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BRONCHIAL SENSITIVITY TESTING IN ASTHMA

An Assessment of the Effect of Hyposensitization in House-dust and Pollen-sensitive Asthmatic Subjects

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Skin sensitivity testing is the method commonly used for the detection of specific allergy in bronchial asthma, and by means of it useful information may often be obtained. The results of skin testing, however, do not always have a direct correlation with the clinical state of the patient, negative skin reactions often occurring when clinical sensitization is present and vice versa. It has also been established that many normal subjects show a proportion of positive skin reactions to allergenic extracts (Grow and Herman, 1936; Herxheimer, McInroy, Sutton, Utidjian, and Utidjian, 1954; Cate, 1954).

Bronchial sensitivity testing consists of provoking an asthmatic reaction in a patient by the inhalation of aerosolysed allergenic extracts, and has been carried out by many workers during the past few years (Lowell and Schiller, 1948; Herxheimer, 1951a; Colldahl, 1952; Cate, 1954). This type of testing shows a much closer correlation with the clinical state of the patient. It is a more lengthy procedure than skin testing, but it is particularly useful where the presence of specific allergy is in doubt or when a quantitative measure of the degree of allergy is required.

Hyposensitization in the treatment of asthma is usually carried out by the subcutaneous injection of allergenic extracts in increasing strength, and the results of such treatment have been assessed by clinical methods only. Considerable doubt has arisen as to the value of this treatment. Recently, however, Citron, Frankland, and Sinclair (1958) assessed the results of hyposensitization by injection in pollen-sensitive asthmatics by measuring the degree of the bronchial reaction produced by large doses of inhaled pollen given before and after treatment. Their results showed that an increase of tolerance to the pollen was achieved in most of their patients after treatment.

A technique for hyposensitization of patients by inhalation of aerosolysed allergenic extracts was developed by Herxheimer (1949). The aerosol was introduced into a closed spirometer circuit and the patient could be exposed to measured amounts of the allergen. The results of this type of treatment have been encouraging (Herxheimer, 1951b; Herxheimer and Prior, 1952; Cate, 1954).

In this paper, an attempt is made to compare the results of hyposensitization by injection with those by inhalation in dust-sensitive and pollen-sensitive asthmatic subjects. The bronchial sensitivity reaction is used as an indicator.

SELECTION OF PATIENTS

Patients selected for study were taken from the Asthma Clinic at University College Hospital. Those in whom asthmatic symptoms were intermittent and in whom either a grass-pollen or house-dust sensitivity was suspected on clinical grounds were subjected to bronchial testing with the appropriate allergens. Those whose asthma was severe enough to prevent them recording a stable basal vital capacity were excluded because their persistent symptoms would interfere with the interpretation of the bronchial tests. Altogether, 200 patients were tested, and, of these, a positive result (indicating a specific bronchial sensitivity) was found in 78%. A final number of 100 patients was selected for study, 60 being sensitive to house dust and 40 to pollen. No patients who were bronchially sensitive to both dust and pollen were included, but all were sensitive on skin testing to one or more other allergens. They were taken in order of first attendance and irrespective of age or sex.

METHOD

The method used for bronchial testing was essentially that of Herxheimer (1951a).

The patient breathed through the mouthpiece of a closed-circuit spirometer (Fig. 1). A soda lime chamber absorbed the CO_2, and oxygen was replaced into the circuit at approximately 600 c.cm. per minute, to keep the amount of air in the spirometer bell constant. A side circuit contained an air pump with manometer and pressure regulator, and several nebulizers for the allergenic solutions and for a solution of 2% "isoprenaline." By means, aerosol can

be run into the main circuit under constant pressure and density.

The vital capacity of the patient was recorded several times, until a constant volume was obtained (less than 150 c.cm. variation). The appropriate allergen was then aerosolysed by opening a clip on the nebulizer and switching on the pump at a pressure of 5 lb. per sq. in. The time for which the aerosol was blown into the circuit was accurately measured on a stopwatch, and the patient continued to breathe normally, through the spirometer mouthpiece, throughout the period and for 60 seconds afterwards.

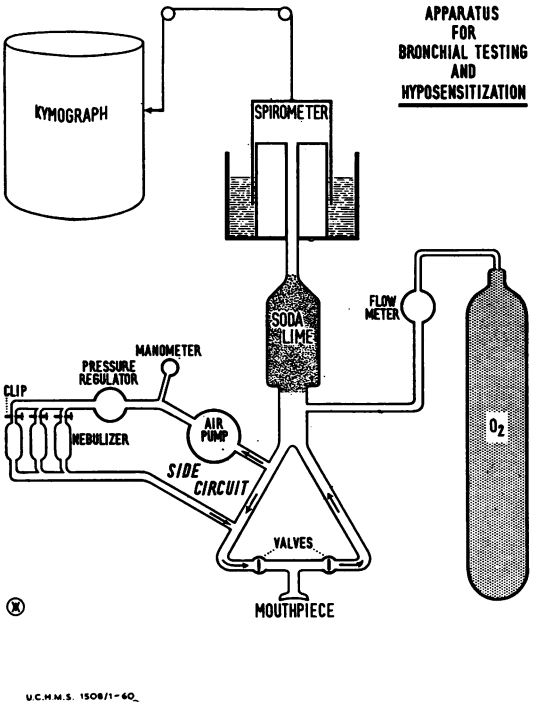

FIG. 1

The vital capacity was then measured again and at three-minute intervals thereafter for 15 minutes. The vital capacity has been found to be a very satisfactory indicator for this method of bronchial testing, and has the advantage of being simple to carry out and quick to determine. In all cases, maximum expiration was carried out first, followed after a few normal breaths by maximum inspiration. This method avoids the increased airway resistance often seen after exhaling forcefully from the point of maximum inspiration.

For the purpose of bronchial testing, it is essential that the patient is free from wheezing and records a constant reading of the vital capacity. Also, he must not be under the influence of antispasmodic, antihistaminic, or corticosteroid drugs.

The allergenic solutions used in this investigation were Bencard's mixed pollen in a strength of 2,000 Noon units per ml., and "domogen" house dust antigen in a 1:100 solution.

As the output of the individual nebulizers varied slightly, the same nebulizers were used for each solution throughout the investigations. The time taken for bronchial testing as above was about 30 minutes.

INTERPRETATION OF THE BRONCHIAL TEST

If then within 15 minutes of the exposure to the allergen the vital capacity of the patient diminished by more than about 10%, it was taken that an immediate bronchial reaction had occurred. This decrease in vital capacity was usually accompanied by a slowing of the expiratory rate, and, if greater than 400 ml., often by a subjective wheeze.

A certain number of patients (approximately 30%) did not produce an immediate reaction, but experienced a mild attack of asthma four to 24 hours later. This delayed or late reaction (Herxheimer, 1952) is more difficult to recognize and may be mistaken for the ordinary symptoms of the patient. Usually, however, it is noted as occurring at an unusual time for such an attack and, if the test is repeated, the time interval between the exposure to the allergen and the late reaction is found to be constant.

As the first exposure time, one second was chosen. If no immediate or late bronchial reaction occurred, the time period was trebled and trebled again, the exposures being given at intervals of three to seven days, until 180 seconds was reached. If no reaction occurred at or before this level, bronchial sensitivity was taken to be absent or negligible.

In order to exclude placebo reactors, the test was repeated using aerosolysed normal saline instead of the allergenic extract in those patients who produced a positive bronchial reaction at the first test.

If at any level a positive reaction occurred, confirmation was sought by repeating the test at the same level at the next attendance. If there was then no reaction, the exposure was increased by 50%, because the previous inhalation might have had a hyposensitizing effect. If this 50% increase produced a further reaction, it was taken as confirmation of the previous bronchial reaction.

If at any level a doubtful reaction occurred the exposure time was again increased, after an interval, by 50%, and if the reaction then became definitely positive it was taken as confirmation of the previous doubtful reaction.

If after any exposure a rapid decrease of the vital capacity (by 30% or more) or a late reaction lasting more than two to three hours occurred, this was regarded as too great a reaction and would probably have produced hypersensitization (Herxheimer, 1951b). Repetition of the same exposure would then produce an even more severe reaction and even a frank asthmatic attack. The next exposure time in this situation was therefore reduced to one tenth or less of

the previous one. The bronchial testing was then started again from this point, and, to prevent a further excessively severe bronchial reaction suddenly being encountered, the dosage was doubled instead of trebled at each sitting.

If it were necessary to go below the time of one second, dilutions of 1:10 or 1:100 of the standard extracts were used. The initial exposure time of one second is not, in actual fact, an exact dose, as it takes the air pump longer than this time to reach the required pressure of 5 lb. per sq. in. It is regarded as a test dose at the beginning of the investigation in order to establish those patients with a very low tolerance to the allergen who, therefore, need to have the diluted solutions used for their testing. Positive reactions occurrring at one second exposure were therefore confirmed using a 1:10 dilution of the appropriate extract.

In this way it may be seen that bronchial sensitivity reactions can be used to assess the smallest amount of allergen which will cause a bronchial reaction. This is a measure of the bronchial tolerance of the patient to the inhaled allergen.

We have found that this method of bronchial testing is entirely without danger and that hypersensitivity reactions of any significance do not occur. It is, however, essential to begin the testing with a very small exposure of a diluted allergenic solution. The whole procedure involved the attendance of the patients on an average of four or five occasions.

Assessment of Patients Before Treatment

The bronchial tolerance to either house dust or mixed pollen was established and confirmed in each of the 100 patients, and a record was made of the clinical state of each as judged by the frequency and severity of the asthmatic attacks. Skin sensitivity tests were recorded.

The patients were then divided into five groups: (1) Twenty dust-sensitive patients to have a course of subcutaneous hyposensitization to house dust; (2) 20 dust-sensitive patients to have a course of bronchial hyposensitization to house dust; (3) 20 dust-sensitive patients to have a course of placebo bronchial hyposensitization; (4) 20 pollen-sensitive patients to have a course of subcutaneous hyposensitization to mixed pollen; and (5) 20 pollen-sensitive patients to have a course of bronchial hyposensitization to mixed pollen.

Treatment

Groups (1) and (4) were treated by the method usually employed for hyposensitization and received injections of house dust antigen ("domogen") or mixed pollen (Bencard's) at intervals of three or four days. Any local or systemic hypersensitivity reactions were regarded as an indication to reduce the dosage markedly and then to proceed by smaller increases until the end of the course. Reactions were not encountered in the dust-sensitive groups, but three pollen-sensitive patients had to have their course modified. The course was continued until in each case a final dose of 1 mg. of house dust or 5,000 Noon units of pollen was received. The length of time taken for each course varied a little, but all were completed in 12 weeks.

Groups (2) and (5) were treated with inhalations of aerosolysed allergen from the same apparatus as was used for bronchial testing. The initial dose was 30% of the bronchial tolerance and the inhalation time was increased by 30% at intervals of four to seven days. If any further bronchial reaction occurred, it was taken as an indication that the dose was too great and the inhalation time was then cut to one tenth of the previous inhalation, the increases thereafter being reduced to 20%. Mild reactions were encountered in more than half the dust-sensitive patients and in approximately one third of the pollen patients. It was decided to continue bronchial hyposensitization until 200 seconds of the respective solutions could be tolerated in each case. This proved impossible in some of the patients, however, in whom bronchial reactions repeatedly occurred, in spite of the smaller increases in dosage at each session. The length of time taken over the bronchial hyposensitization courses was, on the whole, longer than for the injection courses, particularly in the dust-sensitive group. The pollen-sensitive patients' treatment was in some cases cut short by the approaching pollen season.

No testing or treatment was given during the main pollen season in any of the groups, nor were inhalations of allergen given during the presence of an upper respiratory infection. The pollen-sensitive patients were not tested or given treatment between the months of April and August and the dust-sensitive patients were not tested or treated during foggy weather.

The control group (3) patients was treated in every respect in the same way as group (2), apart from receiving inhalations of aerosolysed normal saline instead of house dust. No bronchial reactions were encountered during the treatment of the control group.

During the treatment of all three groups of dust-sensitive patients they were naturally exposed to small quantities of house dust in their environment. All efforts were made to avoid overexposure to this, and the environmental factors in the three groups were checked and found to be comparable. Accidental overexposure to house dust resulted in one case (a man who thoughtlessly emptied a vacuum cleaner bag) being hyposensitized by the bronchial method. This was followed by a bronchial reaction at the next treatment session, and the bronchial tolerance was found to have decreased to one tenth of its previous value. Hyposensitization was then continued from the new lower level of tolerance and proceeded uneventfully thereafter. Bronchial reactions during the treatment of some other of the patients may have been due to unknown overexposure to environmental house dust, but after foggy weather the bronchial tolerance was not usually decreased.

Assessment of Patients After Treatment

After the appropriate course of treatment was completed, each patient was subjected to further bronchial testing and a new estimation of their bronchial tolerance was made. The clinical state was also reassessed.

Results

Initial Comparability of Groups.—It will be seen that the initial bronchial tolerance is comparable in the three groups of dust-sensitive patients and in the two groups of pollen-sensitive patients (Table I). The proportion of immediate to late reactions is also comparable, as are the skin sensitivity reactions and the age groups of the patients. There is, however, a much higher proportion of men to women in the bronchially hyposensitized dust patients than in the other groups.

Response to Treatment.—Table II shows the distribution of the various responses to treatment. The two pollen groups show no great difference, there being a definite improvement in about half of the cases treated by either method. The dust groups show greater differences. The improvement in bronchial tolerance after treatment tends to be much higher in the group treated by bronchial hyposensitization, and this is clearly significant. The group treated by injection also gives better results than the control group, but the difference is not significant. On looking at

TABLE I
INITIAL COMPARABILITY OF GROUPS

		No. of Cases				
		Dust Patients			Pollen Patients	
		Injection Hyposensitization	Bronchial Hyposensitization	Controls	Injection Hyposensitization	Bronchial Hyposensitization
Level of bronchial tolerance before treatment (sec.)	1	0	4	1	0	0
	1–	2	1	2	0	1
	2–	1	0	2	6	7
	4–	4	1	2	2	5
	8–	8	7	6	8	3
	16–	3	2	3	3	2
	32–	2	5	2	1	2
	64–	0	0	2	0	0
Total		20	20	20	20	20
Sex	Female	11	5	10	10	8
	Male	9	15	10	10	12
Type of reactor	Immediate	15	12	16	15	14
	Late	5	8	4	5	6
Skin sensitivity	0	5	6	5	1	1
	+	15	14	15	16	16
	Not done				3	3
Age (years)	10	6	2	3	4	5
	20	10	15	15	7	10
	35	4	3	2	9	5

Level of bronchial tolerance is the shortest time of inhalation of allergen which will cause a bronchial reaction.

TABLE II
RESPONSE TO TREATMENT

	No. of Patients				
	Dust Patients			Pollen Patients	
	Injection Hyposensitization	Bronchial Hyposensitization	Controls	Injection Hyposensitization	Bronchial Hyposensitization
Bronchial tolerance less than before treatment	2	0	3	2	1
Bronchial tolerance the same or improved less than 3-fold	11	1	13	8	8
Bronchial tolerance improved 3- to 10-fold	6	9	2	9	8
Bronchial tolerance improved more than 10-fold	1 (7)	10 (19)	2 (4)	1 (10)	3 (11)
Clinical state not improved	11	3	18	8	6
Clinical state improved	9	17	2	12	14

TABLE III
CORRELATION OF SKIN REACTIONS, TYPE OF BRONCHIAL REACTION, SEX, AND AGE OF PATIENTS WITH RESULTS OF TREATMENT

No. of Patients	Dust Injection Group (1)		Dust Inhalation Group (2)		Dust Control Group (3)		Pollen Injection Group (4)		Pollen Inhalation Group (5)	
	Bronchial Tolerance Improved	Bronchial Tolerance Unimproved	Bronchial Tolerance Improved	Bronchial Tolerance Unimproved	Bronchial Tolerance Improved	Bronchial Tolerance Unimproved	Bronchial Tolerance Improved	Bronchial Tolerance Unimproved	Bronchial Tolerance Improved	Bronchial Tolerance Unimproved
Skin test positive*	5	10	13	1	4	11	7	9	9	7
Skin test negative	2	3	6	0	0	5	1	0	1	0
Immediate bronchial reactions	5	10	11	1	2	14	9	6	8	6
Late bronchial reactions	2	3	8	0	2	2	1	4	3	3
Males	2	7	15	0	2	8	7	3	8	4
Females	5	6	4	1	2	8	3	7	3	5
Age 10–	2	4	3	0	0	2	2	2	4	1
,, 20–	2	8	14	1	4	11	5	2	6	4
,, 35–	3	1	2	0	0	3	3	6	1	4

* Six pollen cases not skin tested.

the subjective state of the patient, it is again seen that the group treated by bronchial hyposensitization to dust stands out, although more than 50% of the treated pollen-sensitive patients were improved clinically. During the course of all forms of treatment, clinical improvement did not occur until shortly before the end of the course.

The skin reactions, type of bronchial reaction, sex, and age of the patient (Table III) do not appear to have any bearing on the response to treatment.

The follow-up figures (Table IV) are disappointing in all groups; only 30% of the patients tested after six months had retained their increased bronchial tolerance and in most cases the tolerance reverted to its original level or near. It must be pointed out here, though, that at a later date most of the dust- and pollen-sensitive patients were restored to their former high bronchial tolerance by a further course of bronchial hyposensitization.

TABLE IV
FOLLOW-UP RESULTS OF BRONCHIAL TOLERANCE LEVELS SIX MONTHS AFTER TREATMENT

	Cases Improved*	Cases Followed-up	Cases Relapsed 100%	Cases Relapsed 50% or Less	Cases Not Relapsed
Pollen injection course	10	10	6	2	2
Pollen inhalation course	11	10	4	2	4
Dust injection course ..	7	4	3	0	1
Dust inhalation course	19	11	4	4	3
Controls .	4	2	0	0	2
Total ..	52	37	17	8	12

* Cases improved denotes more than a three-fold improvement in bronchial tolerance after treatment.
Cases relapsed 100%=total loss of acquired tolerance. Cases relapsed 50% or less=loss of acquired tolerance of 50% or less.

DISCUSSION

Three main points arise out of the results. First, that in pollen asthma an improvement in tolerance to inhaled pollen may be achieved by both injection and bronchial hyposensitization. Secondly, that in house-dust asthma there is no evidence in this series that attempted hyposensitization by subcutaneous injection is of value in raising the bronchial tolerance. Thirdly, that a good degree of hyposensitization to house dust may be achieved by the bronchial method.

It is unexplained why the subcutaneous injection of house dust antigen appears to be of little value, whereas bronchial hyposensitization with the same substance is relatively successful. It may be possible that the solution when injected subcutaneously is changed by the body's activity so that its effect as an antigen is much reduced, whereas when it is inhaled it is deposited directly on the "shock organ" itself and might, therefore, be more effective. Also, the usual course of house dust hyposensitization with a maximum dose of 1 mg. of dust was possibly too weak to produce an increased bronchial tolerance, and better results might have been seen following injections of much greater strength.

In view of the fact that environmental house dust did not apparently interfere with the bronchial hyposensitization treatment, except when large amounts were accidentally encountered, it may be concluded that the amounts of house dust antigen reaching the bronchi during treatment are considerably greater than the normal day-to-day exposure to dust in the average patient. In the case of the injected patients, the converse may be true.

It is interesting to note that some of the patients who did not show any objective improvement were subjectively improved, and no one method of treatment was favoured by these patients.

It has frequently been observed that a number of asthmatic patients improve clinically with placebo treatment. Herxheimer and Prior (1952) found that 20% of their patients treated by bronchial hyposensitization showed a marked clinical improvement without any increase in bronchial tolerance. The reason for the improvement in bronchial tolerance of four of the control cases in this present series remains obscure.

SUMMARY

One hundred asthmatic patients with house dust or pollen sensitivity were subjected to treatment with (*a*) a course of specific hyposensitization by subcutaneous injection; or (*b*) a course of specific bronchial hyposensitization by inhalation; or (*c*) a course of placebo inhalations.

The bronchial tolerance to the appropriate allergen was measured before and after treatment.

Pollen-sensitive patients showed an improvement in tolerance when treated either subcutaneously or bronchially.

House-dust-sensitive patients showed no significant improvement when treated by injection but a considerable improvement when treated by bronchial hyposensitization.

A limited follow-up showed a tendency to relapse within six months in both types of patient following either type of treatment.

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