

Prognosis of positive allergy skin tests in an asymptomatic population

A three year follow-up of college students

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Histories of allergy were obtained from 1,836 freshmen college students, and 1,243 of these students were also scratch tested with 15 allergens. Three years later, 1,352 of these students participated in a follow-up study designed to determine new allergies which had developed since their entrance into college as freshmen. Sixty-four new cases of hay fever, nonseasonal allergic rhinitis, and/or bronchial asthma were identified in the population. The frequency of new hay fever that developed among 614 senior students who had no clinical manifestation of allergy as freshmen is over ten times higher in students with initially positive pollen scratch tests (18.2 per cent) than in students with negative pollen scratch tests (1.7 per cent). Students with a 2+ or greater pollen scratch test reaction subsequently developed hay fever significantly more frequently than students with no positive pollen scratch tests. The data also suggest that the positive pollen scratch test reaction precedes the onset of clinical symptoms of hay fever. Cumulative prevalence rates of asthma, nonseasonal allergic rhinitis, and seasonal hay fever by age of onset of each condition are given. Of the students who first had onset of hay fever and were at risk to develop asthma, only 5.3 per cent have subsequently developed asthma.

Little work has been done to determine the risk of developing an allergic condition, particularly hay fever, in individuals who do not manifest clinical symptoms of an allergy but who have positive skin test reactions to specific pollens. The cutaneous reaction is used regularly by the allergist as an aid in establishing the diagnosis of pollinosis in patients who express clinical symptoms of an allergy. However, the meaning of positive cutaneous reactions in clinically asymptomatic individuals is not yet established.

Patients with one allergy may develop subsequently another allergy. Chambers and Glaser¹ followed up 68 private patients who had various types of clinical allergies as well as positive skin test reactions to ragweed pollen extract in the absence of ragweed pollinosis. Over 50 per cent of these patients developed ragweed hay fever. Of those affected, 64 per cent of the patients developed symptoms within five years and 88 per cent developed symptoms within ten years.

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Are scratch tests useful to identify a segment of the population which has a higher risk for developing clinical symptoms of an allergy? How predictive of clinical allergies are positive scratch tests for individuals who, as yet, have not manifested clinical symptoms?

We have approached these questions through studies of allergies and scratch test reactions in college students. Our² initial study was done on 1,836 freshmen students (99.2 per cent) who entered Brown University and Pembroke College during two consecutive years. Clinical symptoms of bronchial asthma and/or allergic rhinitis were reported by 25.0 per cent of these freshmen. We completed skin scratch tests on two thirds of the freshmen population. Of the students who had no clinical symptoms of any allergy, 17 per cent had a positive reaction to at least one of the 15 commercial allergens which we used.

We now report the results of a follow-up study which was done on senior students three years after their initial study as freshmen.

MATERIALS AND METHODS

Initial study of freshmen students²

The following information and criteria, established in our initial study of freshmen students, are significant for the follow-up study:

1. Skin tests were done by medical personnel on the anterior forearm of freshmen students by the scratch technique. Fifteen glycerinated extracts* were used: birch, 1/20; elm, 1/20; maple, 1/20; timothy, 1/20; June grass mixture, 1/20; short ragweed, 1/20; giant ragweed, 1/20; feather mixture, 1/10; kapok, 1/10; cat dander, 1/10; dog dander, 1/10; cow's milk, 1/10; egg white, 1/10; wheat, 1/10; *Alternaria*, 1/10 (used only during the second year of study); and a saline control. Scratch test sites were read by an allergist 20 minutes after application of extracts. Positive sites were evaluated on a reading scale of 1+ to 4+; 1+ equals erythema definitely larger than the control, 2+ equals moderate erythema with a central wheal, 3+ equals marked erythema with beginning small pseudopods, and 4+ equals marked erythema with large wheals and pseudopods.³

2. Information was ascertained from freshman students in the following ways: (1) personal contact with freshmen to complete an initial questionnaire of their personal and family history of allergy; (2) corroboration of the information given by freshman by correspondence with their parents; and (3) additional information on histories obtained by personal interview of freshmen at the time of scratch tests. The diagnosis of allergy was established by using information given by students and parents, as well as by consulting the results of the physical examination and chest roentgenogram which were given to each student during the first week of school at the University Health Center. However, the results of scratch tests were not used to classify individuals as affected with a given condition.

3. The following criteria were used to classify specific allergy diagnoses: (1) bronchial asthma—a history of recurrent episodes of wheezing and dyspnea not caused by any known organic condition. (All students in this group had been previously and independently diagnosed as asthmatic by their family physician.) (2) hay fever (seasonal allergic rhinitis)—a history of watery, itchy eyes, rhinorrhea, and sneezing occurring during the same seasonal period for at least two consecutive years. (3) nonseasonal allergic rhinitis—a history of similar symptoms as hay fever, but occurring nonseasonally and associated with exposure to particular antigens, e.g., animal danders.

Follow-up study of senior students

The follow-up study was conducted three years after the initial information was obtained from freshmen. Efforts were made to contact all students who had participated in the fresh-

*Products of Hollister-Stier Labs.

TABLE I. The college students, classified as freshmen by the presence of allergy, who were followed up as seniors

Study	Sex	Group 1 (A/HF/AR)	Group 2 (other allergy)	Group 3 (no allergy)	Total
Initial study as college freshmen	Men	333	106	840	1,279
	Women	126	74	357	557
Total		459	180	1197	1,836
3 Year follow-up study as college seniors	Men	234	84	617	935
	Women	87	59	271	417
Total		321	143	888	1,352
% Follow-up in each group		69.9	79.4	74.2	73.6

Group 1 includes students with asthma (A), seasonal hay fever (HF), and/or nonseasonal allergic rhinitis (AR). Group 2 includes students with an allergy other than those specified in Group 1. Group 3 includes students with no clinical symptoms of allergy.

men study. Most students who enter Brown University and Pembroke College complete their four-year program, and a great majority of the students were still on campus. Students who had left the University were traced by sending requests for follow-up information to their home address.

A two-page follow-up questionnaire was used. Each student was asked to give the following information for the three-year period covered by the follow-up: (1) any type of allergy or problem related to an allergy which had developed, (2) the season, if any, of occurrence, (3) the symptoms manifested, (4) the year of onset and duration of symptoms, and (5) the causes of symptoms if they were known. Skin tests were not repeated in the follow-up study.

RESULTS

Our² initial study of 1,836 freshmen students included 1,279 men and 557 women. Some type of allergy was reported by 34.8 per cent of these freshmen. The frequency of bronchial asthma was 5.3 per cent; seasonal hay fever, 21.1 per cent; and nonseasonal allergic rhinitis, 5.2 per cent. One or more of these three allergies was reported by 25.0 per cent of the freshmen population.

We adopted the following grouping for studying the freshmen population, and this classification has been continued in our follow-up study of seniors: Group 1—students with asthma, hay fever, and/or nonseasonal allergic rhinitis; Group 2—students with an allergy other than those specified in Group 1, for example, atopic eczema, urticaria, food allergy, and drug allergy; Group 3—students with no clinical manifestations of any allergy (asymptomatic).

Table I gives the number of freshmen in each group and the subsequent number of seniors who participated in the follow-up study. The 1,352 seniors represent 73.6 per cent of the freshmen population. Essentially proportional numbers of seniors are followed up in Groups 1, 2, and 3.

We were able to scratch test 67.7 per cent of the freshmen (1,243 students). The proportion of this scratch-tested population who participated in the follow-up study was 79.6 per cent (Table II). Essentially equivalent sampling has occurred among each group of students, as well as among men and women students.

Students who were not skin tested but who did participate in the freshmen

TABLE II. Students who were scratch tested as freshmen and who participated in the follow-up study as seniors

	Group 1 (A/HF/AR)		Group 2 (other allergy than A/HF/AR)		Group 3 (No allergic manifestation)		Total	
	No. ST	No. FU	No. ST	No. FU	No. ST	No. FU	No. ST	No. FU
Men	245	189	87	73	545	433	877	695
Women	87	65	59	48	220	181	366	294
Total	332	254	146	121	765	614	1243	989
% FU in each group		76.5		82.9		80.3		79.6

A = asthma, HF = seasonal hay fever, AR = nonseasonal allergic rhinitis; ST = scratch tested as freshmen with 15 allergens; FU = followed up by history as seniors.

TABLE III. New cases of asthma, hay fever, and nonseasonal allergic rhinitis reported by senior students

New allergic symptoms reported by seniors	Information obtained from freshmen students		
	Allergy history only	Allergy history and scratch tests	Totals
Hay fever (HF)	8	34	42
Asthma (A)	1	1	2
Nonseasonal allergic rhinitis (AR)	2	15	17
Combinations of these allergic symptoms*		3*	3*
Total number of seniors with new allergic symptoms	11	53	64
Number of senior students followed up	363	989	1,352
% of Group	3.0	5.4	4.7

*Includes one of each of the following combinations: HF + A, HF + AR, A + AR.

study by giving an allergy history were also followed up. Only 61.2 per cent of this group returned follow-up information (363 out of 593 students).

Table III lists new cases of bronchial asthma, seasonal hay fever, and nonseasonal allergic rhinitis which senior students developed during the three-year period covered by the follow-up study. Sixty-four students (4.7 per cent) developed at least one of these allergies, including 44 (3.3 per cent) with symptoms of seasonal hay fever, 4 (0.3 per cent) with symptoms of bronchial asthma, and 19 (1.5 per cent) with symptoms of nonseasonal allergic rhinitis. The proportion of newly affected men and women students was not significantly different (4.9 per cent male to 4.3 per cent female). However, seniors who were scratch tested as freshmen reported a higher frequency of these new allergies than seniors who were not scratch tested as freshmen (Table III).

In addition, 10 seniors (8 male, 2 female) reported allergies which they had developed earlier in life but which they had not reported as freshmen. Eight

TABLE IV. New allergies reported by college seniors who were scratch tested as freshmen

Classification of students as freshmen		Seniors studied in follow-up				
		Total seniors	Number of new cases of A, HF, AR			
Presence of allergy	Scratch tests		Total	HF	AR	A
Group 1 (A, HF, &/or AR)	All negative (%)	93	5 5.4	2 7.1*	3 4.2*	0 —
	One or more positive (%)	161	10 6.2	3 15.0*	7 5.6*	1 0.8*
Group 2 (other allergy than A, HF, AR)	All Negative (%)	88	5 5.7	3 3.4	2 2.3	0 —
	One or more positive (%)	33	3 9.1	2 6.1	1 3.0	2 6.1
Group 3 (No clinical symptoms of allergy)	All negative (%)	506	11 2.2	9 1.8	2 0.4	0 —
	One or more positive (%)	108	19 17.6	18 16.7	2 1.9	0 —

A = bronchial asthma, HF = seasonal hay fever, AR = nonseasonal allergic rhinitis.

*Per cent based on the number of seniors who did not have this allergy as freshmen: Negative scratch test Group—HF absent in 28, AR absent in 72, A absent in 72; positive scratch test Group—HF absent in 20, AR absent in 126, A absent in 121.

of these allergies were hay fever and two were asthma. These cases are not included with those which developed during the three year follow-up period. They do not significantly affect the initial frequencies of hay fever and asthma which were reported by freshmen students.

In Table IV new cases of asthma, hay fever, and nonseasonal allergic rhinitis, which were reported by senior students, are tabulated in relation to two criteria: (1) presence or absence of clinical symptoms of an allergy as freshmen and (2) positive or negative scratch test reactions as freshmen. These data were collected from 989 seniors, 254 of whom belong to Group 1 (asthma, hay fever, and/or nonseasonal allergic rhinitis), 121 to Group 2 (an allergy other than those specified in Group 1), and 614 to Group 3 (no clinical symptoms of allergy). In all instances new cases of asthma, hay fever, and nonseasonal allergic rhinitis occur with a higher frequency among students who had been shown, as freshmen, to have at least one positive scratch test reaction, rather than among students who had all negative scratch test reactions (Table IV). However, only one of these differences is statistically significant. Group 3 students who had no clinical manifestation of allergy as freshmen have developed symptoms of seasonal hay fever significantly more often ($p < 0.01$) if they had had at least one positive scratch test in the battery of 15 allergens used to test freshmen students.

Seven pollens were used in our test battery of allergens. In Table V data are reclassified to show the risk of developing hay fever for each group of students when only pollen scratch test reactions were evaluated. New cases of hay fever occurred significantly more ($p < 0.01$) only in Group 3, among asymptomatic students who had positive pollen scratch tests (18.2 per cent) than among asymptomatic students who had negative pollen scratch tests (1.7 per

TABLE V. Prognosis of a positive pollen scratch test in the development of hay fever

Classification as freshmen	Risk of developing hay fever						
	Number with a positive pollen scratch test	New cases of hay fever		Number with negative pollen scratch tests	New cases of hay fever		p Value*
		Number	%		Number	%	
Group 1 (A or AR with- out HF)	16	2	12.5	32	2	6.3	NS
Group 2 (other allergy than A, HF, AR)	30	2	6.7	91	3	3.3	NS
Group 3 (no clinical symp- toms of allergy)	99	18	18.2	515	9	1.7	<0.01

A = bronchial asthma, HF = seasonal hay fever, AR = nonseasonal allergic rhinitis.

*p less than 0.01 = highly significant; NS = not significant.

TABLE VI. New cases of hay fever and degree of pollen reaction in students who initially had no clinical manifestation of allergy

Maximum degree of scratch test reactions to any of 7 pollens	Group 3 students (No clinical symptoms of allergies)		
	Number followed up	New cases of hay fever	
		Number	%
Negative (all pollens)	515	9	1.7
1+	31	2	6.5
2+	38	6	15.8
3+	23	7	30.4
4+	7	3	42.9
Total	614	27	

cent). The season in which symptoms occurred correlated with the season associated with the positive pollen skin test in 16 out of 18 individuals.

In Table VI, asymptomatic freshmen who developed new symptoms of hay fever are classified by their degree of scratch test reactivity to pollens. This classification shows that as reactivity to pollens increases, the frequency of asymptomatic students who developed new symptoms of hay fever also increases. Among students who had negative scratch test reactivity to all pollens, 1.7 per cent developed symptoms of hay fever. In like manner, of those with 1+ pollen reactivity, 6.5 per cent developed hay fever; 2+ reactivity, 15.8 per cent; 3+, 30.4 per cent; and 4+, 42.9 per cent. No statistically significant differences were found when these frequencies of new hay fever were compared between adjacent groups, i.e., 0 to 1+, 1+ to 2+, 2+ to 3+, and 3+ to 4+. However, differences between alternate groups were significant. The 2+ group had significantly more students who developed symptoms of hay fever than did the group who had all negative pollen scratch tests ($p < 0.01$); also, the 3+ group was significantly higher than

TABLE VII. Prognosis of scratch tests in the development of nonseasonal allergic rhinitis

Scratch test	Freshmen with asthma and/or hay fever (Group 1)			
	Number followed up	New cases of AR		p Value*
		Number	%	
Positive to pollen	115	3	2.6	NS
Negative to pollen	83	7	8.4	
Positive to allergen other than pollen†	48	5	10.4	<0.05
Negative to allergen other than pollen†	150	2	1.3	

*p less than 0.05 = significant; NS = not significant.

†Includes the following allergens: dog dander, cat dander, feather mixture, kapok, and Alternaria.

the 1+ group ($p < 0.01$). Thus, among these asymptomatic students, the development of new symptoms of seasonal hay fever was significantly correlated with 2+ or greater scratch test reactivity to these pollens. At present, the group of students who have shown only 1+ skin test reactivity cannot be classified reliably with either the negative or the other positive groups. If the size of the sample were increased and the present trend maintained, then the 1+ group should become significantly different from the negative group.

Freshmen students were classified as affected with hay fever only if they manifested clinical symptoms for the same two consecutive seasons. Twenty-eight freshmen reported that they had their onset of hay fever symptoms during the year in which the freshmen study was made. They were classified as asymptomatic with questionable hay fever, since their symptoms existed for only one season. We were able to follow-up 24 of these students when they were seniors. Our initial decision to be conservative in accepting the diagnosis of hay fever was substantiated, since only 7 students had continued to have symptoms of hay fever. These included one who had all negative scratch tests, 5 who had positive pollen scratch tests, and one who had not been scratch tested. We have re-evaluated the frequency of new cases of hay fever in Group 3 students by excluding these students who had been symptomatic for a single season. Then, the number of students in Group 3 who had no symptoms of hay fever when they were scratch tested as freshmen and who were followed up as seniors is: 94 with at least one pollen scratch test positive, 13 of whom had developed hay fever as seniors (13.8 per cent); 514 with no positive pollen scratch tests, 8 of whom had developed hay fever as seniors (1.6 per cent). Again, the frequency of new cases of hay fever was very significantly correlated ($p < 0.01$) with the presence of positive pollen scratch tests, suggesting that the positive skin reaction may precede the onset of clinical symptoms of hay fever.

In the follow-up study, 13 seniors reported that hay fever symptoms began for the first time one season prior to the follow-up. These students now are classified as asymptomatic with questionable hay fever.

New cases of nonseasonal allergic rhinitis were not found to be related to

the presence or absence of a positive pollen scratch test in our battery of allergens. However, allergic students in Group 1 who had asthma and/or hay fever developed new cases of nonseasonal allergic rhinitis with significantly higher frequency if they had a positive scratch test to one of the following: dog dander, cat dander, feather mixture, kapok, *Alternaria* (Table VII). This relationship was not found for the asymptomatic group of students.

No conclusions can be drawn about new cases of asthma in relation to positive scratch tests since only 3 of the students who were scratch tested developed asthma between their freshman and senior years. Each of these students had previously had some type of allergy as well as positive scratch test reactions.

DISCUSSION

Freshman college students who had no clinical manifestation of an allergy but who had a positive pollen scratch test reaction have been found to develop within three years clinical symptoms of seasonal hay fever over ten times as frequently as their peers who had only negative pollen scratch tests. Furthermore, individuals with 2+ or greater reactions to these pollens developed hay fever over thirteen times as frequently as individuals who had negative pollen reactions.

Pollen extracts were selected for the study which represented allergens common to the southern New England area. Entering freshman students varied in their exposure to environmental allergens, but as seniors nearly all had natural exposure to most of these pollens.

Conclusions drawn from population studies are restricted by both sampling and study methods. Our study includes only native Caucasian students who are drawn from a middle to upper socioeconomic group and have high intellectual selection. Since we obtained information from 99 per cent of these freshmen, we are able to relate observations on the frequency of allergies to the total population of freshmen we have defined. The follow-up study included only 73.6 per cent of the freshmen population so that conclusions about new symptoms of allergies must be limited to this group. Fortunately, equal cooperation was received in the follow-up study from students who had clinical symptoms of allergies and from students who had no clinical symptoms of allergies. However, students who were scratch tested as freshmen gave more cooperation as seniors than students who were not scratch tested as freshmen.

Large, unselected samples are necessary to evaluate the association of scratch tests with the development of new allergies within the population. While we were able to scratch test only three quarters of the freshmen, equivalent numbers of clinically allergic and clinically asymptomatic freshmen participated in the scratch tests. Also, in the follow-up of seniors, equivalent numbers of students who had positive and negative scratch tests were drawn from the clinically allergic and clinically asymptomatic groups of freshmen.

Conclusions about frequencies of allergies in the population must be related to the age structure of the population. In a study of the total population of Tecumseh, Michigan, Broder and co-workers⁴ found a twofold rise in the

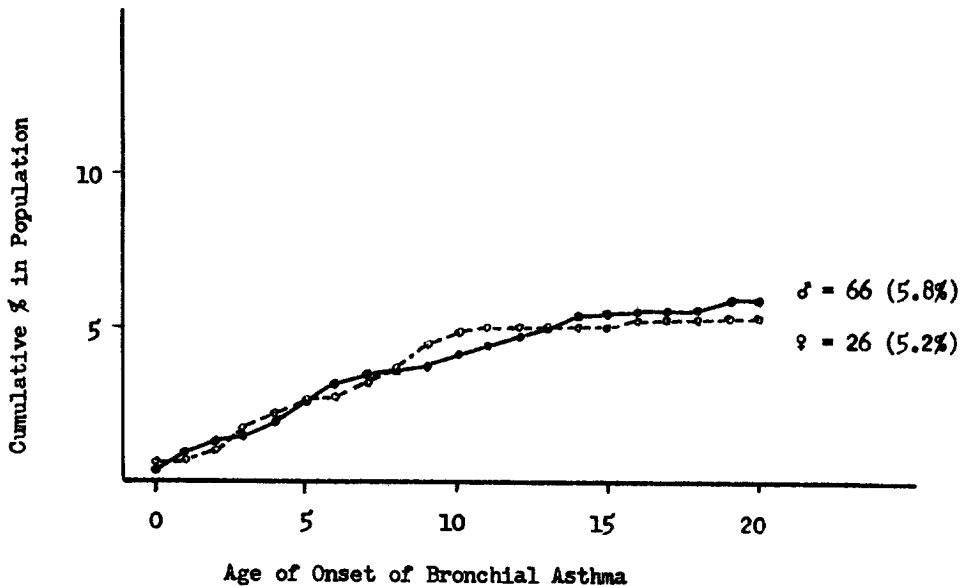


FIG. 1. Cumulative frequency of bronchial asthma by age of onset in college students.

cumulative prevalence rate of hay fever from 6 to 9 years through 25 to 29 years, but more variable prevalence rates in older age groups.

The mean age of our freshmen students was 17.9 years, and 388 students (21.1 per cent) reported hay fever. Within the next three years 44 additional students developed hay fever. Also, 8 other seniors reported hay fever for the first time, but with earlier ages of onset. Therefore, within the population of 1,836 students, 440 cases of hay fever have now been reported. This represents 23.9 per cent of the population, even though less than 75 per cent of the population has been followed up.

Age of onset may vary for different allergic conditions, and cumulative prevalence rates of specific allergies in the population provide meaningful comparisons. Figs. 1, 2, and 3 show the cumulative frequency of asthma, non-seasonal allergic rhinitis, and seasonal hay fever, respectively, in our student population. Cumulative frequencies are determined from the age of onset reported by individuals who were affected with one or more of these allergies. The frequency of each allergy at each age has been summated on a yearly onset basis in men and women. Individuals who did not report a specific year of onset for a given condition have been omitted from the population. Accordingly, the total population size has been adjusted to maintain the same frequency of the allergy which has been reported by the total population.

The cumulative frequency of asthma is very similar in men and women (Fig. 1). The total cumulative prevalence rate is 5.8 per cent in men and 5.2 per cent in women. When cases of asthma with onset from less than one year through 4 years of age are pooled, this group includes 42 per cent of all affected women and 33 per cent of all affected men. By 11 years of age 5.0 per cent of the female population had asthma. Only one girl developed asthma

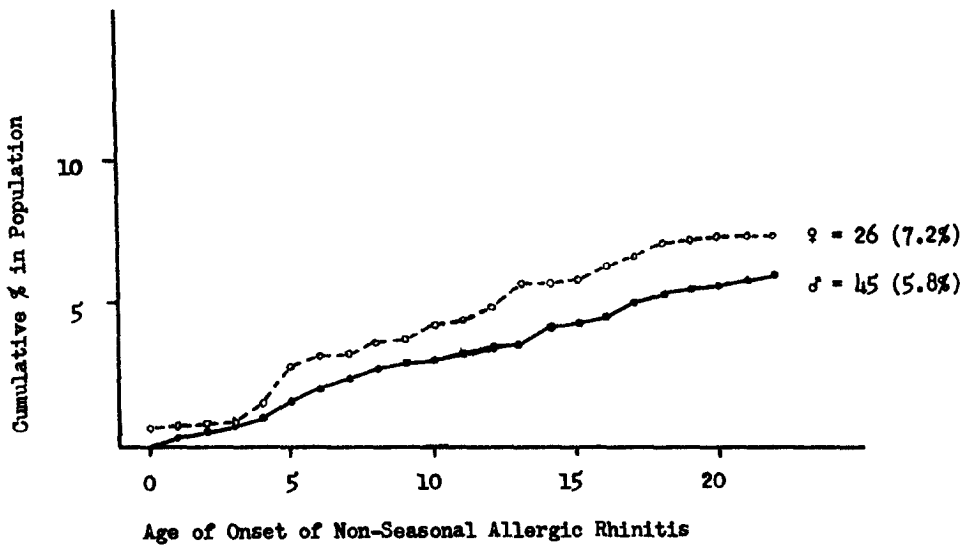


FIG. 2. Cumulative frequency of nonseasonal allergic rhinitis by age of onset in college students.

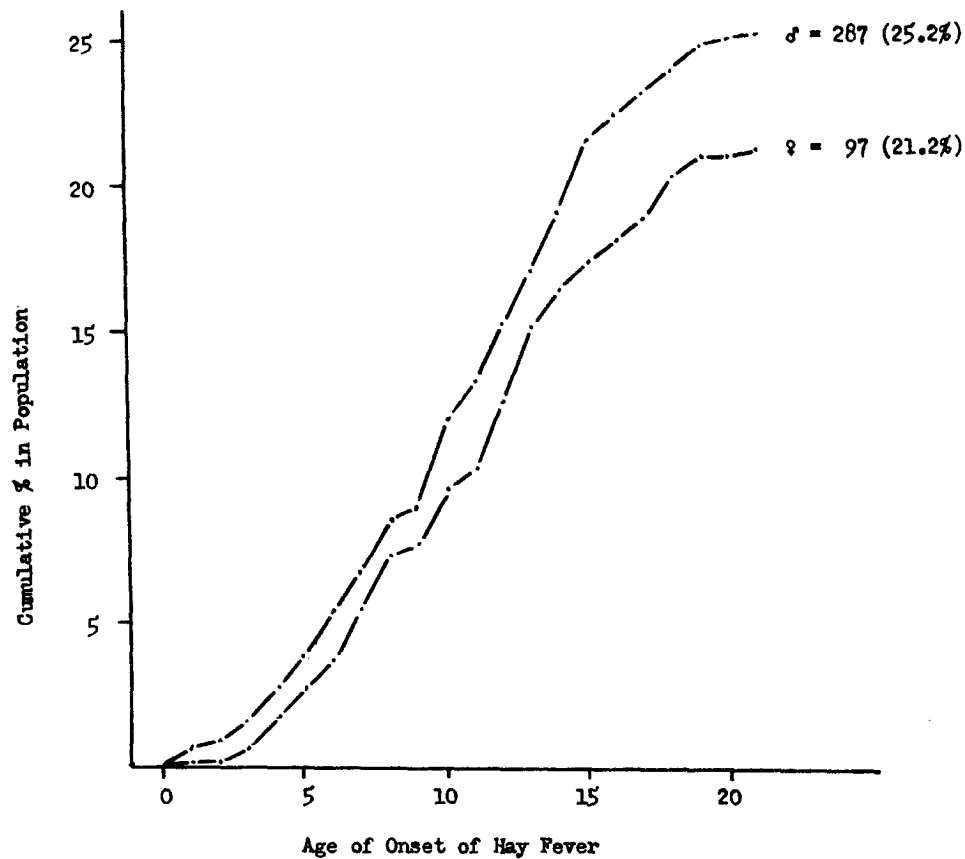


FIG. 3. Cumulative frequency of seasonal hay fever by age of onset in college students.

later than this, at age 16. In the male population 5.3 per cent developed asthma by 14 years of age. Additionally, asthma onset occurred in one boy at age 16 and in 5 at age 19 (3 ascertained through the follow-up study). The early age onset pattern observed in the population is complemented by the low frequency of new cases of asthma reported in the follow-up study.

The cumulative prevalence rate of nonseasonal allergic rhinitis (Fig. 2) is 5.8 per cent in men and 7.2 per cent in women. A gradual yearly increase tends to occur in men. The greatest number of women are affected at 5 years of age, suggesting the possibility of rounding errors in reporting ages of onset.

The onset of seasonal hay fever (Fig. 3) tended to be later than the onset of asthma. Of all individuals in the population who developed hay fever, 10.2 per cent had onset by 4 years of age, 25.8 per cent from 5 to 9 years, 40.4 per cent from 10 to 14 years, and 22.4 per cent from 15 to 19 years. Very similar frequencies of affected males and females occurred in these onset age groups. However, the total cumulative prevalence rate of hay fever is somewhat higher in men (25.2 per cent) than in women (21.2 per cent).

The increased frequency of hay fever observed at 10 years of age in both males and females may also be rounding errors of reporting, since lower frequencies of onset are reported by both sexes at age 9. The highest rate of increase occurs in females at ages 12 and 13 and in males at ages 12, 14, and 15. This suggests a possible association of age of onset of seasonal hay fever with development at puberty. At later ages the rate of increase of hay fever is considerably less, so that the cumulative frequency curves tend to level off for each sex.

The frequencies of hay fever in our population, when compared by age groups to the population studied by Broder and associates,⁴ are significantly higher in the 5 to 9, 10 to 14, and 15 to 19 age groups. Also, we have found significantly higher frequencies of asthma than they observed in the 5 to 9 and 10 to 14 age groups. Some of the variation between the two studies may be related to the reliability of reporting onset ages for allergies. Broder and co-workers⁵ analyzed data which were collected from nearly all individuals 8 years or older in the community of Tecumseh, Michigan. Perhaps the most significant relationship between our study and that of Broder and associates is that we all observed that asthma generally has an earlier age of onset than does hay fever. Also, in the Tecumseh population 5 to 10 per cent of individuals who first had onset of hay fever subsequently developed asthma. In our population 5.3 per cent of the students who first had onset of hay fever have subsequently developed asthma.

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