

Where is the allergic reaction in ragweed asthma?

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As ragweed pollen grains are 20 μ in diameter and too large to penetrate into the bronchi, it is conceivable that an allergic reaction in the nose might cause asthma through reflex or other mechanisms. Eight patients with ragweed asthma were challenged by direct application to the nasal mucosa of solutions of increasing concentrations of histamine and, on another day, of increasing amounts of dry ragweed pollen. One to 20 mg. of histamine was required to produce sneezing, rhinorrhea, and nasal stuffiness, but a drop in FEV₁ was not observed in any subject. Pollen grains applied directly to the nasal mucosa provoked severe hay fever, but doses up to 1,500 grains did not cause a drop in FEV₁. On the other hand, inhalation of 100 to 500 grains through the mouth on a different day did provoke coughing and a 20 per cent drop in FEV₁. Up to 5,000 grains placed on the posterior third of the tongue provoked drop in FEV₁ in 2 of the 8 patients. We conclude that ragweed asthma is not initiated by an allergic reaction in the nose. If obstruction of small airways arises through reflex mechanisms, the sensory arc of this reflex originates below the oropharynx.

Although aerosols of ragweed extract cause asthma, pollen grains are 20 μ in diameter and too large to penetrate to the bronchi. Most will lodge in the nose and upper airway.

For the past 100 years the importance of the nasobronchial reflex as a causative factor in asthma has been debated. Early experiments suggested that irritation of the nose caused bronchoconstriction, although some authors^{1, 2} reported no effect. Early investigators used irritants such as caustic chemicals on the nasal mucosa, but more recently Nadel and Widdicombe,³ using mechanical stimulation in cats, found increased total lung resistance after stimulation of the laryngeal mucosa but no effect from stimulation of the nasal mucosa. On the other hand, Kaufman and Wright⁴ found that silica particles applied to the nasal membranes of nonatopic persons increased airway resistance slightly. Patients with asthma have increased sensitivity to aerosols of histamine and many irritants,⁵ and it is conceivable that the response to nasal stimulation might also be exaggerated.

Almost all particles larger than 10 μ are removed from the airstream during its passage through the nose and, therefore, have little probability of penetrating to the bronchi.⁶ Ragweed pollen grains are about 20 μ in diameter. Almost all of

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TABLE I. Bronchial reactions to application of histamine or pollen to the nasal mucosa

Histamine 5 mg.	Ragweed pollen 1,500 grains
0/8*	0/8

*Number of subjects with a decrease in FEV₁ of more than 20 per cent per number of subjects tested.

them will be deposited in the upper airway and presumably an allergic reaction will be initiated there. The objective of this study was to see if ragweed pollen would provoke asthma by reacting in the upper airway.

METHODS

We studied 8 adult, ragweed-sensitive patients who had asthma during the previous ragweed season. The studies were done at the same time in the morning, during the winter when they were free from symptoms. Seven of the 8 were receiving injection treatment with ragweed extract. The duration of treatment and dose of antigen varied greatly. At least 48 hours elapsed between each challenge. The subjects took no medication for at least 24 hours, and none was steroid dependent. Histamine was applied to the nasal mucosa in serially increasing doses of 0.1 to 5 mg. of the base. Blood pressure and pulse were determined every 15 minutes. The number of pollen grains contained in a small scoop holding 0.03 ml. was determined by counting in a hemocytometer. Dilutions were prepared by mixing the dry pollen with powered lactose. Pollen was applied directly to the nose or the tongue with the scoop. Dry pollen was applied to the nasal mucosa in increasing amounts from 100 to 1,500 grains. All subjects ultimately received the maximum dose. On another day, 1,500 to 5,000 grains of pollen was applied to the posterior third of the tongue, and the patients drank one glass of water each. Finally they were challenged with oral inhalations of increasing amounts of pollen up to a dose of 1,500 grains. The pollen was administered by delivery from a side arm of a Venturi tube into the stream of air during a deep inspiration. Most of the pollen was deposited on the tongue and palate. Penetration into the trachea was uncertain, so if the inhalation of dry pollen was unsuccessful in producing a drop in FEV₁ the patients were challenged with an aerosol of a suspension of ragweed pollen in isotonic saline delivered from a DeVilbiss No. 40 nebulizer. The bronchial response was estimated every 15 minutes using a McKessen Vitalor. A decrease of 20 per cent in one-second forced expiratory volume (FEV₁) was considered a positive response.

RESULTS

One to 5 mg. of histamine base applied in drops to the nasal mucosa was required to produce marked sneezing, thin watery rhinorrhea, and nasal stuffiness leading to complete blockage of the nasal airway on the side of application. None of the patients showed a significant decrease in FEV₁ (Table I). There were no changes in blood pressure or pulse, but one patient did develop flushing of the face and edema of the uvula. Several also had bilateral conjunctivitis and obstruction of the contralateral nasal airway.

Dry ragweed pollen grains applied to the nasal mucosa provoked severe hay fever symptoms, but even the maximum dose (1,500 grains) did not produce a significant drop in FEV₁ (Table I).

Up to 5,000 dry ragweed pollen grains placed on the posterior third of the tongue caused the FEV₁ to fall greater than 20 per cent in only 2 of 8 patients (Table II). On a later occasion these 2 patients were given the same amount of

TABLE II. Bronchial reactions to pollen applied to the tongue or inhaled

Oropharynx 1,500 grains	Inhaled dry		Aerosolized pollen suspension 800 grains
	Grains	No.	
	200	1	
	800	1	
	1,500	2	
Total 2/8*	4/8		4/4†

*Number of subjects showing a decrease in FEV₁ of more than 20 per cent per number of subjects tested.

†The 4 subjects who did not react to the dry pollen.

pollen in a gelatin capsule, and no decrease in FEV₁ occurred. Four of 8 patients had 20 per cent or more decrease in FEV₁ after inhalation of 200 to 1,500 dry pollen grains. The other 4 patients required inhalations of an aqueous suspension of 800 pollen grains for a significant decrease in FEV₁.

DISCUSSION

With the exception of the 2 patients who had asthma after pollen was placed on the back of the tongues, the only successful route of challenge was inhalation through the mouth. These 2 subjects might well have inhaled a few grains from the tongues, since they did not develop asthma from the same amount of pollen applied to the nasal mucosae or three times as much swallowed in a capsule. Both the ragweed pollen and histamine severely irritated the nasal membranes, producing a profuse rhinorrhea and sneezing, but did not stimulate significant bronchial obstruction. We therefore believe ragweed asthma is not initiated by an allergic reaction in the nose. Furthermore, it is unlikely that antigen absorbed from the mucosa of the upper airway and carried to the bronchi by the circulation causes asthma by an allergic reaction in the bronchi.

We cannot say how many of the pollen grains inhaled through the mouth from the Venturi device actually reached or passed the larynx, but it must have been a very small number because the tongue and palate were coated with pollen. The aerosol from the DeVilbiss nebulizer contained not only pollen grains but also droplets 5 μ and smaller of soluble antigen extracted from the pollen. These droplets doubtless penetrated much farther into the lung than the pollen and could cause bronchial obstruction.

We cannot exclude the possibility that fragments of ragweed pollen or other parts of the ragweed anther which carry the antigen⁷ may be in the ambient air during the ragweed season. If there are such amorphous ragweed particles 1 to 5 μ in size, they could penetrate to the bronchi and initiate the allergic reaction there.

Reflex bronchoconstriction initiated by sensory neurons in the bronchial mucosa with the efferent arc in the vagus has been well demonstrated in animals.⁸ In man similar reflex bronchoconstriction seems to occur; it is greatly accentuated in patients with asthma and is blocked by atropine.⁹ Atropine also partially blocks bronchoconstriction induced by aerosols of antigen solutions.¹⁰

In any event, we can conclude that, if obstruction of airways in asthma arises through reflex mechanisms, the sensory arc of this reflex originates below the oropharynx.

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