

EVIDENCE OF ALLERGY IN PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

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THE frequent association of asthma and cystic fibrosis of the pancreas is well recognized. Table I summarizes data on this association obtained from three large published series of cases.¹⁻³

This asthma has generally been assumed to be due to obstruction of the bronchi by the abnormal viscid secretion characteristic of this disease and by secondary infection and edema. Squamous metaplasia of tracheal and bronchial epithelium due to vitamin A deficiency, consequent to pancreatic steatorrhea, may have played a role in some cases. Pneumonia, atelectasia, emphysema, cyanosis, rhinitis, sinusitis, and clubbing of the fingers have been prominent associated findings. Progressive pulmonary infection and insufficiency have caused death in many cases. The importance of distinguishing asthma due to cystic fibrosis of the pancreas from allergic bronchial asthma is obvious and has been emphasized by many.³⁻⁵

TABLE I. PUBLISHED DATA ON THE ASSOCIATION OF ASTHMA WITH CYSTIC FIBROSIS OF THE PANCREAS

AUTHOR	TOTAL NUMBER OF PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS	PATIENTS WITH ASTHMA ASSOCIATED WITH CYSTIC FIBROSIS OF THE PANCREAS	
		NUMBER	PER CENT
Bodian ¹	116	13	11
Abbott and associates ²	102	10	10
Derbes and associates ³	68	33	49

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At The John Hopkins Hospital during the past three years we have observed six asthmatic patients who have had evidence of both atopic allergy and cystic fibrosis of the pancreas. They have presented many problems in differential diagnosis, management, and interpretation of pathogenesis. In order to define these problems more clearly, the following study was undertaken.

MATERIALS AND METHODS

We reviewed the records of 135 patients with cystic fibrosis of the pancreas studied by the pediatric service of The Johns Hopkins Hospital since 1939. All had satisfactory clinical evidence of the disease, and the diagnosis was confirmed in 132 by demonstrating one or more of the following: deficiency of duodenal trypsin, sweat chloride concentration exceeding 60 mEq. per liter, or autopsy evidence of the disease. Each record was carefully searched for evidence indicating that the patient might have had atopic allergy in addition to cystic fibrosis. For the purposes of this study, one or more of the following was accepted as evidence of allergy: hay fever, nasal polyps, eczema, urticaria, and characteristic skin test reactions to pollens and other inhalant antigens. Asthma, chronic rhinitis, and family history of allergy were not accepted as evidence of atopic sensitivity per se.

This was a retrospective study. The records were well documented, and it is probable that most instances of hay fever, nasal polyps, eczema, and urticaria were reported. Only nineteen of the 135 patients had skin tests, however, and these tests revealed characteristic reactions to pollens and inhalants in thirteen. Had more of the 135 patients received skin tests, more cases of atopic allergy might have been detected. This study was restricted to patients referred to the pediatric service at The Johns Hopkins Hospital, and these referred patients could differ from the general population of cystic fibrosis patients with respect to incidence of allergy and age.

By the criteria just outlined, nineteen cystic fibrosis patients had evidence of atopic allergy. Data on these nineteen allergic cystic fibrosis patients were analyzed and compared with similar data on the total group of 135 cystic fibrosis patients.

The high incidence of allergy in patients with asthma and cystic fibrosis prompted a search for cystic fibrosis among patients with a diagnosis of atopic bronchial asthma in the pediatric allergy clinic of The Johns Hopkins Hospital. The demonstration of an excessive concentration of sodium and chloride in the sweat of almost all patients with cystic fibrosis of the pancreas has permitted a single test for detecting such cases.⁶ The recent introduction by Gibson and Cooke⁷ of local pilocarpine iontophoresis for induction of sweating has allowed the sweat test to be done safely, rapidly, and without discomfort. By this method, sweating is induced in a small area by local iontophoresis of pilocarpine. Thereafter, sweat is collected for thirty minutes on a previously weighed filter paper disk which is covered with a plastic sheet to prevent evaporation. Weight and chloride concentration of collected sweat can be determined easily.

Dr. Lewis Gibson measured the concentration of chloride in the sweat of forty-seven patients of the pediatric allergy clinic with a diagnosis of atopic bronchial asthma, using the iontophoresis method described above. The results were compared with similar measurements obtained from sixty-four control and twenty-one cystic fibrosis patients.

RESULTS

In Table II the evidence of cystic fibrosis in the nineteen patients with cystic fibrosis and allergy is compared with that in the total group of 135 patients. The evidence is similar in the two groups.

TABLE II. COMPARISON OF THE EVIDENCE OF CYSTIC FIBROSIS IN THE GROUP OF NINETEEN PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY WITH THAT IN THE TOTAL GROUP OF 135 PATIENTS WITH CYSTIC FIBROSIS

	GROUP OF PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY		TOTAL GROUP OF PATIENTS WITH CYSTIC FIBROSIS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total number	19	100	135	100
Family history of cystic fibrosis	6	32	40	30
Abnormal stools	17	90	129	96
Pancreatic enzyme deficiency demonstrated	15	79	100	73
Rectal prolapse	2	11	14	10
Meconium ileus	2	11	10	7
Respiratory disease symptoms	19	100	130	96
Pulmonary infiltrate	19	100	123	91
Emphysema	15	79	82	61
Wheezing	12	63	51	38
Clubbing of fingers	15	79	61	45
Rhinitis	18	95	106	79
Sinus x-rays obtained	10	53	28	21
X-ray evidence of sinusitis	10	53	25	19
Failure to thrive	18	95	129	96
Sweat chloride				
Not measured	12	63	103	76
Normal	1	5	1	1
Elevated	6	32	31	23
Died of cystic fibrosis	6	32	56	41
Autopsy evidence of cystic fibrosis	3		37	
No autopsy	3		19	

In Table III the evidence of allergy in the nineteen patients with cystic fibrosis and allergy is compared with that in the total group of 135 patients. The method of selection required that the allergic group contain all patients with nasal polyps, hay fever, eczema, urticaria, or positive skin reactions to pollens and other inhalants. The criteria for selection of the allergic group did not require the inclusion of patients with asthma or familial allergy, but nevertheless the incidence of both was higher in the allergic group.

The nineteen patients with cystic fibrosis and allergy may be divided into two groups. The first group (Table IV) consists of eight patients with objective clinical evidence suggesting respiratory tract allergy. Seven had nasal polyps. These caused sufficient obstruction to necessitate surgery in four cases, and histologic study of the excised material revealed typical findings.

TABLE III. COMPARISON OF THE EVIDENCE OF ALLERGY IN THE GROUP OF NINETEEN PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY WITH THAT IN THE TOTAL GROUP OF 135 WITH CYSTIC FIBROSIS

	GROUP OF PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY		TOTAL GROUP OF PATIENTS WITH CYSTIC FIBROSIS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total number	19	100	135	100
Family history of allergy				
Parents or siblings	5	26	20	14
Other than parents or siblings	8	42	14	10
Asthma	12	63	51	38
Rhinitis	18	95	106	79
Nasal polyps	7	37	7	5
Hay fever	4	21	4	3
Eczema	7	37	7	5
Urticaria	3	16	3	2
Positive intracutaneous tests				
Pollens	7	37	7	5
Other inhalants	13	68	13	10
Foods	5	26	5	4
Bacteria	6	32	7	5
Negative intracutaneous tests	0	0	5	4
Intracutaneous tests not done	6	32	116	86

TABLE IV. CLINICAL DATA ON EIGHT PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS AND ALLERGY WHO HAD OBJECTIVE EVIDENCE OF RESPIRATORY TRACT ALLERGY

	D. H.	R. S.	M. R.	S. P.	K. C.	B. G.	C. N.	B. M.
Age in years								
Last observation	19	18	20	18	11	16	12	12
Death	Living	Living	Living	Living	11	Living	12	Unknown
Family history of allergy								
Parents or siblings	0	+	0	0	+	0	0	0
Other than parents or siblings	+	+	0	0	+	0	0	0
Age in years at onset of								
Asthma	16	15	12	1	2	16	-	1
Rhinitis	4	3	5	1	1	7	1	1
Nasal polyps	10	9	12	-	10	7	6	8
Hay fever	11	14	-	<10	-	7	-	-
Eczema	-	-	-	3/12	-	7	-	-
Urticaria	-	14	5	0	-	-	-	-
Respiratory symptoms								
near animals	<14	-	5	<10	-	7	-	-
Intracutaneous tests								
Pollens	+	+	Neg.	+	+	+	ND	ND
Other inhalants	+	+	+	+	+	+	ND	ND
Foods	ND	ND	Neg.	ND	ND	+	ND	ND
Bacteria	+	+	+	+	+	Neg.	ND	ND

Four patients had seasonal hay fever associated with characteristic positive intracutaneous reactions to pollens. Desensitization therapy was given to all four, with apparent benefit to three. Four patients noted lacrimation, sneezing, coughing, and/or wheezing when they were near various animals, associated with characteristic intracutaneous reactions to the appropriate animal dander. Corticosteroid therapy was used to advantage to control asthma in two patients. It is important to emphasize that these were relatively old

cystic fibrosis patients and that nasal polyps, hay fever, and respiratory symptoms near animals were noted no earlier than 5 years of age and usually at 10 years of age or later. Six of these patients had other manifestations of allergy (urticaria, eczema, and positive skin tests), and three had a family history of allergy.

The second group of patients with cystic fibrosis and allergy contains eleven who had no objective clinical evidence of respiratory tract allergy (Table V). This was a younger group of patients, most of whom had not attained the age at which nasal polyps and hay fever had appeared in the previous group.

TABLE V. CLINICAL DATA ON ELEVEN PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS AND ALLERGY WHO HAD NO OBJECTIVE EVIDENCE OF RESPIRATORY TRACT ALLERGY

	M. D.	R. H.	D. D.	P. G.	R. M.	S. B.	T. A.	M. B.	R. N.	L. B.	S. C.
Age in years											
Last observation	2	$\frac{3}{12}$	4	8	2	2	6	3	1	1	1
Death	Living	$\frac{3}{12}$	Living	Un- known	3	Un- known	Living	4	Un- known	1	Un- known
Family history of allergy											
Parents or siblings	+	+	0	0	+	0	0	0	0	0	0
Other than par- ents or sib- lings	+	+	0	0	0	+	+	0	+	0	0
Age in years at onset of											
Asthma	$\frac{1}{12}$	$\frac{3}{12}$	2	$\frac{7}{12}$	-	-	$\frac{9}{12}$	-	-	-	-
Rhinitis	$\frac{1}{12}$	$\frac{3}{12}$	$\frac{1}{12}$	$\frac{7}{12}$	$\frac{4}{12}$	$\frac{8}{12}$	$\frac{3}{12}$	$\frac{1}{12}$	$\frac{1}{12}$	$\frac{10}{12}$	$\frac{5}{12}$
Nasal polyps	-	-	-	-	-	-	-	-	-	-	-
Hay fever	-	-	-	-	-	-	-	-	-	-	-
Eczema	-	-	<1	-	$\frac{7}{12}$	-	-	$\frac{1}{12}$	$\frac{2}{12}$	$\frac{9}{12}$	$\frac{6}{12}$
Urticaria	-	-	-	-	-	-	-	-	-	-	-
Intracutaneous tests											
Pollens	Neg.	ND	Neg.	+	Neg.	Neg.	Neg.	ND	ND	ND	ND
Other inhalants	+	+	+	+	+	+	+	ND	ND	ND	ND
Foods	ND	+	+	+	+	Neg.	Neg.	ND	ND	ND	ND
Bacteria	+	ND	Neg.	ND	Neg.	Neg.	Neg.	ND	ND	ND	ND

TABLE VI. COMPARISON OF GENERAL DATA ON THE GROUP OF NINETEEN PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY WITH DATA ON THE TOTAL GROUP OF 135 PATIENTS WITH CYSTIC FIBROSIS

	GROUP OF PATIENTS WITH CYSTIC FIBROSIS AND ALLERGY		TOTAL GROUP OF PATIENTS WITH CYSTIC FIBROSIS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total number	19	100	135	100
Male	9	47	78	58
Female	10	53	57	42
White	18	95	131	97
Negro	1	5	4	3
Age in years when last observed				
1 or less	4	21	53	39
2 to 5	5	26	50	37
6 to 10	2	11	18	13
11 to 15	3	16	8	6
16 to 20	5	26	6	4

In Table VI general data on the nineteen patients with cystic fibrosis and allergy are compared with data on the total group of 135 patients with cystic fibrosis. Sex and race distribution were similar in the two groups. The allergic patients tended to be older; 42 per cent of the allergic group and only 10 per cent of the total group were 11 years of age or older.

Table VII shows the percentage of cystic fibrosis patients in a given age group with evidence of allergy. The age reported is that which obtained at the time the patient was last seen. It is evident that with increase in age there was progressive increase in incidence of cases of allergy.

TABLE VII. NUMBER AND PER CENT OF CYSTIC FIBROSIS PATIENTS IN A GIVEN AGE GROUP WITH EVIDENCE OF ALLERGY

	TOTAL NUMBER OF PATIENTS	NUMBER OF PATIENTS WITH EVIDENCE OF ALLERGY	PER CENT OF TOTAL NUMBER OF PATIENTS WITH EVIDENCE OF ALLERGY
Total	135	19	14
Age in years when last observed			
1 or less	53	4	8
2 to 5	50	5	10
6 to 10	18	2	11
11 to 15	8	3	37
16 to 20	6	5	83

CASE REPORTS

CASE 1.—The patient was R. H., a baby boy.

Family History.—The mother and the maternal grandmother had hay fever, and a maternal uncle and the maternal grandfather had asthma. A brother died in 1941, at the age of 18 months, of pulmonary infection and asthma. Postmortem examination was reported to have revealed evidence of tuberculosis. It was impossible to determine subsequently whether or not this brother actually had cystic fibrosis of the pancreas.

Present Illness.—The patient had frequent pale, foul stools from the time of his birth in March, 1948. By the age of 3 months, he had "rasping" respirations. By the age of 5 months, he was having frequent respiratory infections associated with cough, wheezing, and nasal obstruction. Symptoms improved temporarily following the administration of penicillin.

At the age of 7 months, he was seen by a prominent allergist in another city, who noted that the nasal turbinates were pale and swollen. X-ray examination revealed clouding of both maxillary sinuses. Examination of the chest revealed typical wheezing. Skin tests revealed positive reactions to house dust, cat dander, orris root, pyrethrum, egg, beef, veal, apricot, peach, orange, coffee, chocolate, peas, beets, spinach, tomato, and cottonseed. Skin tests were negative to tree pollen, grass pollen, ragweed pollen, wheat, barley, corn, rice, chicken, lamb, plum, prune, grapefruit, tea, Coca-Cola, carrot, celery, Irish potato, and yeast. A diagnosis of atopic asthma and allergic rhinitis with superimposed infection was made. The diagnosis of cystic fibrosis was not considered.

At the age of 7 months the patient was admitted to The Johns Hopkins Hospital. Pale, swollen nasal turbinates and wheezing were still present. Chest x-ray studies revealed widespread linear infiltrations through both lung fields. Cultures of stools, nose, and throat revealed *Pseudomonas aeruginosa*. The patient had trouble expectorating thick tenacious sputum. Despite therapy with penicillin, streptomycin, sulfadiazine, digitalis, and

bronchodilators, there was increasing evidence of pulmonary insufficiency and fever, and the patient died at the age of 8 months.

Studies of the duodenal enzymes during the patient's Johns Hopkins hospitalization revealed an almost complete absence of trypsin activity.

Autopsy revealed evidence of cystic disease of the pancreas with obstruction of the pancreatic ducts by inspissated secretion and scarring and atrophy of the acinar tissue. There was evidence of acute purulent bronchitis and fresh and organizing lobular pneumonia. Cultures of the lung revealed *Pseudomonas aeruginosa*, *Staphylococcus aureus hemolyticus*, and *Aerobacter aerogenes*. There was atresia of the cystic duct, as well as a mucocele of the gall bladder. There was evidence of vitamin A deficiency consisting of keratinizing metaplasia of the tracheal and bronchial epithelium, keratinized cysts of the base of the tongue, and keratinizing Hassall's corpuscles in the thymus.

Comment.—This case clearly demonstrates how the diagnosis of cystic fibrosis of the pancreas may be overlooked in the presence of a strong family history of allergy, bronchial asthma, morphologic evidence suggesting allergic rhinitis and sinusitis, and positive skin tests. The presence of steatorrhea, pulmonary infiltrates, and respiratory symptoms should have suggested the diagnosis of cystic fibrosis.

CASE 2.—This patient was D. H., a white girl.

Family History.—A maternal uncle of the patient had urticaria following ingestion of aspirin, and a paternal cousin has asthma. There was no family history of cystic fibrosis of the pancreas.

Present Illness.—The patient had pneumonia at the age of 2 but was otherwise essentially well until 1942, when she was 4 years old. Then she began to have frequent, frothy, foul-smelling stools. Prolapse of the rectum occurred. A low-fat diet, vitamins, and pancreatin were given, and improvement in these intestinal manifestations ensued. Duodenal enzymes were not measured.

At the age of 4, the girl also began to have chronic cough and nasal discharge and frequent respiratory infections. The tonsils and adenoids were removed at the ages of 4 and 8, respectively. Windows were inserted in the maxillary antra when the patient was 6 years old. These operations did not relieve her symptoms.

At the age of 6 years she was examined at the University of Virginia Medical Center and was found to be allergic to various inhalant antigens and foods. She was desensitized for two years, and a diet was imposed. Apparently no improvement followed.

Nasal polyps were detected when she was 10, and these were removed at the ages of 10 and 12 years.

At the age of 14, she was seen for the first time at The Johns Hopkins Hospital. Examination revealed nasal polyps and chronic maxillary sinusitis. Bilateral radical antrum and nasal polypectomy were performed, and histologic studies of the polyps revealed typical findings. Chest x-ray studies revealed emphysema and infiltrations in both lungs. The patient complained of symptoms of hay fever of three years' duration in May, August, and September, and intracutaneous tests revealed reactions to tree, grass, and ragweed pollen extracts. Nasal infections and bronchitis were more frequent when she had hay fever. She noted sneezing, itching eyes, and cough when she was near dogs, cats, rabbits, and horses and after exposure to house dust. Intracutaneous tests revealed typical reactions to extracts of the offending danders, dust, feathers, kapok, orris root, wool, and molds. Desensitization was given to extracts of ragweed pollen, grass pollen, tree pollen, dust, orris root, feathers, kapok, wool, horse dander, dog dander, mixed bacterial vaccines, and staphylococcus toxin, and her symptoms of seasonal hay fever and asthma improved in the ensuing years.

At the age of 17, the patient had her first episode of asthma. This occurred for three days at the start of the ragweed season and in conjunction with symptoms of hay fever. Adrenalin relieved the paroxysms.

When she was 17 she was again hospitalized at The Johns Hopkins Hospital. Submucous resection, nasal polypectomy, ethmoidectomy, and antrotomies into the sphenoid sinus and both maxillary sinuses were performed.

When she was 19 three episodes of pneumonia occurred, the first beginning in the early part of the ragweed season. During the last of these episodes, she was in The Johns Hopkins Hospital. The chest x-ray is shown in Fig. 1 and presents a unique combination of infiltration, emphysema, and cyst formation. Sputum culture revealed *Pseudomonas aeruginosa*. Sweat chloride was elevated to 80 mEq. per liter. The fingers were noted to be clubbed. She recovered slowly on combined antibiotic-prednisone therapy. During the next year she was maintained on prednisone therapy and antibiotics as indicated, and she gained weight, noted fewer respiratory symptoms, and was able to enter college.

Comment.—This case demonstrates well the association of chronic infection and atopic allergy in cystic fibrosis. Specific desensitization and prednisone seemed to be important adjuncts to therapy.

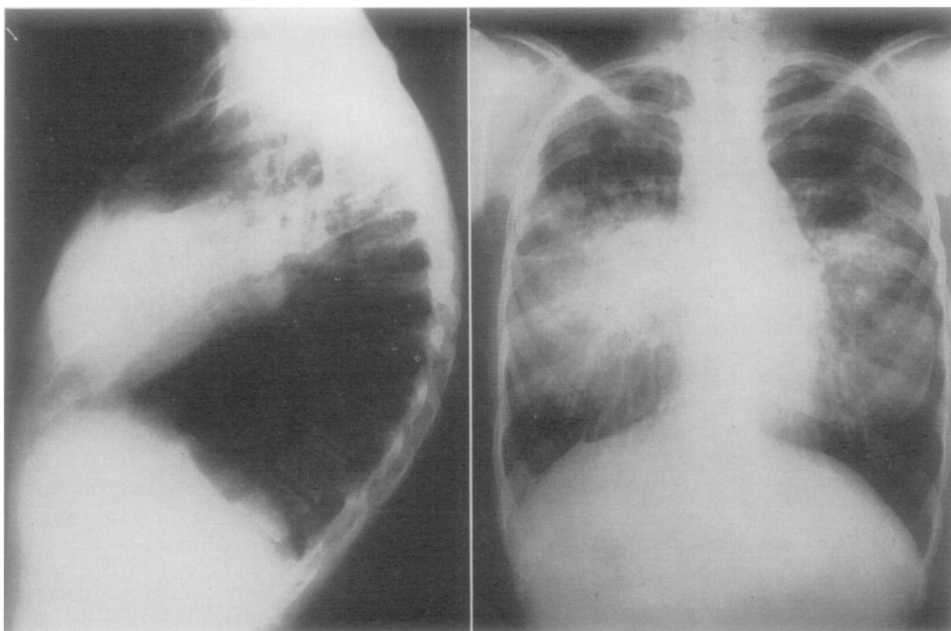


Fig. 1.—Case 2, Patient D. H. Roentgenograms of the chest, taken when the patient was 19 years of age, showing emphysema, infiltrations, and cysts.

Table VIII shows the concentration of chloride in the sweat of forty-seven patients with a diagnosis of atopic bronchial asthma. These results are compared with similar measurements obtained from control and cystic fibrosis patients. It is evident that the sweat chloride concentration of the asthmatic patients fell within the normal range; in no instance was it in the high range observed in patients with cystic fibrosis of the pancreas.

DISCUSSION

It is clearly apparent that patients with cystic fibrosis of the pancreas may have evidence of atopic allergy. The diagnosis of cystic fibrosis may be difficult in those with asthma, emphysema, chronic rhinitis, sinusitis, nasal

TABLE VIII. CONCENTRATION OF CHLORIDE IN THE SWEAT OF SIXTY-FOUR CONTROLS, FORTY-SEVEN PATIENTS WITH BRONCHIAL ASTHMA, AND TWENTY-ONE PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

	CONTROLS	ATOPIC BRONCHIAL ASTHMA	CYSTIC FIBROSIS OF THE PANCREAS
Total number of patients	64	47	21
Concentration of chloride in sweat (mEq. per liter)			
0-9	3	2	
10-19	31	30	
20-29	14	10	
30-39	8	2	
40-49	5	3	
50-59	1		
60-69	1		
70-79	1		1
80-89			5
90-99			3
100-109			6
110-119			3
120-129			2
130-139			1
Median	18.0 mEq./L.	14.0 mEq./L.	102 mEq./L.
Mean	23.0 mEq./L.	18.0 mEq./L.	101 mEq./L.

polyps, hay fever, urticaria, eczema, positive skin tests, and familial allergy. The aspects of the case suggesting allergy may cause one to overlook these signs indicating cystic fibrosis. However, such patients will usually have abnormal stools, pulmonary infiltrates, and clubbing of the fingers, and these supplementary clinical findings should lead one to suspect cystic fibrosis of the pancreas and to initiate confirmatory studies.

Management of these patients should include treatment of the allergic problem. Respiratory tract hypersensitivity to pollens, animal danders, and other inhalants may be treated through avoidance of causative antigens and specific desensitization with benefit to some patients. Corticosteroid therapy has been used effectively in some.

The absence of a sweat abnormality characteristic of cystic fibrosis in forty-seven patients with a diagnosis of atopic bronchial asthma indicates that cystic fibrosis patients with asthma had been previously excluded from the group by accurate differential diagnosis. This study suggests that not many patients with undiagnosed cystic fibrosis will be inadvertently included in the group of patients with atopic asthma treated in the average allergy clinic or practice. It is important to emphasize, however, that we have made such a mistake twice in the past three years.

The association of allergy and cystic fibrosis in the same patient may represent the chance coincidence of two unrelated disorders. This contention is supported by the observation that the incidence of familial allergy is higher in the allergic cystic fibrosis cases reported here than in total groups of cystic fibrosis cases reported here and elsewhere.⁸

An interrelationship between cystic fibrosis and allergy is suggested by the evidence indicating an increase in incidence of concomitant allergic disease with increase in age, and one may wonder whether there is something about cystic fibrosis that favors the development of allergy or something about allergy which favors survival in cystic fibrosis. The final proof that incidence of allergic disease increases with age in cystic fibrosis patients, however, demands methodical allergy studies on total cystic fibrosis populations and repeated studies on the same patient as he grows older. The data presented here, derived from a retrospective study of referred patients, must be regarded as suggestive only.

SUMMARY

Review of the records of 135 patients with cystic fibrosis of the pancreas revealed that nineteen had evidence of atopic allergy. The diagnosis of cystic fibrosis was easily overlooked in patients with classical manifestations of atopic allergy, such as asthma, nasal polyps, hay fever, urticaria, eczema, positive skin tests, and familial allergy. Optimal therapy for many of these patients included treatment of the allergic problem as well as the usual regimen for cystic fibrosis.

Forty-seven patients with atopic bronchial asthma had no evidence of the sweat chloride abnormality characteristic of cystic fibrosis of the pancreas.

The nature of the relationship between cystic fibrosis of the pancreas and atopic allergy is not clear.

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