalation tests								Total number
			Breathing sound before test								
			Normal				Rough				
			+	?	—	Total	+	?	—	Total	
M.N.	36	f.	1	—	—	1	—	—	—	—	1
R.S.	32	m.	—	—	—	—	2	—	2	4	4
E.E.	28	f.	3	2	1	6	2	—	1	3	9
I.P.	31	f.	1	—	3	4	—	—	—	—	4
A.A.	30	m.	—	1	—	1	1	1	—	2	3
I.P.	17	f.	1	—	2	3	—	—	—	—	3
V.A.	52	m.	1	—	—	1	—	—	—	—	1
B.S.	16	f.	1	—	—	1	—	—	—	—	1
A.A.	21	m.	—	—	—	—	1	1	—	2	2
I.G.	31	f.	—	1	—	1	—	—	—	—	1
M.B.	26	f.	—	—	—	—	2	1	1	4	4
J.L.	41	m.	—	—	1	1	—	—	5	5	6
B.O.	35	f.	—	—	1	1	3	1	—	4	5
J.O.	15	m.	—	1	—	1	2	2	1	5	6
J.E.	15	m.	—	—	—	—	1	—	1	2	2
B.H.	37	m.	2	—	2	4	1	2	1	4	8
T.N.	50	m.	—	—	—	—	1	—	—	1	1
A.Å.	57	f.	1	—	1	2	—	1	3	4	6
D.S.	49	f.	—	—	—	—	—	—	3	3	3
A.E.	35	f.	—	—	—	—	1	—	1	2	2
L.K.	41	f.	—	—	—	—	—	2	5	7	7
M.P.	70	f.	—	—	—	—	2	1	5	8	8
A.K.	41	f.	—	—	1	1	—	1	1	2	3
			11	5	12	28	19	13	30	62	90

In this investigation, therefore, provocation tests were performed both on patients with absolutely normal findings of the lungs before the test and on patients with a rough breathing sound with or without some ronchi. Only patients who felt themselves subjectively symptom-free were examined.

TABLE I

Initials	Age	Sex	Number and outcome of inhalation tests								Total number
			Breathing sound before test								
			Normal				Rough				
			+	?	—	Total	+	?	—	Total	
S.K.	32	m.	1	—	2	3	2	—	3	5	8
A.B.	51	m.	—	—	—	—	1	—	—	1	1
N.O.	54	m.	—	—	—	—	1	—	1	2	2
L.L.	44	f.	1	—	—	1	1	—	1	2	3
M.E.	34	f.	1	—	1	2	—	—	1	1	3
N.N.	41	f.	2	—	1	3	2	—	3	5	8
H.N.	16	m.	1	—	1	2	—	—	2	2	4
S.A.	61	f.	—	1	2	3	—	—	1	1	4
L.L.	30	m.	—	—	—	—	1	1	3	5	5
S.N.	20	m.	—	—	—	—	—	—	1	1	1
K.R.	30	f.	—	—	—	—	2	—	—	2	2
M.S.	35	f.	—	—	—	—	1	—	1	2	2
H.S.	31	m.	1	—	—	1	1	1	5	7	8
N.A.	26	m.	—	—	—	—	1	—	3	4	4
G.L.	28	m.	1	—	1	2	—	—	—	—	2
A.N.	50	f.	—	—	6	6	—	—	—	—	6
N.P.	40	f.	—	—	—	—	1	1	2	4	4
E.O.	47	m.	—	—	2	2	—	—	—	—	2
G.N.	21	f.	1	—	4	5	—	—	—	—	5
B.A.	14	f.	3	—	—	3	—	—	—	—	3
M.M.	46	m.	—	—	—	—	1	—	1	2	2
			12	1	20	33	15	3	28	46	79
			11	5	12	28	19	13	30	62	90
Total Sum:			23	6	32	61	34	16	58	108	169

METHOD

For a period of about 14 months 180 patients, about 90 % of whom had bronchial asthma, have been examined for allergy with intradermal tests. Most of the extracts were produced by Apoteksvarucentralen Vitrum, Stockholm. Dif-

ferent dust extracts were included in the routine test series. The auto-dust extracts were prepared by the author in the Allergy Laboratory, Med. Clin., Lund. These extracts were tested on healthy subjects in order to ensure that no unspecific skin reactions occurred. On 44 patients examined by provocation tests skin titrations were performed with those antigens that had given distinct positive reactions, (at least a one + reaction with an antigen concentration = 10^{-3}). With extracts of these antigens, especially those which might be suspected to be of etiological importance, inhalation tests were made. For the inhalations a Barach spray, driven by air, was used. If the skin sensitivity by titration was less than one + with an extract concentration of 10^{-5} , the inhalation experiment was begun with that concentration. Of each concentration the patient had to inhale 1 ml., a procedure which took about 10 minutes. Before the inhalation experiment started, the patient always had to inhale 1 ml. of Coca's solution, which was used for the preparation of the extracts. If the patients were more sensitive by skin titration than one + with a concentration of 10^{-5} , the inhalation experiment was begun with the weakest concentration that gave a one + reaction. The patient was examined by auscultation before the test started and after the inhalation of the Coca's solution, and then after every, or every second inhalation. The last concentration inhaled was, when possible, always 10^{-1} , if the patients had not had any breathing difficulties before that. Only one antigen was tested each day.

About 30 inhalation experiments were objectively registered by the above mentioned method, worked out for these problems by Colldahl and Lundin (1952). In some inhalation experiments the vital capacity was measured after each inhalation. In the other experiments the result was judged from the type of breathing, from the auscultatory findings on the lungs, and from the subjective feeling of the patient. In positive provocation tests an asthmatic type of breathing with participation of the auxiliary breathing muscles appeared. To varying degrees ronchi were heard on

auscultation and the patients felt a more or less pronounced narrowing of the chest.

The results of the inhalation tests have been indicated as positive, wherever there was no doubt at all that difficulties of an asthmatic type had started during or in connection with the inhalations, and as negative when no signs at all of asthmatic difficulties appeared. If the outcome could not with certainty be referred to any of these groups, it was indicated as doubtful. In the tables the results of the inhalations are indicated as +, ?, —.

During the experiments the patients inhaled through the mouth and regulated the nebulisation with the help of an Y-tube, a mist being produced only during the inspiration.

In the tables skin sensitivity means the inverted value of the antigen concentration giving by intradermal titration just a positive intradermal reaction, and the bronchial sensitivity means the inverted value of the antigen concentration giving by inhalation just a positive provocation test.

RESULTS

In order to obtain information about the important question of whether it is possible to perform provocation tests with reliable results even if the patients had a rough breathing sound by auscultation before the tests began, the material has been divided into two groups. To one of them belong the patients with a rough breathing sound (Table 2) and to the other those patients that had absolutely normal auscultatory findings on the lungs before the provocation tests were started (Table 3). On patients belonging to the first group 108 provocation tests were performed and on patients belonging to the second one 61. The number of provocation tests performed on patients belonging to the first group was therefore nearly double the number of those performed on patients belonging to the second one. The provocation tests turned out positively in 31 % of the patients belonging to the first group, and in about 38 % of those belonging to the

second. This shows that a positive outcome of the provocation test is at least not more common in the group in which the patients had a rough breathing on the lungs before the test. If one includes the uncertain cases with the positive ones, one gets about 46 % for the first group and 48 % for the second. One may therefore conclude that the fact that a patient has a rough breathing sound does not prevent provocation tests being performed with the same reliability as in cases where the patient has had normal findings on the lungs before the test.

This result confirms, using more extensive material and a different method, the earlier observations by Colldahl and Lundin (1952) as to the possibility of performing provocation tests even if the auscultatory findings on the lungs are not quite normal. But that does not mean that it is possible to perform reliable provocation tests on patients who, before the test, have breathing difficulties.

As is seen from table 1, if several provocation tests are performed on the same patient some of the provocation tests may turn out positively and some negatively. It cannot therefore be the case that some patients have a tendency always to react positively in an unspecific way.

If only those patients are selected who have been tested with provocation tests both when they have a normal breathing sound before the tests and when the breathing sound was rough before the test one would expect a higher percentage of positive results when the breathing sound was rough if the breathing difficulties depended on an unspecific reaction. This is, however, not the case. 32 provocation tests were performed when the breathing sound before the test was normal. On the same patients 52 tests were performed when the breathing sound was rough. In cases of normal breathing sound the result was 13 positive, 5 questionable and 14 negative provocation tests (i.e. 40 %, 16 % and 44 % respectively). In cases of a rough breathing sound before the tests the result was 15 positive, 9 questionable and 28 negative tests (i.e. 29 %, 17 % and 54 % respectively). One can there-

fore conclude with certainty that the fact that the patients have a rough breathing sound before the tests does not prevent provocation tests being performed with the same reliability as when the patients have normal auscultatory findings on the lungs before the tests.

DISCUSSION

It is a well-known fact that symptoms may be provoked on allergic patients in an active phase of the disease by different irritating factors of an unspecific character. A hay-fever patient, for instance, can during the pollen season become worse as a result of different kinds of unspecific irritations. In this case we have an unspecific irritation which is added to an already existing specific irritation of the mucous membranes, which latter may in itself be subclinical.

Coca's solution in this investigation has proved itself non-irritant, except in one case when breathing difficulties already existed. On that occasion the patient also reacted with aggravated breathing difficulties after inhalation of physiological salt solution. After a week the patient was better and did not have any breathing difficulties when inhaling the physiological salt solution or Coca's solution.

The antigen extracts used in this investigation have shown themselves to be non-irritant; had they been otherwise a larger percentage of positive provocation tests on patients with a rough breathing sound before the tests should have occurred. During the provocation experiments the patients therefore suffer no further irritation if the Coca's solution itself does not provoke any symptoms and if the mucous membranes are not sensitive to the antigen inhaled. This may be the reason why provocation tests do not become positive in a higher percentage of cases when the patients have a rough breathing sound before the tests. This rough breathing sound before the tests may depend either on a specific or an unspecific irritation or on a combination of both.

SUMMARY

On 44 asthma patients 169 provocation tests were performed. Immediately before 108 provocation tests the patients had a rough breathing sound and before 61 provocation tests the breathing sound was absolutely normal. The percentage of positive and questionable positive results, taken together, is the same for the two groups (46 % and 48 % respectively).

This investigation therefore shows that provocation tests can with the same reliability be performed on patients who have a rough breathing sound before the tests as on patients with a normal breathing sound before the tests. This fact is of practical importance as the number of patients belonging to the former group is about double that of patients belonging to the latter.

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