

The epidemiologic relationship of clinical nasal allergy to eosinophils and to goblet cells in the nasal smear

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Three hundred and fifty-four Vancouver primary school children were studied. Half had a hearing loss and half were control subjects with normal hearing. A trained nonmedical interviewer presented a precoded questionnaire of allergy symptoms to their mothers, and a pediatric allergist examined the children's noses for signs of allergy. Two nasal smears were made from each and were numbered consecutively. One was stained by Hansel's and the other by Papanicolaou's method. A technician scored the former positively if there were 10 eosinophils per high power field in any 2 high power fields and the latter positively if 6 goblet cells were found in the entire slide. There was a highly significant association between clinical evidence of nasal allergy and a nasal secretion eosinophilia. No significant association could be found between clinical evidence of nasal allergy and goblet cells or between eosinophils and goblet cells. The presence of goblet cells does not appear to help in making the diagnosis of nasal allergy in children.

Both history and physical findings may be equivocal in nasal allergy, and skin tests are not always reliable.¹ This is particularly so when a food is the offending allergen.² Evermann³ reported that nasal-secretion eosinophilia was a useful diagnostic aid being more commonly found in patients who were hypersensitive, as diagnosed by positive skin tests or by characteristic clinical findings, than in those who were not hypersensitive. Since then, nasal smears have

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been made when the cause of nasal symptoms is in doubt, and the finding of an eosinophilia has been taken as corroborative evidence of allergy. There still remained a proportion of patients with symptoms suggestive of nasal allergy, but with inconclusive physical signs and skin tests, and no eosinophils in the nasal smear. In 1959, Bryan and Bryan⁴ reported a marked increase in goblet cells as a constant and reliable feature in nasal smears from allergic patients. This has become accepted by some as a useful diagnostic procedure.^{5, 6}

The present study was undertaken to find whether there is, indeed, an association between clinical evidence of nasal allergy and the presence of eosinophils or of goblet cells in the nasal smear.

METHODS

Population sample

Three hundred fifty-four Vancouver primary school children were studied as part of a survey of hearing loss: Half had impaired hearing and half were control subjects with normal hearing. Details of the procedure for selecting the schools and a probability sample of children with hearing loss were given elsewhere.^{7, 8} In this present analysis both groups are combined to examine the relationship between nasal allergy and nasal smear cytology.

Season of examination

In order to minimize the effect of season, 210 children were seen in the winter months, between November and February, and 144 were seen between March and June, the spring pollen season in Vancouver.⁹ The results were pooled for data analysis.

Study by the research team

The trained nonmedical interviewer interrogated mothers in one room of the school and the pediatric allergist examined the children in another room. Nasal smears were numbered consecutively and later processed in a laboratory by the technician. No member of the team knew which children had a hearing loss, which were control subjects, or what anyone else had found.

The questionnaire. A trained nonmedical interviewer asked the mother whether she had noticed any of 6 symptoms in her child during the past 12 months and whether they had been present for as long as 3 weeks at a time. The symptoms were much nose rubbing, fits of sneezing, snorting or nasal stuffiness, and sniffing or runny nose. If the mother had noticed a nasal discharge, she was asked whether it was clear or colored.

The physical examination. The pediatric allergist inspected the child's nose and recorded the condition of the turbinates as follows: (1) wet if several broad strands of mucus adhered to them or if there was a pool of mucus; (2) pale or violaceous if one or both of these characteristics were marked, as compared with the mucous membranes of the lower lip; and (3) swollen if one or more bulged out far enough to touch the nasal septum. He marked a nasal crease as present if there was a permanent line across the top of the nose in the position where a crease formed when the tip of the nose was pushed up.

Details of the questionnaire and physical examination have been given elsewhere.⁸

The nasal smears.

1. One smear was made from nasal secretions blown onto a cellophane square. If the child was unable to produce enough secretion, a cotton tipped toothpick was inserted along the floor of one nostril and left for one minute. The secretions were then transferred to a glass slide and teased out with another toothpick. The smear was fixed with 95 per cent methyl alcohol and later stained by Hansel's method.¹⁰ It was mounted in "Harleco synthetic resin," and a 22 mm. by 40 mm. glass cover slip was affixed. With the use of the low power magnification of the microscope (10 by 10), the technician examined all the cells under the glass cover slip. Where eosinophils were found in maximum concentration, they were counted with a $\times 10$ wide angle eye piece and a $\times 40$ oil immersion objective. The area seen with this combination corresponds to the high power field commonly used in clinical practice. When 10 or more eosinophils were seen in any 2 separate high power fields, the slide was graded as positive for eosinophils.

2. Another smear was made of secretion and cells wiped from the nasal mucous membrane. It was immediately fixed with Cytospray and was later stained by Papanicolaou's method.¹¹ A glass cover slip was affixed as previously mentioned. With the low power magnification (10×10), all cells under the cover slip were examined. Any resembling goblet cells were inspected under oil immersion (10×100). They were counted as goblet cells only if they were columnar epithelial cells with edematous and vacuolated cytoplasm.⁴ If 6 such cells were found, the slide was scored positively for goblet cells.

Definition of nasal allergy

This was made a priori to eliminate bias.

A child with Probable Nasal Allergy was one who had any of certain combinations of symptoms and signs. Each combination was considered to be strongly suggestive of allergy, rather than of some other nasal condition. An attempt was made to exclude combinations of a symptom and sign which probably indicate the same feature, e.g., nose rubbing and nasal crease.

The following were the combinations: (1) a history of nose rubbing and clear nasal discharge, with the finding of wet turbinates; (2) a history of nose rubbing, with the finding of pale or violaceous turbinates; (3) a history of nose rubbing, with the finding of swollen turbinates; (4) a history of fits of sneezing, with the finding of wet turbinates; (5) a history of fits of sneezing, with the finding of pale or violaceous turbinates; (6) a history of fits of sneezing, with the finding of swollen turbinates; (7) a history of fits of sneezing, with the finding of a nasal crease; (8) a history of snorting or stuffed up nose, with the finding of pale or violaceous turbinates; (9) a history of snorting or stuffed up nose, with the finding of a nasal crease; (10) a history of sniffing or runny nose, with the finding of pale or violaceous turbinates; and (11) a history of sniffing or runny nose, with the finding of a nasal crease.

One with Possible Nasal Allergy was a child who did not meet the above

definition, but did have one or more symptoms and/or signs listed in it. A child with No Nasal Allergy had none of these symptoms or signs.

Statistical method

The data reported here were tested for statistical significance by Goodman's gamma test.^{12, 13} This test is appropriate when the classification systems have an inherent and meaningful order. A *significant* value occurred when the 95 per cent confidence interval of γ did not include zero ($P \leq 0.05$); a *highly significant* value occurred when the 95 per cent confidence interval of γ did not include zero ($P \leq 0.01$).

RESULTS

There was a highly significant statistical association between nasal allergy, as defined, and the presence of eosinophils in the nasal smear (Table I). An eosinophilia was found in 32 per cent of those with Probable Nasal Allergy and in 17 per cent of those with No Nasal Allergy. Of the 8 individual symptoms and signs of allergy, nose rubbing, sneezing, and wet and swollen turbinates were highly significantly related to eosinophils, sniffing or runny nose was significantly related, and the other 3 showed no significant relationship (Table II).

There was no relationship between goblet cells and any of the following: nasal allergy, as defined (Table III), any of the individual symptoms or signs (Table IV), or eosinophils (Table V).

DISCUSSION

The prevalence of nasal secretion eosinophilia in this sample of school children increased as the clinical evidence for nasal allergy became stronger, at least in terms of a compounding of symptoms or signs. It was almost twice as high when symptoms and signs occurred in combinations suggestive of nasal allergy as when there were none. This finding is compatible with the view that the union of antigen with reagin exerts an eosinophilotactic effect.¹⁴

The statement by Bryan and Bryan⁴ that a marked increase in goblet cells is a constant and reliable feature in nasal allergy has not been substantiated in this study population. There was, for example, little difference noted in the

Table I. *Relationship between nasal smear eosinophils and nasal allergy*

	<i>10 eosinophils per high power field in any 2 high power fields</i>			
	<i>Present</i>		<i>Absent</i>	
	<i>No.</i>	<i>Per cent</i>	<i>No.</i>	<i>Per cent</i>
Probable Nasal Allergy	22	32.4	46	67.6
Possible Nasal Allergy	49	28.8	121	71.2
No allergy signs or symptoms	20	17.2	96	82.8
Total	91	25.7	263	74.3

Significance: $\gamma = 0.2577$ (highly significant).

Table II. Relationship between nasal smear eosinophils and signs and symptoms of nasal allergy

	10 eosinophils per high power field in any 2 high power fields					
	Present		Absent			
	No.	Per cent	No.	Per cent	γ	Significance
<i>Nose rubbing</i>						
Yes	17	41.5	24	58.4	0.3917	Highly significant
No	74	23.6	239	76.4		
Total	91	25.7	263	74.3		
<i>Sneezing</i>						
Yes	15	60.0	10	40.0	0.6663	Highly significant
No	76	23.1	253	76.9		
Total	91	25.7	263	74.3		
<i>Snorting/stuffed nose</i>						
Yes	35	30.7	79	69.3	0.1856	Nil
No	56	23.3	184	76.7		
Total	91	25.7	263	74.3		
<i>Sniffing/runny nose</i>						
Yes	31	32.6	64	67.4	0.2327	Significant
No	60	23.2	199	76.8		
Total	91	25.7	263	74.3		
<i>Wet turbinates</i>						
Yes	25	47.2	28	52.8	0.5199	Highly significant
No	66	22.0	234	78.0		
Total*	91	25.8	262	74.2		
<i>Pale/violaceous turbinates</i>						
Yes	17	30.4	39	69.6	0.1422	Nil
No	73	24.7	223	77.7		
Total*	90	25.6	262	74.4		
<i>Swollen turbinates</i>						
Yes	29	36.7	50	63.3	0.3368	Highly significant
No	61	22.3	212	77.7		
Total	90	25.6	262	74.4		
<i>Nasal crease</i>						
Yes	33	30.3	76	69.7	0.1614	Nil
No	58	23.9	185	76.1		
Total*	91	25.9	261	74.1		

*Some information left blank for clinical signs.

Table III. Relationship between nasal smear goblet cells and nasal allergy

	6 goblet cells per smear			
	Present		Absent	
	No.	Per cent	No.	Per cent
Probable Nasal Allergy	45	59.2	31	40.8
Possible Nasal Allergy	101	62.3	61	37.7
No Nasal Allergy	61	53.0	54	47.0
Total*	207	58.6	146	41.4

Significance: $\gamma = 0.0974$ (not significant).

*1 goblet cell count not available.

Table IV. Relationship between nasal smear goblet cells and signs and symptoms of nasal allergy

	6 goblet cells per smear				γ	Significance
	Present		Absent			
	No.	Per cent	No.	Per cent		
<i>Nose rubbing</i>						
Yes	23	56.1	18	43.9	-0.0615	Nil
No	185	59.1	128	40.9		
Total	208	58.8	146	41.2		
<i>Sneezing</i>						
Yes	17	68.0	8	32.0	0.2112	Nil
No	191	58.1	138	41.9		
Total	208	58.8	146	41.2		
<i>Snorting/stuffed nose</i>						
Yes	62	54.4	52	45.6	-0.1314	Nil
No	146	60.8	94	39.2		
Total	208	58.8	146	41.2		
<i>Sniffing/runny nose</i>						
Yes	52	54.7	43	45.3	-0.1121	Nil
No	156	60.2	103	39.8		
Total	208	58.8	146	41.2		
<i>Wet turbinates</i>						
Yes	31	58.5	22	41.5	-0.0036	Nil
No	176	58.7	124	41.3		
Total*	207	58.6	146	41.4		
<i>Pale/violaceous turbinates</i>						
Yes	33	58.9	23	41.1	0.0100	Nil
No	173	58.4	123	41.6		
Total*	206	58.5	146	41.5		
<i>Swollen turbinates</i>						
Yes	51	64.6	28	35.4	0.1474	Nil
No	157	57.5	116	42.5		
Total*	208	59.1	144	40.9		
<i>Nasal crease</i>						
Yes	70	64.2	39	35.8	0.1546	Nil
No	138	56.8	105	43.2		
Total*	208	59.1	144	40.9		

*Some information left blank for clinical signs.

prevalence of goblet cells between the group with Probable Nasal Allergy and the group with No Nasal Allergy. Nor was a gradient found in the occurrence of goblet cells with increasing likelihood of nasal allergy, as we defined it. Bryan and Bryan⁴ found large numbers of goblet cells when many eosinophils were present; in our population goblet cells were found as frequently when an eosinophilia was absent as when it was present.

The normal nasal epithelium is made up of goblet and ciliated columnar cells, and both types are found in the nasopharyngeal washings from normal people.¹⁵ Larger numbers of these cells are obtained when the nasal mucosa is wiped. The reasons for an increase in the proportion of goblet cells in some of our smears is not known. In several it was the predominating cell. Reed¹⁶ found

Table V. *Relationship between nasal smear goblet cells and eosinophils*

10 eosinophils per high power field in any 2 high power fields	6 goblet cells per smear			
	Present		Absent	
	No.	Per cent	No.	Per cent
Present	53	58.2	38	41.8
Absent	154	58.8	108	41.2
Total*	207	58.6	146	41.4

Significance: $\gamma = 0.0111$ (not significant).

*1 goblet cell count not available.

that an irritant, sulfur dioxide, caused an increase in the number of goblet cells in the peripheral airways of rats. The same may be true for the human nose.

The failure to substantiate the relationship between goblet cells and nasal allergy in this study is of more than clinical interest. Those of us who are clinicians do not see a random sample of a population of diseased persons. Therefore, when we study the relationship between 2 factors, we may be misled by a spurious association which would not be seen if the relationship was viewed epidemiologically, i.e., from the total diseased and nondiseased population. This spurious relationship, often called the Berkson fallacy,¹⁷ would occur if 2 factors were unrelated to each other but were in turn each independently related to that which is being studied in the clinical sample. For example, suppose persons with nasal allergy and irritative conditions of the respiratory mucosa were more prone to see an allergist; then eosinophils and goblet cells might occur more frequently together in any group of sufferers of nasal allergy which are studied out of a clinic population, even though these 2 findings are unrelated to each other.

CONCLUSION

A strong association between clinical evidence of nasal allergy and a nasal secretion eosinophilia has been confirmed.

There was no significant association between goblet cells and the symptoms and signs of nasal allergy, either collectively or individually, or between goblet cells and eosinophils. The presence of goblet cells does not appear to help in making the diagnosis of nasal allergy in children.

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