THE ATTENUATION OF EXERCISE-INDUCED BRONCHOSPASM BY ASCORBIC ACID[1,2]

E. NEIL SCHACHTER, M.D., and ALAN SCHLESINGER, M.D.

In order to study the potential benefit of ascorbic acid in asthma we investigated its role in exercise-induced bronchospasm (EIB). Twelve asthmatic subjects were recruited on the basis of findings compatible with EIB. On two subsequent days the subjects ingested 500 mg of ascorbic acid or a placebo. The study was performed in a double-blind randomized fashion. Partial and maximal expiratory flow volume (PEFV and MEFV) curves were used to determine pulmonary function changes. Pretreatment with ascorbic acid led to a significant attenuation of the bronchospasm seen five minutes after exercise compared to placebo, as measured by FVC (0.23 ± 0.08 L decrease after ascorbic acid, 0.48 ± 0.14 L decrease after placebo) and by FEV_1 (0.24 ± 0.06 decrease after ascorbic acid, 0.44 ± 0.14 decrease after placebo) (Mean ± SE). These results suggest a mild antibronchospastic action of ascorbic acid in subjects with EIB.

Introduction

THE ROLE OF ASCORBIC ACID (vitamin C) in asthma has long been debated. As early as 1803 Reisseissen suggested that vitamin C prevents the wheezing observed in patients with scurvy.[1] More recently, animal studies have shown that ascorbic acid may prevent anaphylaxis and other allergic phenomena.[2,3] In guinea pigs ascorbic acid has been shown to reduce the airway obstruction induced by 5-hydroxytryptamine, bradykinin, and histamine.[4] In healthy human subjects Zuskin et al demonstrated that vitamin C inhibits histamine-induced bronchospasm.[5] These findings suggest that vitamin C may have an antibronchospastic effect, although some authors have failed to find evidence to support these results.[6,7]

In order to further study the potential role of ascorbic acid in patients with asthma we investigated the effect of vitamin C on exercise-induced bronchospasm (EIB), a well-defined common asthmatic syndrome that can be easily reproduced under controlled laboratory conditions.[8]

Materials and Methods

Twelve subjects with asthma as defined by the American Thoracic Society's criteria,[10] five male and seven female, were recruited and informed consent was obtained as approved by the Yale University Human Investigation Committee. Asthmatics were selected from among members of the University and hospital community. None of our subjects had been hospitalized for asthma and none had ever required corticosteroid therapy. Each subject completed a detailed questionnaire concerning the presence of respiratory symptoms, allergies and exercise-induced bronchospasm. The subjects' anthropometric data and selected responses to the questionnaire appear in Table I. All twelve subjects gave a characteristic description of EIB.

Maximal and partial expiratory flow-volume curves (MEFV, PEFV curves) were used to measure forced expiratory flow rates and volumes.[11] A pneumotachograph-integrator system[12] continuously monitored flow and volume and curves representing these quantities were recorded on a Brush 500 (Gould, Cleveland, Ohio) X-Y recorder. From these curves we determined the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR), and flow rates measured at 60% of the baseline vital capacity below the total lung capacity on maximal and partial flow volume curves MEF40% and MEF40%(P) respectively (see Figure 1.). In addition, the flow rate after exhalation of 50% of the vital capacity following a maximal inspiration (Vmax50%) was measured for the baseline curves. Pre-challenge pulmonary function data measured on the screening day for all subjects appear in Table I. All subjects performed the exercise studies on a cycloergometer (Monark). Cardiac frequency was meas-

From the Department of Internal Medicine, Pulmonary Section, Yale University School of Medicine. Dr. Schachter is Associate Professor, Internal Medicine, Department of Internal Medicine, Pulmonary Section, Yale University School of Medicine, New Haven, Connecticut.

Table I. Anthropometric Data on 12 Asthmatic Subjects (Mean ± SD). Pulmonary Function Expressed as a Percentage of Predicted.*

Number	Age	M	F	Atopic history	Smokers	FVC	FEV_1	PEFR	$\dot{V}Max50\%$
12	26 ± 5.0	5	7	12	2	87 ± 11.5	75 ± 18.1	78 ± 19.6	62 ± 31.1

* Schoenberg, J. S., Beck, G. J., Bouhuys, A. B.: Growth and decay of pulmonary function in healthy Blacks and Whites. Resp Physiol 33: 367–393, 1973.

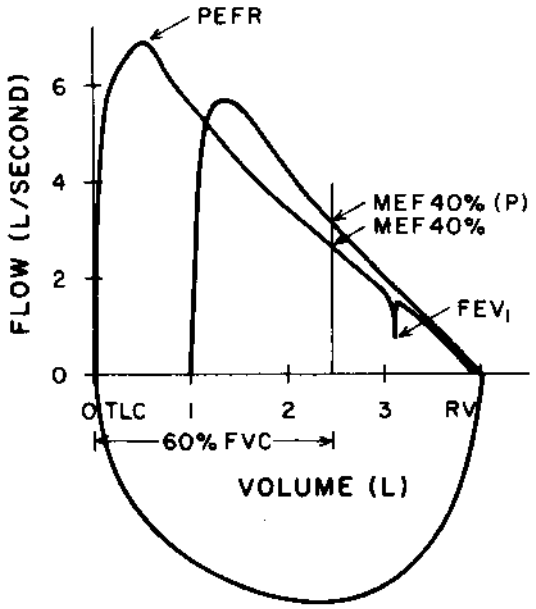

Figure 1. Maximal and partial flow volume curves.

ured with an electrocardiograph (Hewlett-Packard model 1500 B). Baseline heart rate was obtained and exercise was begun at a constant speed of 20 kilometers per hour against zero workload. At the end of each one minute interval cardiac frequency was measured and the workload was increased by 150 kilopondmeters per minute, keeping pedalling speed constant throughout the experiment. Exercise against progressively larger workloads was continued until either the heart rate reached 170 beats per minute or the subject fatigued.

All twelve subjects were instructed to take no medications for at least eight hours prior to each challenge experiment. They were similarly instructed to refrain from foods or beverages containing large amounts of methylxanthines or ascorbic acid (coffee, fruits, juices, etc.). On the initial screening day baseline pulmonary function tests were obtained by having the subjects perform the partial and maximal flow volume maneuvers three times, at one minute intervals, generating three pairs of MEFV and PEFV curves (baseline curves). Exercise was then performed as described above. After completion of exercise three new pairs of MEFV and PEFV curves were obtained at one minute intervals (immediate post-exercise curves). A third set of three pairs of curves was generated five minutes after the termination of exercise (five-minute post-exercise curves). Two inhalations (0.65 micrograms each) of metaproterenol sulphate were then administered from a metered aerosol container. Ten minutes later three final pairs of MEFV and PEFV curves were obtained (post-bronchodilator curves). FVC, FEV_1, PEFR, MEF40% and MEF40%(P) values were determined for the four sets of curves by averaging the values obtained from the three pairs of MEFV and PEFV curves in each set. Those subjects who demonstrated sufficient EIB (20% reduction in MEF40% or MEF40%(P) after exercise) were invited to proceed to the remaining challenges. These parameters have been demonstrated to be particularly sensitive to small degrees of airway obstruction in exercise challenge studies involving mild asthmatics.[13]

On the second and third days each subject ingested vitamin C (500 mg) or placebo (sucrose). The vitamin C and placebo were given in identical capsules in a double-blind random order one and a half hours prior to exercise challenge. Pulmonary function was again measured before exercise, after exercise and after metaproterenol on these two study days.

Because the temperature and humidity of ambient air have been shown to affect EIB[15] exercise was performed in a centrally air-conditioned laboratory, keeping the conditions within narrow limits. On the vitamin C day the average temperature (T) was 71 ± 3.8°F and the relative humidity (RH) was 59 ± 7.0%. On the placebo day the T was 70 ± 2.3°F and the RH was 59 ± 8.9% (Mean ± SD).

Results

Figure 2 displays the average change in FVC, FEV_1, PEFR, MEF40% and MEF40%(P) after exercise on the screening day. The pulmonary function variables are expressed as a percent of the baseline value. All five parameters demonstrated the typical responses for patients with EIB, with mild bronchodilatation immediately following exercise, bronchoconstriction commencing within five minutes after exercise and a bronchodilatation after inhalation of metaproterenol sulfate. Significant post-exercise bronchoconstriction can be appreciated ($p < 0.01$). Following the administration of metaproterenol all parameters increased significantly compared to baseline ($p < 0.05$) with the exception of FVC.

There were no statistically significant differences between the response to exercise on the placebo day and the screening day, implying no placebo effect.

The measured change in pulmonary function after exercise on the two drug days (placebo and vitamin C) are summarized in Tables II through IV. In Table II the increase from baseline immediately following exercise is compared for the two days. A consistently larger increase

is seen for all parameters on the vitamin C day than on the placebo day but significant differences were obtained only for PEFR. Other parameters such as FEV_1 and MEF40%(P) were marginally significant.

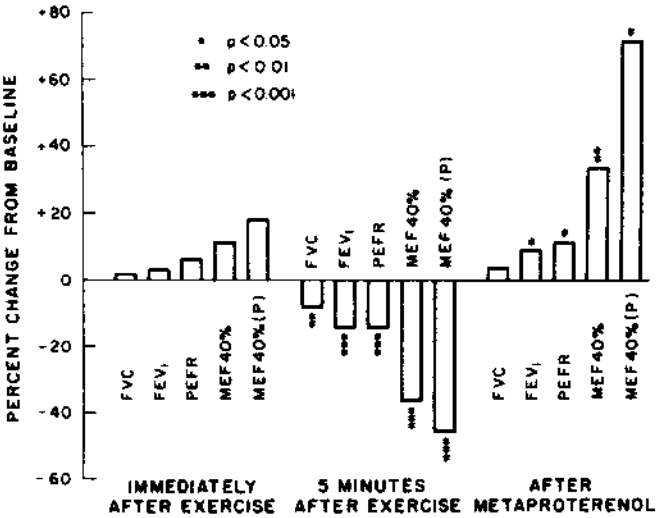

Figure 2. Percentage of change, compared to pre-exercise values, of all flow volume parameters in the post-exercise period.

In Table III the drop from baseline five minutes following exercise is compared for the two days. All volumes and flow rates demonstrated consistently less decrease on the vitamin C day than on the placebo day. Statistical significance was achieved for the FVC and very nearly achieved for FEV_1. Percent decreases compared to baseline values are shown in Figure 3.

Post-bronchodilator increases in pulmonary function were greater (compared to baseline) on the vitamin C day than on the placebo day (see Table IV.) This was statistically significant for all parameters except MEF40%(P). Percent increases are shown in Figure 4.

Because the post exercise fall in pulmonary function on the vitamin C day had been less than that of the placebo day we questioned whether the difference in post-bronchodilator responses seen on two days resulted from the attenuating effect of vitamin C on EIB or whether in addition there might be an enhancing effect of this agent on the response to metaproterenol. In order to examine this question we compared the increase in function following metaproterenol from the level immediately before bronchodilator, i.e. five minutes after exercise. Analysis similar to that of the preceding tables showed no enhancement by ascorbic acid, suggesting

Table II. Post-exercise Change (Δ = After-Before) on the Placebo and Vitamin C Days, Seen Immediately After Exercise.

Subject	Δ FVC (L)		Δ FEV_1 (L/Sec)		Δ PEFR (L/Sec)		Δ MEF40% (L/Sec)		Δ MEF40%(P) (L/Sec)	
	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C
1	+0.2	−0.2	+0.1	−0.1	+0.9	+0.4	+0.4	−0.1	+0.4	0.0
2	−0.2	−0.3	0.0	+0.2	−0.2	0.0	0.0	−0.1	−0.1	+0.1
3	−0.2	+0.4	−0.1	+0.2	−0.2	+0.7	−0.1	+0.3	−0.3	0.0
4	−0.3	−0.1	−0.3	+0.2	−1.0	+0.4	−0.5	+0.3	−0.7	+0.2
5	+0.1	+0.2	+0.6	+0.4	+1.6	+1.4	+0.6	+0.7	−0.4	+0.8
6	0.0	−0.2	+0.2	0.0	+0.3	+0.2	+0.5	0.0	+0.4	+0.6
7	0.0	+0.1	+0.2	+0.3	+0.3	+0.3	+1.4	+1.2	+0.7	+1.7
8	−0.1	+0.3	+0.1	+0.4	+0.4	+0.9	+0.2	+0.5	+0.3	+0.8
9	+0.1	+0.3	+0.3	+0.4	+0.5	+1.0	+0.8	+0.8	+1.0	+1.3
10	+0.2	+0.1	+0.4	+0.2	+0.8	+1.3	+1.2	+0.3	+1.7	+0.4
11	0.0	+0.4	−0.3	+0.4	−1.3	+0.9	−0.6	+1.3	−0.5	+1.6
12	−0.1	+0.2	−0.2	−0.1	−0.9	−0.4	−0.3	−0.2	−0.7	−0.7
Mean	−0.03	+0.10	+0.08	±0.21	+0.10	+0.59	+0.30	+0.42	+0.15	+0.57
SEE	±0.05	±0.07	±0.08	±0.06	±0.25	±0.16	±0.19	±0.14	+0.21	±0.21
	t = 1.51 p = 0.16		t = 1.46 p = 0.18		t = 2.3 p < 0.05		t = 0.56 NS		t = 1.66 p = 0.13	

Table III. Post-exercise Change (Δ = After-Before) on the Placebo and Vitamin C Days Five Minutes After Exercise.

Subject	Δ FVC (L)		Δ FEV_1 (L/Sec)		Δ PEFR (L/Sec)		Δ MEF40% (L/Sec)		Δ MEF40%(P) (L/Sec)	
	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin
1	−0.2	0.0	−0.3	−0.2	−0.3	−0.3	−0.7	−0.5	−0.9	−0.8
2	−1.1	−0.7	−0.7	−0.4	−1.6	−0.9	−0.9	−0.4	−1.0	−0.5
3	−1.2	−0.5	−0.8	−0.4	−1.1	−1.6	−0.7	−0.3	−0.8	−0.4
4	−0.9	−0.1	−0.9	−0.1	−2.2	+0.2	−1.0	0.0	−1.1	0.0
5	+0.1	+0.3	0.0	0.0	+0.2	−0.8	−0.2	0.0	−0.4	−0.4
6	+0.1	−0.1	0.0	−0.3	−0.2	−0.2	0.0	−0.8	−0.4	−0.7
7	−0.1	−0.2	0.0	−0.1	−0.3	−0.3	−0.2	−0.6	−0.6	−0.2
8	−0.2	−0.2	−0.1	0.0	+0.1	0.0	0.0	−0.1	0.0	−0.1
9	−0.4	−0.1	−0.4	−0.2	−0.7	0.0	−0.6	−0.2	−0.6	−0.4
10	−0.1	−0.2	+0.1	0.0	0.0	−0.2	+0.3	+0.3	+0.5	−0.5
11	−1.1	−0.6	−1.4	−0.7	−3.6	−3.2	−2.6	−1.1	−2.8	−1.2
12	−0.7	−0.4	−0.8	−0.5	−1.7	−1.5	−1.2	−0.9	−1.6	−1.6
Mean	−0.48	−0.23	−0.44	−0.24	−0.95	−0.73	−0.65	−0.38	−0.81	−0.57
SEE	±0.14	±0.08	±0.14	±0.06	±0.40	±0.28	±0.22	±0.12	+0.24	±0.13
	t = 2.73 p < 0.05		t = 2.13 p = 0.057		t = 0.90 NS		t = 1.54 p = 0.15		t = 1.27 NS	

Table IV. Post-exercise Change (Δ = After-Before) on the Placebo and Vitamin C Days, Post Bronchodilator.

Subject	Δ FVC (L)		Δ FEV_1 (L/Sec)		Δ PEFR (L/Sec)		Δ MEF40% (L/Sec)		Δ MEF40%(P) (L/Sec)	
	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C
1	+0.1	+0.1	+0.2	+0.3	+0.7	+1.1	+0.8	+0.9	+1.7	+1.1
2	+0.2	+0.2	+0.2	+0.3	+0.2	+0.4	+0.2	+0.6	+0.4	+1.0
3	+0.3	+0.7	0.0	+0.3	−0.1	+0.7	0.0	+0.4	+0.2	+0.7
4	+0.2	+0.1	+0.3	+0.4	+1.5	+2.1	+0.6	+0.7	+0.9	+1.2
5	+0.2	+1.1	+0.8	+1.5	+1.9	+1.7	+1.1	+2.3	+1.2	+1.7
6	0.0	0.0	+0.2	+0.1	0.0	+0.4	+0.4	+0.6	+1.1	+0.8
7	+0.1	+0.1	+0.2	+0.4	+0.3	+0.1	+1.1	+2.3	+0.6	+2.2
8	+0.5	+0.7	+0.6	+0.8	+1.1	+1.4	+1.0	+1.1	+1.6	+1.8
9	+0.2	+0.4	+0.5	+0.6	+0.9	+1.3	+1.4	+1.5	+2.3	+2.6
10	+0.1	+0.3	+0.4	+0.5	+0.9	+1.3	+1.3	+0.8	+3.5	+1.7
11	−0.2	+0.1	−0.3	+0.2	−1.2	+0.8	−1.0	+0.3	−0.6	+0.6
12	−0.6	−0.1	−0.5	−0.3	−1.5	−1.3	−0.9	−0.6	−1.2	−1.4
Mean	+0.09	+0.31	+0.22	+0.43	+0.39	+0.83	+0.50	+0.91	+0.98	+1.17
SEE	±0.08	±0.10	±0.10	±0.12	±0.29	±0.26	±0.23	±0.24	±0.36	±0.29
	$t = 2.66$ $p < 0.05$		$t = 3.42$ $p < 0.01$		$t = 2.69$ $p < 0.05$		$t = 2.58$ $p < 0.05$		$t = 0.76$ $p < 0.05$	

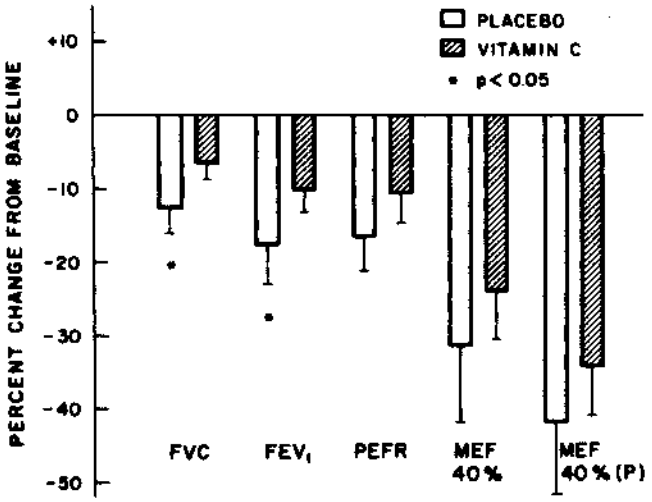

Figure 3. Percentage of changes in pulmonary function five minutes after exercise.

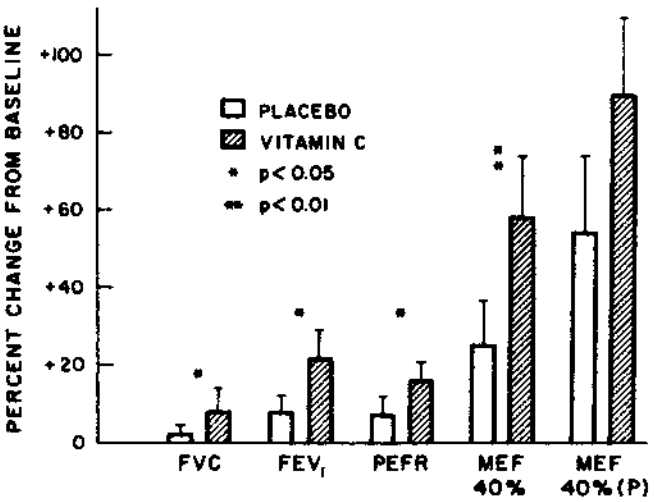

Figure 4. Percentage of changes in pulmonary function 10 minutes after metaproterenol inhalation.

that the differences in Table IV reflect the effect of ascorbic acid on EIB and not on the response to bronchodilator.

Baseline pulmonary function for the placebo and the vitamin C days measured immediately before exercise challenge are listed for all subjects in Table V. Comparisons of mean values for both days show small but significant differences between the baseline flow rates on the vitamin C and placebo days.

Discussion

Our results suggest that ascorbic acid partially protects against exercise-induced airway obstruction in subjects with asthma. This is confirmed by a smaller absolute fall in parameters of flow-volume following exercise as well as an enhanced response relative to baseline to metaproterenol after EIB has been induced. Differences in baseline flow rates between vitamin C and placebo days may be interpreted in two ways. Day-to-day variations in asthmatics are known to cause significant variations in baseline function. Such variations may have fortuitously occurred to render the vitamin C baseline lower. A second possibility is that vitamin C may exert a bronchoconstrictor effect on resting airway tone in asthmatics. Although the data is consistent with such a hypothesis previous studies with vitamin C[5,15] have not demonstrated such an effect in healthy subjects or asthmatics. This difference in baseline does not alter our interpretation of differences in lung function following exercise in that absolute changes from baseline are recorded. In fact, based on the observations of other studies[13,16] a lower baseline should normally be associated with a more marked fall in ventilatory function following exercise.

Several studies have explored the ability of ascorbic acid to attenuate various forms of induced airway obstruction other than EIB. Our results agree with those of Zuskin,[5] who demonstrated protection against histamine-induced bronchoconstriction by vitamin C. Although Kreisman et al[6] failed to find significant differ-

Table V. Comparison of Baseline Pulmonary Function on Placebo and Vitamin C Days

Subject	FVC		FEV_1		PEFR		MEF40%		MEF40%(P)	
	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C
1	3.5	3.7	2.8	2.8	6.3	6.1	2.5	2.2	2.1	1.7
2	5.0	5.1	2.8	3.0	5.5	5.7	1.4	1.4	1.3	1.2
3	4.5	4.3	2.2	2.0	4.9	4.3	1.1	0.9	1.0	0.8
4	3.4	3.4	2.4	2.1	5.2	4.1	1.6	1.2	1.7	1.2
5	5.1	4.5	2.9	2.4	6.3	6.3	1.8	1.3	1.8	1.1
6	3.5	3.5	2.8	2.7	5.9	5.2	2.8	2.3	2.6	1.5
7	3.1	2.7	2.9	2.3	6.0	5.3	3.7	2.3	4.1	2.4
8	3.5	3.1	2.1	1.8	4.3	3.9	1.1	1.0	1.0	0.9
9	3.4	3.2	2.7	2.5	6.1	5.4	2.1	1.8	1.9	1.8
10	5.8	6.1	4.2	4.4	9.1	9.7	2.8	2.9	2.2	3.0
11	3.2	2.9	2.7	2.1	6.5	5.1	2.8	1.6	3.0	1.8
12	3.8	3.7	2.5	2.5	5.7	5.6	1.6	1.8	2.0	2.4
Mean	4.0	3.9	2.8	2.6	6.0	5.6	2.1	1.7	2.1	1.7
SEE	1.0	0.9	0.5	0.7	1.2	1.5	0.8	0.6	0.9	0.7
	$t = 1.73$ $p = 0.11$		$t = 2.51$ $p < 0.05$		$t = 2.63$ $p < 0.05$		$t = 2.74$ $p < 0.05$		$t = 2.04$ $p = 0.07$	

ences when challenging asthmatics with histamine they only examined MEF40% and MEF40%(P), and as in our study they did not find significant protection using these parameters. In a study by Valic et al[17] ascorbic acid was shown to partially prevent decreases in FEV_1 occurring after exposure to flax dust, suggesting that this parameter may be more useful in demonstrating the action of vitamin C.

Our results may indicate that ascorbic acid's effects are more readily characterized by parameters such as FEV_1 or FVC and not by flow rates at low lung volumes. It has been suggested that such flow rates at low lung volumes reflect primarily small airway obstruction.[11] This may indicate that ascorbic acid's effect was more prominent in the larger airways. Our finding that PEFR was not useful in distinguishing the two days at the five minute post-exercise measurement is at variance with this interpretation. However, because PEFR is known to be effort-dependent and therefore a somewhat more variable parameter this finding does not necessarily rule out this explanation.

In a related study Kordansky et al[7] found that ascorbic acid did not protect against ragweed-antigen-induced bronchospasm as measured by changes in FEV_1. This negative study may indicate that the pattern and perhaps mechanism of airway obstruction initiated by antigen challenge is different from that stimulated by exercise or flax dust.

Four general mechanisms have been invoked to explain ascorbic acid's effects on smooth muscle contractile states. These include (1) the effect of vitamin C in accelerating the metabolism of histamine,[2,18-22] (2) the direct effect of vitamin C on smooth muscle,[4,23-25] (3) vitamin C's effect on cyclic AMP metabolism[26] and (4) the modulation of prostaglandin production by vitamin C.[27-29] These effects seen both *in vivo* and *in vitro* suggest indirect or direct mechanisms by which vitamin C could attenuate bronchospasm following exercise in asthmatics.

Whether the partial protection of ascorbic acid reflects non-specific bronchodilation or a modulation of the underlying mechanism of EIB cannot be decided from this study. Although the effect of vitamin C that we have demonstrated does not suggest that by itself this agent offers potent protection against EIB its role should be explored further as a pharmacologic agent potentially useful in investigating the mechanisms involved in EIB and as a possible adjunct to standard therapy.

Acknowledgment

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Requests for reprints should be addressed to:
E. Neil Schachter, M.D.
Department of Internal Medicine
Pulmonary Section
Yale University School of Medicine
P.O. Box 3333
333 Cedar Street
New Haven, Connecticut 06510