

Hyposensitization With Bacterial Vaccine in Infectious Asthma

A Double-Blind Study and a Longitudinal Study

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Infectious asthma differs from extrinsic infection-triggered asthma in children. Only 25% of children who have asthma attacks associated with infection have true infectious asthma. In a double-blind study with placebos, infectious asthma was treated by hyposensitization with large doses of mixed respiratory bacterial vaccine. There was significant statistical benefit in the vaccine-treated patients, and similar results were obtained in a larger longitudinal prospective study group with the method of paired data for controls. Indiscriminate use of such vaccines in asthma associated with infection is not justified and has less than one chance in four of being effective.

The role of infection in childhood asthma has been the subject of a great deal of controversy. Some allergists believe that hypersensitivity to infectious agents or their products is the mechanism involved while others feel that infection is a precipitating or accentuating agent of extrinsic sensitivities, or even a nonspecific cause of spasmodic bronchostenosis. Infectious agents and their products are antigens which can and do produce hypersensitivity, both immediate and delayed, and controlled studies have confirmed this.¹⁻⁵ Between 1953 and 1958, we followed and studied the cases of more than 100 children who had asthma attacks associated with infection. It became apparent to us that probably both of these causes were correct and that infection plays two different roles in childhood asthma. The differential diagnosis between these two types depends on the following

criteria which require detailed histories and careful observation. There is no single diagnostic point that makes this clinical differentiation.

Infectious asthma usually has its onset between infancy and 5 years of age and rarely develops after 8 years of age. Once it develops, the patient has attacks with every respiratory infection and is symptom-free between infections. With viral respiratory infections, infectious asthma does not develop until 24 to 48 hours after the onset. There is no clinical evidence of extrinsic sensitivities. Skin tests are usually negative or, if any are positive, they do not have clinical significance. Elimination of extrinsic allergens by diet or environmental control has no effect on the attacks when an infection occurs. Bronchodilator drugs have progressively less effect with successive attacks, but attacks subside when the infection subsides, and this usually occurs promptly with the administration of antibiotics. With the acute attack, the differential white blood cell count (WBC) shows increased polymorphonuclear leukocytes, a finding consistent with a bacterial infection. But eosinophils are usually low in number or absent, while between attacks eosinophil counts become elevated.

Extrinsic asthma triggered or accentuated by infection usually has its onset after the age of 5 years. Although attacks occur with respiratory infections, there frequently is a history of respiratory allergic symptoms between infections, and occasionally there may be a respiratory infection without an attack of asthma. Viral infections usually precipitate an attack at their onset or in the prodromal stage. These patients are very likely to have clinically significant positive skin tests. Elimination of these allergens by diet or environmental control, or hyposensitization with them is frequently followed by reduction or elimination of asthma with respiratory infections. Infection-triggered extrinsic asthma usually continues to respond to

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Read in part before the Section on Allergy of the American Academy of Pediatrics, Washington, DC, Oct 21, 1967, and the International Congress of Allergology, Montreal, Nov 6, 1967.

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Table 1.—Age of 14 Patients at Onset of Attacks and at Start of Treatment (Double-Blind Study)

	1-3 yr	4-6 yr	7 yr and Up
Age at onset of attacks, No. of patients	8	5	1
Age at start of treatment, No. of patients	3	7	4

bronchodilators, but the attacks do not necessarily subside when the infection subsides. During and between the attacks, the level of circulating eosinophils remains elevated.

Our studies also indicated that of all children having attacks of asthma associated with infection, only 25% had infectious asthma while 75% had extrinsic infection-triggered asthma. Some patients may have a combination of infectious and extrinsic asthma and this results in more difficulty in diagnosis and treatment.

Hyposensitization has been shown to be a specific form of treatment,^{6,7} and clinical results are dose-related.^{8,9} It is obvious that success of hyposensitization is, therefore, directly proportional to the accuracy of the etiologic diagnosis and to the administration of the maximum tolerated doses of the offending allergen.

Previous reports of double-blind or controlled studies¹⁰⁻¹⁴ with bacterial vaccines in childhood asthma have not made any differentiation between infectious asthma and infection-triggered extrinsic asthma. Doses used were very small, and it could be predicted that such indiscriminate use of bacterial vaccines in such small doses would not result in benefit for many of these children, and, further, that if all such children were so treated they would show little or no difference from a placebo-treated group.

Materials and Methods

Although the previously outlined supportive diagnostic factors were present in varying frequency, all of the patients in this study met the following diagnostic criteria: (1) All attacks of asthma occurred with respiratory infections. (2) No wheezing occurred between respiratory infections. (3) All attacks were of a severity requiring visits by or to a physician, or to an emergency clinic, or hospitalization.

As stated above, this is not always a simple differential diagnosis to make. It necessarily must be based on historical data including interpretation of

Table 2.—Respiratory Infections in 14 Patients Before and After Treatment (Double-Blind Study)

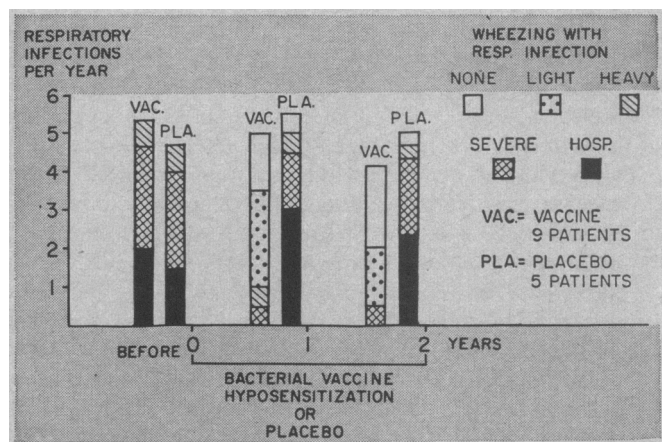
	Vaccine Group (9 Patients)		Placebo Group (5 Patients)	
	With Asthma	Without Asthma	With Asthma	Without Asthma
Respiratory infections, No./yr				
Before treatment	5.2	0	4.6	0
With treatment				
First yr	3.3	1.6	4.9	0.5
Second yr	1.8	2.1	4.1	0.3

Table 3.—Respiratory Infections Scored According to Severity of Associated Asthma (Double-Blind Study)*

Case No.	No. of Infections														
	Before Treatment					First yr of Treatment					Second yr of Treatment				
	H	S	HE	L	O Score	H	S	HE	L	O Score	H	S	HE	L	O Score
Vaccine Group															
45	3	1	1		17		1	2	3	4	1		1	2	4
3	1	4			16			4	2	4				2	0
27	2	3	1		19		1	4		6	1		3	2	6
21	2	2			14			4		4			3		3
39	2	4	1		22	2	1			8		2	2		6
9	3	1			15			2	4	2				3	0
15	1	4			16			4		4			4		4
33	4	0			16				3	0				4	0
49	1	4	2		20	1	1		2	5	1			4	3
7†	3	0	0		12	1		2	1	6					
35†	5	1			17				4	0					
11†	4	0	1		18			1	2	2					
Placebo Group															
22	2	2			14	3	2	1		20	3	1			15
46	3	2			18	4	4			28	2	3	2		21
30		4			12				3	0				2	0
42	2	2	1		16	5				20	3	3			21
48	1	2	2		14	2	1	2		15	1	2	1		12

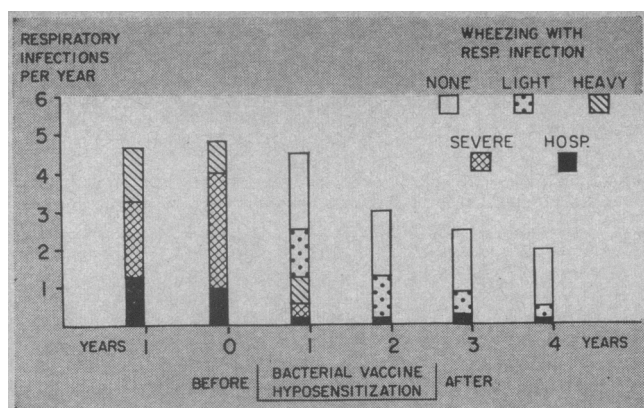
*Scoring is as follows: H indicates respiratory infections with asthma which required hospitalization (4); S, infections with severe wheezing (3); HE, infections with heavy wheezing (2); L, infections with light wheezing (1); and O, infections with no wheezing (0).

†Patients who dropped out of study at end of first year.



1. Average number of respiratory infections per year and severity of associated asthma before and during treatment with bacterial vaccine hypsensitization or placebo (double-blind study of 14 patients with infectious asthma).

the response to previous treatment. The diagnosis of the presence of respiratory infection was made clinically by the finding of various combinations of malaise, cough, fever, nasal discharge, injection of mucous membranes, elevated WBC, and positive culture, plus the strong supporting evidence, in



2. Average number of respiratory infections per year and severity of associated asthma in 62 patients with infectious asthma before, during, and after treatment with bacterial vaccine hyposensitization (longitudinal study).

many instances, of respiratory infection in other members of the household at the same time. In view of the common belief that most respiratory infections are viral and despite the continued popularity of "the virus" diagnosis, it is always surprising to many practicing pediatricians how frequently the symptoms and fever subside promptly when children acutely ill with respiratory infections are treated with antibiotics.

Since all patients in the study had severe attacks requiring attendance by a physician or hospitalization, the margin of error here was probably small, but it is likely that some errors in diagnosis were made which might tend to reduce the percentage of those with clinical improvement. It must be pointed out again that some patients may have a combination of infectious asthma and extrinsic asthma triggered by infection and this results in difficulty and confusion in diagnosis and treatment. Patients suspected of having such a combination were not included in the study.

In 1958 an attempt was made to set up a double-blind study to test the effectiveness of respiratory bacterial vaccine in patients with severe infectious asthma of at least two years' duration. A study group of 50 patients was planned, and numbers from 1 to 50 were placed in a box and withdrawn blindly as each new patient entered the study with odd numbers for vaccine group A and even numbers for placebo group B which received buffered saline solution. Only one person knew the code and administered the injections. Patients were seen at each visit by a physician who recorded all symptoms with all infections and wrote the dose to be given of the stock vaccine described below. We used our previous clinical experience in order to eliminate a dose decision based on local reaction that might betray the code, and a maintenance dose was set at 0.75 ml of undiluted vaccine or placebo with one patient receiving only 0.5 ml because of large local reactions. The physicians did not know the content of the injections and were never present when they were given. The purpose of the study was explained to the parents of each patient, and

they were told that there was a 50-50 chance that their child would receive a placebo. Even though free clinic visits were included, very few parents were willing to have their children enter the study when they understood the placebo feature. Seventeen patients entered the study and were randomly allocated to the treatment and placebo groups. Each of these patients was followed-up according to the protocol, 3 for a period of one year and 14 for a period of two years. Because of lack of numbers and alarming episodes of severe illness in certain children, the placebo study had to be abandoned. However, the data from these small groups have been analyzed statistically and the differences are highly significant.

When the code was broken, the 14 children with a diagnosis of infectious asthma who completed two years of treatment were found to consist of a group of nine children receiving vaccine and five receiving placebo. Age at onset of asthma and age at start of treatment with bacterial vaccine are shown in Table 1.

Eight (60%) of the patients had the onset of their infectious asthma before the age of 3 years. Eleven patients (80%) did not start treatment until they were 4 to 9 years old. There were seven boys and seven girls in the entire group, and ten patients (71%) had a family history of allergy.

Table 2 shows the number of respiratory infections with asthma each year before and during treatment in both groups.

Although the average number of respiratory infections per patient each year remained fairly constant in both groups, there was a significant reduction in the number of respiratory infections with asthma in the group receiving bacterial vaccine.

This is shown more clearly in Fig 1 which also shows that the vaccine-treated patients not only had fewer infections with asthma, but that the asthma was much milder. None were hospitalized, and these patients began to have increasing numbers of nonasthmatic colds. Of the five children receiving placebos, four showed no noticeable change in frequency or severity of infections with asthma and all four required hospitalization for attacks. One of the placebo-treated patients was markedly improved.

The infections were scored according to the severity of the associated asthma from a score of four for each infection requiring hospitalization down to a score of zero for respiratory infections without any asthma. On the basis of average scores, before treatment there was no difference in the severity of the two groups while after treatment there was no significant change in the placebo group, but a very significant improvement in the treated group, corresponding to a probability value of 0.025. Three patients in the study dropped out after one year of treatment (Table 3). All were in the vaccine-treated group. One moved away, and the reason given for the other two was that the child was much improved. One of these had a re-

currence of severe asthma with respiratory infections and returned for further treatment two years later.

Longitudinal Prospective Study

Sixty-two children with diagnosis of infectious asthma were treated and followed by one of us (H.L.M.) over a period of eight years with three years of treatment and one year of follow up for each patient. Before vaccine treatment was started, all patients except one who was started on treatment at age 18 months, had a history of two or more preceding years of infectious asthma. Eleven of the patients had been treated with other methods for a year with poor results before vaccine treatment. Comparison periods with and without vaccine treatment were provided and patients served as their own controls by the method of paired data. These patients were selected using the same diagnostic criteria as required in the double-blind study group. Sixteen (26%) of the 62 patients had mild perennial allergic respiratory symptoms and positive scratch skin tests to environmental allergens. These symptoms subsided almost entirely with environmental control, but the patients continued to have severe asthma with respiratory infections. Age at onset of asthma and age at time vaccine treatment was started are tabulated in Table 4.

The average time which elapsed between the onset of symptoms and the start of vaccine treatment was three years. It is important to note that while 48 (77%) of the patients had the onset of their infectious asthma before the age of 3 years, 44 (71%) were not started on vaccine treatment until they were 4 to 9 years old and almost one third (31%) were not started on treatment until after the age of 7 years. Since marked improvement occurred in the first year of treatment, and in 46 (74%) of the patients marked improvement was reported within four months, it is highly improbable that these patients merely improved with the passage of time in spite of vaccine treatment.

Thirty-eight patients in the study group were boys and 24 were girls, which is the usual expected sex ratio in children with asthma. Fifty-three (85%) had a family history of allergy with 33 bilateral and 20 unilateral family histories. Twelve patients had what were considered such clear-cut histories and clinical findings of infectious asthma with no suspicion of extrinsic sensitivity that skin testing was not done. The remaining 50 patients were given 72 screening scratch tests with the common foods and inhalants. Thirty-six (72%) of the 50 tested had various positive tests but none to allergens which could be correlated with the attacks of infectious asthma. This would indicate that a very high proportion of children with infectious asthma, have other evidence of atopy and is presumptive evidence that bacterial organisms or their products are probably acting as allergens in infectious asthma.

Table 4.—Ages of 62 Patients at Onset of Attacks and at Start of Treatment (Longitudinal Study)

	1-3 yr	4-6 yr	7 yr and Up
Age at onset of attacks, No. of patients	48	11	3
Age at start of treatment, No. of patients	18	25	19

Table 5.—Wheezing and Respiratory Infections in 62 Patients Before and After Treatment (Longitudinal Study)

	1 yr Before Treatment	First yr	Second yr	Third yr	1 yr After
No wheezing with any respiratory infection, No. of patients	0	7	22	30	37
Wheezing with only 1 respiratory infection, No. of patients	1	12	19	17	12
Total	1	19	41	47	49

Treatment

A stock respiratory vaccine of the following composition was used: *Neisseria catarrhalis*, 200 million/ml; *Hemophilus influenzae*, 200 million/ml; *Klebsiella pneumoniae*, 200 million/ml; *Staphylococcus albus*, 200 million/ml; *St. aureus*, 200 million/ml; *Streptococcus pyogenes* and *Str. viridans*, 200 million/ml; and pneumococcus (types I, II, and III), 200 million/ml. The total of organisms in the vaccine was 1,400 million/ml.

Most children will tolerate an initial dose of 50 to 75 million organisms or 0.05 ml of this strength undiluted vaccine, although occasional patients are very sensitive and will need to start with 1 to 5 million organisms in dilutions of 1:10 or 1:100 because of systemic reactions with the undiluted vaccine. Seven of the patients in this study reacted with asthma in periods from 20 minutes to eight hours after receiving the initial or an increased vaccine dose. Increments of dosage were 50% to 100% and were given weekly until the maximum tolerated dose without systemic or excessive local reaction was reached. This dose was then given every three weeks for the first six months and then every four weeks thereafter for a total of three years. The maximum tolerated dose ranged in these 62 patients from 0.3 to 1.0 ml of the undiluted vaccine or from 200 million to 1,400 million organisms. The dose tolerated was roughly inversely proportional to age with the younger children tolerating and needing the larger doses.

Results

Figure 2 shows the decrease in frequency and severity of attacks of infectious asthma in the 62 patients. There was an average per patient of 4.9 respiratory infections with asthma per year preceding the start of vaccine treatment. In the first year of treatment there was a dramatic drop to an average per patient of 2.5 respiratory infections with asthma, and there were seven patients who had no asthma with any respiratory infection (Table 5). In the second year, the respiratory in-

fections with asthma averaged 1.25 per patient per year with 22 patients who had no asthma. The third year showed a further drop to 0.87 respiratory infections with asthma per patient per year and 30 patients who had no asthma. In addition to a reduction in the number of respiratory infections with asthma, there was an even greater reduction in the severity of the asthma with respiratory infections. Of the 155 respiratory infections with asthma in the 62 patients in the first year of treatment, only 22 were severe enough to require attendance by a physician or hospitalization. By the third and fourth year, this was down to five and eight severe attacks, respectively. Previous to treatment these patients had had no respiratory infections without asthma, but subsequently they averaged 1.75 "normal" nonasthmatic colds per patient over the three years of treatment. In the first year of treatment, mothers frequently said, "My child had a cold just like any other child for the first time in years." During the year after vaccine treatment was stopped, 11 of the patients had an increase in severity and frequency of respiratory infections with asthma.

Comment

The use of bacterial vaccines for hyposensitization in asthma associated with infection must be limited to those cases where there is reasonable evidence that the asthma is specifically caused by bacterial allergens. It should not be used in patients with asthma due to extrinsic allergens in whom the asthma has been accentuated or triggered by infection. To be effective, specific hyposensitization treatment must employ the causative allergen and be given in sufficient doses to produce the specific immunologic effect. Infectious asthma is probably caused by a variety of bacterial allergens; and a mixed stock respiratory vaccine, containing most of the organisms commonly cultured from children during respiratory infections, is most likely to contain the necessary allergens.

As in all hyposensitization, the most important part of vaccine treatment is the accurate diagnosis of infectious asthma. Various criteria have been described to differentiate these patients from those in whom infection acts to trigger or accentuate an underlying extrinsic sensitivity, and we emphasize that this may be a difficult differentiation. Since only 25% of children who have asthma associated with infection have true infectious asthma, indiscriminate use of such vaccines, particularly in low doses, can be expected to result in figures comparable to those obtained by placebo administration.

We used maximum tolerated doses of a mixed stock respiratory vaccine only in children with severe infectious asthma in both a small double-blind and a larger longitudinal study, and there was a significant reduction in the number and severity of asthmatic attacks. The results were remarkably similar in both studies except that in the longi-

tudinal study, vaccine administration over a longer period of time was also associated with a reduction in the number of overt respiratory infections with and without asthma. The latter was probably less an immunological than a secondary effect. When severely ill children were relieved of their debilitating attacks, it is probable that with improvement of their general health, there was an accompanying increase in resistance to infection.

Although none of these children who had had infectious asthma for periods of from two to eight years had shown any evidence of infections becoming less frequent or less severe previous to the start of vaccine treatment, it should be recognized that in some children with infectious asthma, particularly the milder cases, their own immunity and decreased sensitivity to respiratory infections does develop as they grow older and they may recover spontaneously. Hyposensitization with a bacterial vaccine is recommended for those children with infectious asthma who have severe attacks and who show no evidence of spontaneous improvement. The practice of tossing "a little vaccine" into a treatment mixture of allergens just because a patient has "asthma with colds" is not justifiable in our opinion.

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