

A double-blind study of the effects of bacterial vaccine on infective asthma

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The effectiveness of bacterial vaccine in the treatment of infective asthma was studied in 22 pairs of patients followed over an eighteen-month period, matched as closely as possible with respect to age, sex, race, duration and severity of asthma, vital capacity, maximal expiratory flow rate (MEFR), and x-ray evidence of hyperplastic sinusitis. According to a strict double-blind technique, one group was given stock bacterial vaccine hyposensitization and the other a saline placebo. They were evaluated as to subjective manifestations (according to a semiquantitative scale), emergency room visits for asthma, vital capacity, MEFR, numbers of asthma pills, steroid tablets, and inhaler prescriptions. In every parameter followed, the vaccinated patients did better. The difference between the two groups was statistically significant with regard to the inhaler prescriptions. Patients with hyperplastic sinusitis did not fare better than the others, but the group may have been too small. There was no significant difference between the two groups in the amount of antibiotics taken.

Bacterial vaccines have been used in the treatment of bronchial asthma for over sixty years. In 1907, Carmolt-Jones¹ reported improvement in 48 of 52 patients with asthma who were treated with injections of a bacterial vaccine. Six years later Pirie² reported excellent results in 7 out of 9 patients with asthma treated with bacterial vaccine for several months.

An extensive literature has been built up on the subject of bacterial allergy.

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Blatt,³ in his 1961-1962 review of microbial allergy, lists 514 references in the previous decade. Nevertheless, there is still much debate concerning the worth of bacterial vaccine hyposensitization in the treatment of asthma.

Despite some opinions to the contrary, the consensus has been that bacterial vaccine is of benefit.³ The reason for this is the empiric observation that most patients seem to improve on bacterial vaccine therapy. There are some fallacies in this reasoning: (1) The effect of the infection may be nonspecific, as, for example, from exertion or fatigue. (2) The patients receive other therapy concurrently. (3) Both the patient and the doctor may be biased in favor of the treatment. (4) Patients with asthma have spontaneous exacerbations and remissions.

In an attempt to evaluate better the effect of bacterial vaccine, a "double-blind" clinical trial was carried out.

MATERIAL AND METHODS

Patient selection

A group of 52 patients attending the allergy clinic was selected. All had a history of bronchial asthma aggravated by infection. On each patient, a complete history and physical examination and a complete blood count, urinalysis, and chest x-ray were performed. The usual allergy work-up included skin tests with a minimum of twenty inhalants. Special studies performed on each patient included sinus x-rays and a determination of vital capacity and maximal expiratory flow rate (MEFR). The patients were then paired by matching as closely as possible with respect to age, sex, race, severity and duration of the disease, pulmonary function studies, and evidence by x-ray of hyperplastic sinusitis (Table I). During the original matching, no patient with sinusitis was matched with one free of the disease.

Bacterial vaccine

The bacterial vaccine used was the stock respiratory vaccine obtained from the Institute of Allergy at the Roosevelt Hospital in New York. Each cubic

milliliter contained in a 1/10 dilution 1.5 billion organisms representing the
begun with the 1960 vaccine and in mid 1962 were continued with the 1962 batch of vaccine. The vaccine was diluted to 1/100 and 1/1,000 concentrations. Identical-appearing vials were filled with sterile saline as the placebo. Because the 1/10 dilution of the bacterial vaccine was very slightly cloudy, the top concentration of both the vaccine and the placebo was placed in vials which had been inked black so that the contents were not visible. The vials were completely identical in appearance. The pharmacist then labeled one batch "Vaccine A" and the other "Vaccine B." With the use of a table of random numbers, the

*One milliliter of vaccine contained: beta hemolytic streptococcus, 17 strains; alpha hemolytic streptococcus, 19 strains; *Neisseria catarrhalis*, 19 strains; pneumococcus, 20 strains; *Staphylococcus albus*, 3 strains; *Staphylococcus aureus*, 16 strains; *Klebsiella pneumoniae*, 2 strains; *Aerobacter aerogenes*, 4 strains; *Bacillus proteus*, 4 strains; *Escherichia coli*, 2 strains; *Pseudomonas aeruginosa*, 2 strains; and *Haemophilus influenzae*, 2 strains.

paired patients were assigned by one of us, H. O., to group A or B (Table I). The pharmacist merely diluted the vaccine and placebo and otherwise had nothing to do with the clinical trial. The key was kept in a sealed envelope by H. O. who had no contact with the patients or the evaluation of them at any time during the study.

Therapeutic trial

The patients continued their previous allergy treatment, including both symptomatic medication and immunization against other allergens. In addition, they received, at one or two week intervals, increased doses of vaccine A or B according to the following schedule: 1/1,000—0.10 c.c., 0.20 c.c., 0.35 c.c., 0.50 c.c., and 0.75 c.c.; 1/100—0.10 c.c., 0.15 c.c., 0.20 c.c., 0.30 c.c., 0.45 c.c., 0.65 c.c., and 0.90 c.c.; and 1/10—0.10 c.c., 0.15 c.c., 0.20 c.c., 0.30 c.c., 0.40 c.c., and 0.50 c.c. When the last dose was reached, it was repeated, thereafter, every four weeks. No preliminary skin testing was done with the vaccine.

The injections were started in October, 1961, and were continued through March, 1963. Observations were recorded from November, 1961, through April, 1963, a total of eighteen months. This period encompassed two winters—the time of year when these patients usually had respiratory infections. No patient was changed from vaccine A to vaccine B or vice versa during the experiment. Eight patients, 2 pairs and 4 others, discontinued treatment within the first year of the study. This left 4 unmatched patients, from whom 2 new pairs were formed (No. 21 and No. 22, Table I). The 2 new pairs appeared to be adequately matched except that pair No. 21 had to consist of one person with and one without evidence by x-ray, of hyperplastic sinusitis. In addition, 3 patients (Nos. 7 (B), 21 (A), and 2 (B) Table I) stopped treatment near the end of the project in November and December of 1962. Their results were extrapolated to an 18 month period to make them comparable to the others, and their vital capacity and MEFR determinations were recorded as of the time that they had stopped treatment.

Method of evaluation

A mimeographed summary sheet was placed in each patient's clinical chart and a record made at each visit of all items except the vital capacity and MEFR.

A sample evaluation sheet

Patient—John Doe (Continued from previous sheets)

<i>Side effects</i>	<i>Date</i>	<i>Symptoms (0 to +4)</i>	<i>Days off school or work</i>	<i>Emergency room visits</i>	<i>Vital capacity (%)</i>	<i>MEFR</i>	<i>Steroid tablets</i>	<i>"Asthma tablets"</i>	<i>Inhaler prescriptions</i>
—	3/20/63	+1	—	—	—	—	15	20	1
—	4/ 3/63	0	—	—	—	—	—	—	—
—	4/17/63	+2 — +3	—	1	—	—	30	30	1
—	4/24/63	0	—	—	83	167	—	—	0
Mean (for 18 months)		13.5	0	2	83	167	115	150	6

Table 1. *Summary of clinical data in selection of patients*

<i>Pair No.</i>	<i>Vaccine</i>	<i>Patient</i>	<i>Age</i>	<i>Race (Negro-Caucasian)</i>	<i>Sex</i>	<i>Length of asthma (years)</i>	<i>Sinus x-ray</i>	<i>Initial vital capacity (%)</i>	<i>Initial MEFR</i>	<i>Severity of asthma</i>
1	A	A. A.	54	N	F	20	Pos.	38	27	Moderate-severe
	B	M. T.	59	C	F	30	Pos.	50	45	Moderate-severe
2	B	M. A.	50	N	F	5	Neg.	78	135	Mild
	A	L. M.	48	N	F	3	Neg.	96	170	Mild
3	A	A. B.	14	N	F	8	Neg.	69	53	Moderate
	B	A. S.	17	N	F	4	Neg.	58	48	Moderate
4	A	E. B.	39	C	F	2	Pos.	93	175	Episodic, severe
	B	W. R.	55	C	F	10	Pos.	77	80	Moderate-severe
5	B	E. B.	38	N	F	10	Pos.	83	225	Mild
	A	S. W.	44	N	F	6	Pos.	83	180	Mild
6	B	M. F.	30	N	F	3	Neg.	74	60	Moderate
	A	R. M.	51	N	F	24	Neg.	73	120	Moderate
7	A	E. H.	36	N	F	1	Neg.	94	300	Episodic, mild
	B	T. H.	32	N	F	1	Neg.	71	180	Episodic
8	B	J. H.	36	N	M	20	Neg.	33	21	Episodic, mild
	A	R. W.	45	N	M	7	Neg.	74	170	Moderate
9	B	B. H.	15	N	F	3	Neg.	85	120	Moderate
	A	L. W.	11	N	F	10	Neg.	70	140	Moderate
10	B	O. J.	55	N	F	50	Neg.	40	15	Moderate-severe
	A	D. P.	56	N	F	15	Neg.	46	33	Moderate-severe
11	A	S. J.	32	N	F	7	Pos.	80	160	Moderate
	B	C. N.	35	N	F	3	Pos.	94	75	Moderate
12	A	N. L.	24	N	F	24	Neg.	62	55	Moderate-severe
	B	I. M.	19	C	F	17	Neg.	55	33	Moderate-severe
13	A	C. C.	34	N	M	29	Pos.	42	24	Moderate-severe
	B	B. L.	34	N	M	7	Pos.	46	60	Moderate-severe
14	A	C. C.	18	N	F	2	Neg.	82	225	Mild
	B	R. K.	20	N	F	6	Neg.	105	120	Mild
15	B	S. D.	25	N	F	5	Neg.	75	110	Moderate
	A	C. T.	13	N	M	8	Neg.	57	110	Moderate
16	A	M. R.	24	N	F	3	Pos.	85	220	Mild
	B	E. S.	23	N	M	9	Pos.	78	200	Mild
17	B	G. S.	41	N	F	15	Neg.	45	20	Moderate
	A	P. Y.	38	N	F	25	Neg.	65	105	Moderate

Table I. Cont'd

<i>Pair No.</i>	<i>Vaccine</i>	<i>Patient</i>	<i>Age</i>	<i>Race (Negro-Caucasian)</i>	<i>Sex</i>	<i>Length of asthma (years)</i>	<i>Sinus x-ray</i>	<i>Initial vital capacity (%)</i>	<i>Initial MEFR</i>	<i>Severity of asthma</i>
18	A	R. S.	26	C	F	16	Neg.	125	250	Slight
	B	V. W.	27	C	M	21	Neg.	120	400	Slight
19	A	E. M.	34	N	F	33	Neg.	74	150	Moderate
	B	L. J.	56	N	F	6	Neg.	47	51	Moderate
20	B	C. H.	59	N	F	18	Pos.	64	170	Moderate
	A	E. W.	51	N	F	7	Pos.	80	160	Moderate
21	B	M. P.	42	N	F	7	Pos.	62	60	Moderate-severe
	A	E. H.	45	N	F	5	Neg.	95	100	Moderate
22	B	F. M.	41	N	M	20	Pos.	107	300	Mild
	A	H. S.	68	C	M	35	Pos.	84	140	Moderate

The number of pills prescribed, not the number supposedly consumed, was recorded, because it was almost impossible to determine how many pills a patient actually had ingested. It was thought that in one and one half years most of the pills would have been used. The patients were evaluated under the following headings:

- a. Symptoms (0 to +4)
 - 0 Completely asymptomatic.
 - +1 Minimal asthma: The patient is aware of tightness or congestion of his chest.
 - +2 Moderate asthma: There is definite wheezing but the patient is not severely handicapped in his daily activities.
 - +3 Severe asthma: The patient is severely handicapped but able to do some things for himself.
 - +4 Incapacitated: The patient is unable to do anything but fight for breath.
- b. Days off from school or work because of asthma.
- c. Emergency room visits if for asthma.
- d. Vital capacity: This was taken over a six-second period on the McKesson Vitalor model VC25A (Fig. 1) and recorded as the percentage of normal for the patient's sex and height.
- e. Maximal expiratory flow rate (MEFR): This, essentially, is the rate at which the patient exhales the 1 L. of air between 0.2 and 1.2 L. of vital capacity during a maximal forced expiration. A straight line is drawn between the points of intersection of the vital capacity curve and the 0.2 and 1.2 L. lines (Fig. 1). Then a line parallel to this is drawn through the zero point of the graph to the edge of the graph paper from which the MEFR is read directly. In practice, this can be done extremely rapidly and provides information almost identical with that obtained from the "percentage of timed vital capacity."
- f. Number of steroid tablets: For our purposes, 5 mg. of prednisone was considered equivalent to 25 mg. of cortisone, 4 mg. of triamecinolone, 4 mg. of methylprednisolone, or 0.75 mg. of dexamethasone.
- g. Number of asthma tablets: Either Tedral, Quadralin, Amesec, or Luasmin or their liquid equivalent was used.
- h. Number of prescriptions for inhalers, whether Medihaler, Isuprel, Mistometer, or similar preparations: A prescription for a bottle of Neo-Synephrine 1 per cent, Isuprel 1:200, or epinephrine 1:1,000 was considered equivalent to an inhaler prescription.

When some of the larger inhalers became available they were counted as two prescriptions.

- i. Constitutional reactions: A typical exacerbation of asthma occurring within the eight to twenty-four hour period following the bacterial vaccine injection.

Statistical evaluation

At the termination of the study in May, 1963, totals for each parameter evaluated were obtained on the individual patients. Mean values were then calculated for each category in both groups of patients (Table II) and were then compared and analyzed for significant differences with the "T" test (Table III).

RESULTS

Difficulties encountered with the evaluation process

Symptoms. It was often difficult to place a patient in one category or the other. Consequently, our records often contained such notations as "0 to +1" or "+2 to +3." It was decided to enter these on the record as halves, i.e., "+1½" or "+2½," etc. Another difficulty was that there was often a marked variation of symptoms during the period between visits. The usual solution was to average the symptoms since the last visit. Since the experiment was double-blind and the same averaging process applied to both groups, a consistent bias was improbable.

Days off from school or work. Because of the character of our clinic population, this parameter proved to be almost impossible to evaluate. Many patients were unemployed and on public welfare. Others worked part time. It was diffi-

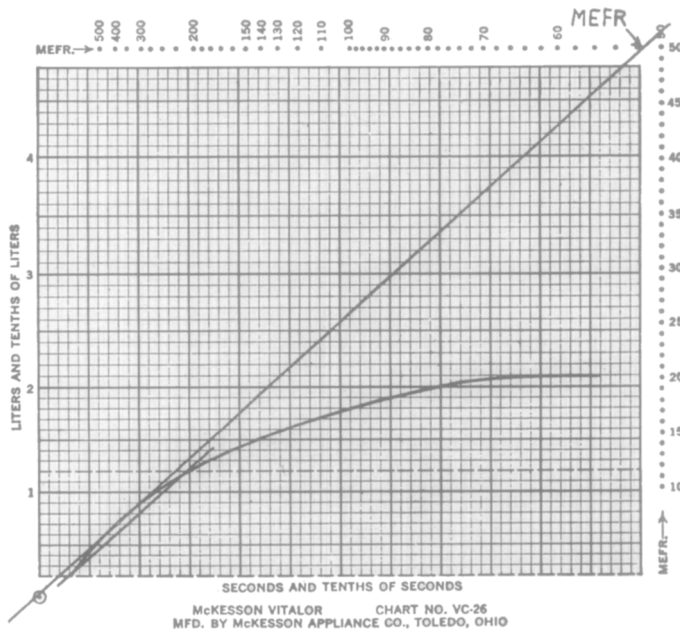


Fig. 1

Sample of a timed vital capacity sheet.

cult to tell whether the patient was not working because of asthma or because of lack of initiative. Accordingly, this parameter of evaluation was dropped during the study.

Vital capacity and maximal expiratory flow rate. These were performed at the beginning and at the end of the experiment. The greatest problem in the use of the Vitalor was in persuading the patient to put forth a maximum effort. Many of them for psychologic reasons, would not exhale as hard and as fast as they were physically able. However, this factor presumably worked equally for both groups.

Constitutional reactions. Only one patient had what we would consider a constitutional reaction:

M. A. (Patient No. 2, Vaccine B, Table II) was a 50-year-old Negro woman with a history of bronchial asthma for five years. She was undergoing immunization to house dust as well as to the bacterial vaccine. There had been a long history of emotional problems. On April 30, 1962, she received a subcutaneous dose of 0.50 c.c. of 1/10 house dust and 0.45 c.c. of 1/100 vaccine B. This was the same vial marked "B" from which others had received injections without difficulty. It had been prepared in the same manner and at the same time as the other vials. She had received medication from this vial before. The dose of dust had not been raised. Two hours later, a severe asthma attack occurred which required treatment in the emergency room with epinephrine and intravenous aminophylline. There was no local reaction. In May and June, 1962, it was her opinion that each injection increased her asthma. Saline placebos on June 4 and June 25 produced neither local nor symptomatic reactions. Her dose was then maintained at 0.30 c.c. of vaccine B, 1/100. In October and November, 1962, unrelated to vaccine therapy, she had severe asthma requiring several emergency room visits and steroid therapy. She did not return to the allergy clinic after December, 1962.

Local reactions. The patients were kept waiting fifteen minutes after the injections and checked for local reactions. They were also to report any delayed local reactions. No local reactions were reported by any patients at any time.

Comparison of the two groups

At no time during the treatment and data recording period were the investigators in the clinic given any hint as to which was the active and which the inactive substance. The vials looked identical. At the end of the clinical trial, a poll taken among three of the clinical allergists (S. E. B., M. F. and H. B.) revealed that all thought that vaccine B was the active substance. The probable reason was the "constitutional reactions" of patient M. A. who was on vaccine B. Only when all data had been recorded was the code broken. We were surprised to find that vaccine A was the active substance. The differences between the two groups of patients are as follows:

Symptoms. The patients in group A (vaccine) had a mean of 18.3 compared to 24.3 in group B (placebo). These values were not significantly different.

Emergency room visits. There was a mean of 1.5 per patient in group A as compared to 2.8 in the control group, B; these values do not differ significantly.

Vital capacity. The group treated with vaccine averaged 77 per cent and the group treated with saline averaged 73.5 per cent at the conclusion of the

experiment. These values did not differ significantly from each other or from the pretreatment averages.

Maximal expiratory flow rate (MEFR). The patients of group A averaged 158 and those of group B averaged 131.5 at the conclusion of the experiment.

Table II. *Summary of the responses of the patients on vaccine A and those on vaccine B*

<i>Patient No.</i>	<i>Symptoms</i>	<i>Emergency room visits</i>	<i>Vital capacity (%)</i>	<i>MEFR</i>	<i>Steroid tablets</i>	<i>Asthma pills</i>	<i>Inhalers</i>
<i>Vaccine A</i>							
1	20	0	41	14	0	180	0
2	68	18	60	58	157	140	20
3	12	1	63	140	0	0	0
4	85	4	84	110	399	850	27
5	5½	0	86	300	0	95	0
6	8½	1	70	130	0	850	0
7	10½	0	78	225	0	80	0
8	8½	0	91	200	0	110	7
9	9	0	72	140	0	30	2
10	21½	1	49	31	0	174	5
11	5½	0	101	260	0	48	0
12	16	2	74	110	0	120	17
13	11	0	42	37	0	290	10
14	8	0	88	225	0	30	2
15	3	0	83	180	0	240	0
16	9	0	81	175	0	0	0
17	38	3	81	115	0	630	8
18	0	0	122	250	0	0	0
19	7	2	77	145	30	135	1
20	18	0	44	160	0	235	3
21*	19	0	89	250	0	180	0
22	19½	0	114	225	0	316	0
Mean	18.3	1.5	77	158	27	215	4.6
<i>Vaccine B</i>							
1	5	0	42	26	0	12	1
2†	63	25	75	100	175	642	21
3	72	4	90	160	230	480	62
4	4	0	71	45	0	0	0
5	2½	0	80	200	0	0	0
6	44	2	—	—	0	780	23
7†	39	18	80	170	0	569	15
8	43	1	35	21	0	540	12
9	13	0	100	185	0	180	2
10	45½	5	50	35	383	630	33
11	51½	1	88	150	185	370	8
12	34	1	52	25	0	405	17
13	31	2	57	67	415	496	16
14	8	0	98	140	0	2	4
15	18½	3	100	210	0	220	2
16	9	0	89	210	0	4	7
17	21	0	50	21	195	563	29
18	4	0	120	400	0	0	0
19	7	0	50	62	0	120	0
20	5½	0	58	140	0	210	0
21	13½	0	62	45	0	410	13
22	0	0	97	350	0	40	0
Mean	24.3	2.8	73.5	131.5	72	303	13

*Discontinued treatment in November, 1962—findings extrapolated to 18 months.

†Discontinued treatment in December, 1962—findings extrapolated to 18 months.

Neither of these values differed significantly from each other or from the control values.

Steroid pills. There was a marked difference between the two groups; group A (vaccine) required an average of 27 pills per patient as compared to 72 in group B (placebo). However, because of marked data scatter, this result was not significant.

Asthma pills. There was a mean of 215 for group A patients compared with 303 for those of group B. This difference is not statistically significant.

Inhalers. There was a mean of 4.6 inhalers in the vaccine group, A, and 13 in the placebo group, B. This difference is statistically significant (P less than 0.05).

It should be noted that although only the "inhaler prescriptions" parameter showed statistical significance, in every other parameter studied the group treated with vaccine fared better. The number of patients was small for a study

Table III. *Comparison of response between treatment group and placebo group by "t" testing of paired differences*

<i>Parameter</i>	<i>Mean of placebo group "A"</i>	<i>Mean of vaccine group "B"</i>	<i>Level of significance</i>
Symptoms	18.3	24.3	$P > .05$
Emergency room visits	1.5	2.8	$P > .05$
Vital capacity (%)	77	73.5	$P > .05$
MEFR	158	131.5	$P > .05$
Steroid pills	27	72	$P > .05$
Asthma pills	215	303	$P > .05$
Inhalers	4.6	13	$P < .05$

Table IV. *Summary of the responses of the patients with hyperplastic sinusitis**

<i>Patient No.</i>	<i>Symptoms</i>	<i>Emergency room visits</i>	<i>Vital capacity (%)</i>	<i>MEFR</i>	<i>Steroid tablets</i>	<i>Asthma pills</i>	<i>Inhalers</i>
<i>Group A (treated with vaccine)</i>							
1	20	0	41	14	0	180	0
4	85	4	84	110	399	850	27
5	5½	0	86	300	0	95	0
11	5½	0	101	260	0	48	0
13	11	0	42	37	0	290	10
16	9	0	81	175	0	0	0
20	18	0	44	160	0	230	3
Mean	21	0.5	68	151	57	242	40
<i>Group B (treated with saline)</i>							
1	5	0	42	26	0	12	1
4	4	0	71	45	0	0	0
5	2½	0	80	200	0	0	0
11	51½	1	88	150	185	370	8
13	31	2	57	67	415	496	16
16	9	0	89	210	0	4	7
20	5½	0	58	140	0	210	0
Mean	16	0.5	69	120	86	156	32

*There was no significant difference between the two groups.

of this nature, and with a larger group some of these values might have become statistically significant.

Hyperplastic sinusitis

An attempt was made to compare the results of therapy on the patients with hyperplastic sinusitis with the group as a whole (Table IV). There did not seem to be any significant difference between the two groups.

Antibiotic dosage

After the study had been completed, the question arose as to whether the two groups were really identical regarding the number of respiratory infections during the experiment. We counted the number of doses of antibiotics taken by the patients in the two groups before and during the period of observation (Table V). The "before" period comprised the eighteen months from May, 1960, through October, 1961. A 250 mg. tetracycline capsule was taken as the standard "dose" and, for the purpose of comparison, was considered equivalent to 250 mg. of erythromycin, 150 mg. of Declomycin, and 150,000 units of penicillin.

The patients in Group A averaged 19 doses of antibiotics during the "before" period and 38 during the vaccine treatment period. The patients in Group B averaged 25 doses of antibiotics "before" and 53 while receiving the placebo. There was no significant difference between the two groups.

Patient drop-outs

Eight of the original patients discontinued allergy injections (Table VI). Four of them did so for no known reasons, one because of other medical problems, one (on the placebo) because of possible side effects after her allergy injections, and 2 because of error. The errors occurred when the vaccine injections had been omitted by mistake and the error not discovered within a month. It is of interest that the same number of patients in each group discontinued injections.

As previously noted, 3 patients discontinued treatment almost at the end of the clinical trial—one in November, 1962 (Patient 21, Group A, Table II) and 2 in December, 1962 (Patients 2 and 7, Group B, Table II). Because they had received treatment throughout almost the entire period, their results were extrapolated to 18/14 and 18/15 of the recorded values, except, of course, for the determinations of vital capacity and MEFR which were left as last recorded. This procedure is considered statistically proper and affected only 3 of 44 patients.

DISCUSSION

Skin testing

There is considerable controversy regarding the importance of skin testing preliminary to the use of bacterial vaccine. Kraft⁴ noted that immediate skin test reactions to bacterial antigens were more frequent in patients with asthma than in the general population but that there was a poor correlation between

positive skin tests and clinical evidence of bacterial allergy. Hajos⁵ compared the inhalation test and the intradermal skin tests of 62 patients. She found that the direct inhalation test of the tracheobronchial tree was more specific

Table V. *Doses of antibiotics* in the two groups before† and during‡ the clinical trial*

No.	Patient	Doses before	Doses during
<i>Group A</i>			
1	A. A.	0	0
2	L. McL.	0	174
3	A. B.	20	130
4	E. B.	143	132
5	S. W.	0	32
6	R. M.	20	0
7	E. H.	0	0
8	R. W.	36	0
9	L. W.	0	16
10	D. P.	0	0
11	S. J.	0	18
12	N. L.	72	113
13	C. C.	50	46
14	C. C.	0	0
15	C. T.	0	16
16	M. R.	48	48
17	P. Y.	0	32
18	R. S.	0	0
19	E. McN.	0	0
20	E. W.	16	76
21	E. H.	20	0
22	H. S.	0	0
Mean		19	38
<i>Group B</i>			
1	M. T.	0	0
2	M. A.	68	77
3	A. S.	96	124
4	W. R.	16	0
5	E. B.	0	32
6	M. F.	0	219
7	T. H.	0	64
8	J. H.	48	70
9	B. H.	0	0
10	O. J.	92	82
11	C. N.	0	76
12	I. M.	0	24
13	B. L.	146	282
14	R. K.	20	18
15	S. D.	0	24
16	E. S.	18	0
17	G. S.	0	32
18	V. W.	31	44
19	L. J.	0	0
20	C. H.	0	0
21	M. J.	16	0
22	F. M.	0	0
Mean		25	53

*Antibiotic dose: 250 mg. tetracycline, 150 mg. Declomycin, 250 mg. erythromycin, or 150,000 u. penicillin.

†Before: The eighteen months from May, 1960, through October, 1961.

‡During: The eighteen months from November, 1961, through April, 1963.

than skin testing. Simon and Rinard⁶ noted no correlation at all between either immediate or delayed skin test results and the patients' reactions. Hampton⁷ described an increased number of positive skin tests to *Neisseria catarrhalis* in patients clinically sensitive to bacteria. Cooke⁸ considered the correlation to be so poor between skin tests and clinical sensitivity to bacteria that he did not routinely perform skin testing before giving bacterial vaccine. Swineford⁹ recorded the results of 3,860 cutaneous tests with 34 crude polysaccharide and nucleoprotein fractions of fourteen kinds of bacteria. He noted a high percentage of both immediate and delayed reactions. However, he concluded that "Diagnostic procedures other than skin tests are needed to establish etiological relationships between bacteria and syndromes of clinical allergy." Because of the conflicting reports cited above and our own previous experience, we did not think that preliminary skin testing would be useful.

Autogenous vaccine

There has been much disagreement as to the beneficial effect of stock bacterial vaccine compared with autogenous vaccine.³ The vaccine used in our study contains all the common strains of organisms found in the nose and throat contrasted with the usual autogenous vaccines which often contain only transient organisms. Also, the use of a stock vaccine was more practical for a double-blind study.

Other "double-blind" studies

We found records of three other "double-blind" studies of bacterial vaccine.

Frankland¹⁰ used a procedure whereby half of the patients received an autogenous vaccine and half a carbol-saline injection. The strength of the vaccine was such that it contained ten million organisms per milliliter of each of the autogenous strains as well as a stock vaccine containing pneumococcus, mixed types of Friedlander's bacillus and staphylococcus, *Bacillus septicus*, *Haemophilus influenzae*, streptococcus, and *Neisseria catarrhalis*. The patients were evaluated as to weight change, drug consumption, frequency and severity of attacks, days in the hospital, days in bed, days off work or school, change in incapacity, and subjective opinion of doctor and patient. A semiquantitative system of scoring was used and the two groups compared; 58 per cent showed improvement on the bacterial vaccine, while 52 per cent showed improvement on the carbol-saline. They concluded that under the conditions of type of vaccine, spacing of injections, type of patient, and the grading system employed, there was no significant difference between the two groups. This paper was immediately criticised by Hajos,¹⁰ who pointed out that the carbol-saline used as a control had some therapeutic value.

Helander¹² compared a group of patients treated with stock bacterial vaccine with another group that received a placebo. The only criterion used was "improved" and "unimproved." There was improvement in 68 per cent of the "vaccine-treated" and in 62 per cent of the "placebo-treated" group. This paper can be criticised in that the only criterion used was "improved" or "unimproved" without any explanation as to how the data were derived.

Johnstone¹³ gave stock bacterial vaccine and autogenous vaccine to a group of children and compared them with control subjects. The patients in the clinic were evaluated by another pediatrician who did not know to which group the patient belonged. However, the private patients were evaluated by the author who was aware of the contents of the injections. They were evaluated as to the "number of asthmatic episodes per year," "number of days school missed per year," and "number of days wheezing per year." Eighty per cent of the patients treated with vaccine had fewer asthmatic episodes in the last year of the study. For the control group, the figure was 91 per cent. An obvious objection to this study is that it was not completely double blind. Another is that all three parameters measured were quite similar.

Discussion of our results

In our study we attempted to evaluate the patients over an extended period by as many different criteria as possible. Our study was completely double

Table VI. *Summary of data on patients who discontinued vaccine injections*

<i>Pa- tient No.</i>	<i>Vac- cine</i>	<i>Age</i>	<i>Sex</i>	<i>Race</i>	<i>Length of Asthma (%)</i>	<i>Sinus x-ray</i>	<i>Vital ca- pacity (%)</i>	<i>MEFR</i>	<i>Se- verity of asthma</i>	<i>Reason for discontinuance</i>
1*	A	38	M	N	15	Neg.	78	350	Mild	Vaccine discontinued by error after a month of severe asthma
2*	B	36	M	N	35	Neg.	89	150	Mild	Discontinued all immunizations because he felt they caused nausea and headache. They have now been resumed without trouble
3*	A	50	M	N	34	Pos.	50	78	Mild	Discontinued all clinic visits for no known reason
4*	B	47	M	N	47	Pos.	62	145	Mild	Discontinued all clinic visits for no known reason
5	A	27	F	N	5	Neg.	62	100	Mod- erate	Discontinued allergy clinic because of gynecologic problems
6	B	11	F	W	6	Neg.	80	240	Mild	Transferred all clinic care to another hospital
7	B	43	F	N	26	Neg.	70	150	Mod- erate	Dropped out early in study and has not been heard from since
8	A	68	M	N	35	Pos.	84	140	Mod- erate	Discontinued by error

*Patients 1 and 2 and patients 3 and 4 had been paired together.

blind; the two groups were as comparable as was possible in a clinical study and our method of evaluation highly objective.

Every attempt was made to eliminate bias in the treatment and evaluation. Our opinions as to which was placebo and which vaccine were colored by the one patient with "constitutional reactions" which occurred late in the clinical trial. As it turned out on this informal survey, our guesses were wrong. In our opinion we were as unbiased as is possible in a clinical situation.

Comparison of the antibiotics taken by the two groups before and during the study revealed a markedly increased intake of antibiotics while under treatment. The most obvious explanation is that the two periods really were not comparable: The control period encompassed two summers and one winter and the treatment period two winters and one summer. There seemed to be slightly but not significantly more antibiotics taken by the placebo group. Two explanations might be given for this: that the vaccine decreased the number and severity of the respiratory infections or that bacterial vaccine will have no effect in preventing a respiratory infection but might decrease an asthmatic response to an infection.

One of the concepts of bacterial allergy has been its association with nasal polyposis and hyperplastic sinusitis.⁸ We compared the patients with hyperplastic sinusitis with the group as a whole (Table V) and could not find any difference between the two groups. However, it is possible that the number of persons with sinusitis was too small.

Double-blind studies with ragweed

Some idea of the difficulties associated with double-blind studies may be noted in the article by Lowell¹⁴ who studied the responses of known ragweed-sensitive patients to injections of ragweed, saline, and histamine. There was no difference in the performance of the two groups during the first year of injection therapy. In fact, for a while, the doctors administering the injections were under the impression that the histamine group was obtaining the most benefit. However, in the second year the group treated with ragweed fared better than the others.

CONCLUSION

If we bear in mind the difficulty associated with proving that ragweed immunization helps ragweed-allergic patients, it is not difficult to understand why there has been such disagreement on the much more complex issue of the use of bacterial vaccine in the treatment of infective asthma. It is interesting to note that in both of the completely double blind studies to date, those of Frankland¹⁰ and of Helander,¹² the patients treated with vaccine fared somewhat better, but not statistically so. With longer treatment, other vaccine, higher doses, or other criteria of evaluation they also might have shown statistically positive results. Our studies similarly indicated that the patients treated with vaccine did somewhat better than those treated with the placebo.

A review of the literature reveals no definite relationship between positive skin tests to bacteria and clinical symptoms. Three previous "double-blind" studies appeared to show the ineffectiveness of bacterial vaccine. However, one

was not completely double-blind; and the other two did show that there was a slight tendency for the group treated with vaccine to do better.

An evaluation of this kind is extremely difficult to perform, and we have neither conclusively proved nor disproved the effectiveness of bacterial vaccine in the treatment of bronchial asthma. However, under the conditions of our study, the data suggest that the bacterial vaccine was an effective adjunct in the treatment of bronchial asthma.

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REFERENCES

1. Carmalt-Jones, D. W.: The Treatment of Bronchial Asthma by a Vaccine, *Brit. M. J.* **2**: 1049, 1909.
2. Pirie, J. H.: Vaccines in the Treatment of Chronic Bronchitis and of Asthma, *Brit. M. J.* **1**: 1268, 1913.
3. Blatt, H.: Microbial Allergy, a Critical Review, 1950 to May, 1960, *Ann. Allergy* **19**: 1037, **19**: 1198, **19**: 1318, **19**: 1434, 1961; **19**: 60, **19**: 134, **19**: 207, **19**: 263, and **19**: 335, 1962.
4. Kraft, B., Mothersill, M., and Nestmann, R. H.: Immediate Urticarial Reactions to Intradermal Injections of Bacterial Antigens, *Ann. Allergy* **7**: 162, 1949.
5. Hajos, M. K.: A Comparative Study of Skin Test and Bronchial Test With Bacterial Solutions in Infective Bronchial Asthma, *Acta allergol.* **15**: 517, 1960.
6. Simon, S. W., and Rinard, L. A.: Bacterial Antigen Complexes (Hoffmann). An Evaluation of Skin Test Specificity Versus Patient Reaction, *Ann. Allergy* **19**: 877, 1961.
7. Hampton, S. F., Johnson, C., and Galakatos, E.: Studies of Bacterial Hypersensitivity in Asthma. I. The Preparation of Antigens of *Neisseria Catarrhalis*, the Induction of Asthma by Aerosols, the Performance of Skin and Passive Transfer Tests, *J. ALLERGY* **34**: 63, 1963.
8. Cooke, Robert: *Allergy in Theory and Practice*, Philadelphia, 1947, W. B. Saunders Company.
9. Swineford, O., and Holman, J.: Studies in Bacterial Allergy. III. Results of 3,860 Cutaneous Tests With 34 Crude Polysaccharide and Nucleoprotein Fractions of 14 Different Bacteria, *J. ALLERGY* **20**: 418, 1949.
10. Frankland, A. W., Hughes, W. H., and Gorrill, R. H.: Autogenous Bacterial Vaccines in Treatment of Asthma, *Brit. M. J.* **2**: 941, 1955.
11. Hajos, M. K.: Autogenous Vaccines in Asthma, *Brit. M. J.* **2**: 1563, 1955.
12. Helander, E.: Bacterial Vaccines in the Treatment of Bronchial Asthma, *Acta allergol.* **13**: 47, 1959.
13. Johnstone, Douglas E.: Study of the Value of Bacterial Vaccines in the Treatment of Bronchial Asthma Associated With Respiratory Infections, *Pediatrics* **24**: 427, 1959.
14. Lowell, F. C., and Franklin, W.: A Double Blind Study of Treatment With Aqueous Allergenic Extracts in Cases of Allergic Rhinitis, *J. ALLERGY* **34**: 165, 1963.

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