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PULMONARY FUNCTION STUDIES IN PATIENTS WITH ASTHMA

*Relation to Clinical Course in Allergic and
Non-allergic Veterans*

By

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INTRODUCTION

This investigation was undertaken to study the evolution of asthma over a period of years, in conjunction with repeated pulmonary function tests.

Effort was made to determine whether immunizing injections, in allergic asthmatic patients, significantly altered the clinical and functional course.

MATERIAL

Seventy three veterans varying in age from 26 to 66 (average 46) years were observed for a period of one to six (average three and a half) years. They were residents of West Virginia, Virginia, Maryland and Pennsylvania. Most of them lived in the country; a few in large cities. Most were farmers; a few worked in mines or quarries.

Definition

The diagnosis of asthma was based on the history of sudden attacks of wheezing with dyspnea, often triggered by respiratory infection or exposure to pollen or other allergens. Between attacks all symptoms and signs disappeared.

METHODS

Clinical Evaluation

In every case, on admission, history, physical examination, blood count, urinalysis, blood sugar and BUN were obtained. Roentgenograms of the chest, para-

nasal sinuses, and teeth were taken. Patients were skin tested intradermally using twenty common inhalants in a concentration of .001 or .01 mg total nitrogen per milliliter (TN/ml). Positive tests which corresponded to the patient's symptoms were repeated using a weaker extract for titration.

The patients fell into three clinical groups:

- (a) Thirty nine were allergic. Of these 26 showed evidence of both infection and allergy.
- (b) Thirty two suffered from infective asthma only.
- (c) Two patients showed no evidence of either allergy or infection.

Pulmonary Function Studies

Each patient was studied in the Pulmonary Function Laboratory only when "at his best", that is, when he had recovered from an acute episode of dyspnea and when any exacerbation of infection had been adequately treated.

(a) *Spirographic tests* were recorded on a 13.5 liter respirometer without soda lime, in the standing position. These tests included the Vital Capacity (VC), Maximum Voluntary Ventilation (MVV) (synonymous with Maximum Breathing Capacity MBC), and Forced Expiratory Volume in one second (FEV₁). VC and MVV are reported as the per cent of the predicted value according to the VA-Army Cooperative Study of Pulmonary Function (3) using age and height as the basis of the prediction. FEV₁ is the per cent of the forced expiratory vital capacity which was expired in one second.

All values above 75 per cent are considered normal. Values between 50 per cent and 75 per cent are slightly to moderately abnormal; values below 50 per cent are markedly abnormal.

(b) *Static lung volumes* were measured by the closed circuit helium dilution method with continuous oxygen replacement (7). In normal men 26 to 70 years of age, the residual volume (RV) ranges from 1,400 to 2,000 ml., and the total lung capacity (TLC) from 5,500 to 7,000 ml. The ratio $\frac{RV}{TLC} \times 100$ is considered abnormal above 35 per cent. In this article this ratio is reported as R/T.

(c) *Arterial blood analysis* was done at least once and in many patients repeatedly. The pH, the arterial oxygen and carbon dioxide tensions were measured by the Astrup method (1) and the oxygen saturation (O₂ Sat.) was calculated. A saturation below 95 per cent at rest, breathing room air, is considered to indicate respiratory insufficiency.

(d) The *distribution of ventilation* was measured with a carbon dioxide analyzer. The method was described recently by Tulou (6). The result is expressed in mmHg as ΔCO_2 , the difference between the partial pressure of CO₂ at the end of quiet expirations (end-tidal CO₂) and at the end of a maximal expiration. Normally this difference is less than 7 mmHg, about 5 mmHg on the average. Values from 7 to 10 indicate slightly abnormal; 10 to 13, moderately abnormal; and above 13, markedly abnormal distribution of ventilation.

Pulmonary function studies were obtained approximately every six months, always when the patient was free from acute exacerbations of respiratory symptoms.

The allergic patients received subcutaneously at weekly intervals increasing doses of antigen, usually ragweed and/or timothy. The most sensitive were maintained on a dose of .01 mg TN every three weeks. The moderately sensitive patients received a maintenance dose of .1 mg TN, and the least sensitive patients .2 mg TN at monthly intervals. Eight patients discontinued immunization within the first year, but 31 patients received adequate immunization for two or more years.

Method of Evaluation of Data

Every patient had repeated function studies (up to eight) during the period of observation. Only the first and last studies will be considered in this report.

For the evaluation of *changes in pulmonary function tests*, five categories (A to E) were established, depending upon the functional status of the patient at the first study as defined above under "Pulmonary Function Studies" and in the Legend of Table 1; Category A includes the least abnormal patients, Category E the most severely disabled patients.

The *clinical impression was compared with the functional findings*, as shown in Table 2. Only the allergic patients who were adequately hyposensitized were included. Immunization was considered adequate if maintained at top dose at monthly intervals for two years.

RESULTS

Functional Changes from First to Last Study (Table 1)

In Table 1 are averaged the pulmonary function tests at first and last study. No marked deviations from the mean were noted in any group. The patients are classified in order of increasing severity of functional damage. In general the older patients showed greater damage.

On the average slight to moderate worsening is seen in each category, equally in allergic and non-allergic patients.

In Category D, the worsening of O₂ saturation in both allergic and non-allergic groups is noteworthy indicating that a restrictive ventilatory insufficiency (low vital capacity) implies a bad prognosis.

TABLE 1
Pulmonary Function Tests Before and After Treatment.
 Average Values (see Legend and Text).

	Age	VC per cent of predicted	MVV	FEV ₁ per cent of VC	R/T per cent	O ₂ Sat.	Δ CO ₂ mmHg
<i>Category A. Normal function at first study</i>							
Allergic 4 cases	36	98	99	78	39	98	4.3
After 2½ years	38	98	73	68	42	97	6.2
Non-allergic 2 cases	36	97	92	79	39	98	—
After 3 years	39	99	88	69	35	98	—
<i>Category B. Slight to moderate obstructive ventilatory insufficiency</i>							
Allergic 11 cases	40	97	65	63	40	98	5.1
After 4 years	44	94	59	58	42	96	7.7
Non-allergic 9 cases	55	96	69	57	46	98	6.8
After 2½ years	58	85	55	58	56	96	8.8
<i>Category C. Marked to severe obstructive ventilatory insufficiency</i>							
Allergic 8 cases	42	81	38	46	55	97	8.1
After 3½ years	45	69	31	40	63	95	10.0
Non-allergic 5 cases	41	80	39	38	52	97	6.0
After 4 years	45	79	37	40	56	97	9.2
<i>Category D. Marked to severe obstr. ventil. insufficiency plus restrictive ventil. insufficiency</i>							
Allergic 13 cases	42	60	26	43	56	97	8.6
After 3 years	45	64	30	45	61	91	8.4
Non-allergic 13 cases	52	61	28	32	60	96	10.7
After 3½ years	55	60	25	36	61	90	11.7
<i>Category E. Respiratory insufficiency at rest</i>							
Allergic 3 cases	43	69	27	29	71	93	9.9
After 1½ years	44	62	23	33	—	96	11.7
Non-allergic 5 cases	61	67	31	34	65	92	15.8
After 3½ years	65	58	20	36	72	89	13.0

Obstructive Ventilatory Insufficiency = MVV below 75 per cent of predicted.
 = FEV₁ below 75 per cent of FEVC.

Restrictive Ventilatory Insufficiency = VC below 75 per cent of predicted. Insufficiency is slight, moderate or severe.

No. = number of patients in the particular group.

All other figures are average values for the group, at the first and last study.

VC (Vital Capacity) and MVV (Maximum Voluntary Ventilation) are expressed in per cent of predicted values.

FEV₁ (Forced Expiratory Volume in one second) is expressed in per cent of the forced expiratory vital capacity.

R/T, ratio of residual volume to total lung capacity $\times 100$.

O₂ Sat. = arterial oxygen saturation, in per cent.

Δ CO₂ = difference between end-tidal and maximum expiration CO₂, in mmHg (see text).

TABLE 2
*Clinical and Functional Status of Asthmatic Patients at the End of 3½ Years
 (Range 1 to 6 Years).*

No.	Clinical impression			Functional findings			
	Im- proved	Un- changed	Worse	Im- proved	Un- changed	Worse	Mixed*
<i>Allergic group, immunized</i>							
31	20	8	3	5	7	4	15
<i>Non-allergic group unknown</i>							
34	11	13	8	2	11	7	14

Comparing immunized allergic and non-allergic patients (eight patients not satisfactorily immunized excluded from this table).

* Mixed means that not all functional tests showed the same direction of change.

Comparison of Clinical Impression and Functional Data (Table 2)

The data of Table 2 demonstrate that many patients improved clinically but few improved functionally. Clinical improvement was observed more frequently in the immunized allergic group, clinical worsening more frequently in the non-allergic group. Functional status was approximately the same in the two groups.

Cases of Death

Five of the 73 patients had died at the end of the period of study. Two, who suffered from infection as well as allergy had been immunized. Three were non-allergic. All deaths were due to aggravation of the respiratory disease. All five had low VC (restrictive ventilatory insufficiency) and low oxygen saturation at the last study and sometimes before.

CASE HISTORIES

Case No. 1. Asthma, allergic, without infection. Immunization with marked clinical improvement. No functional improvement.

G. K. from age three to age twelve suffered from colds with wheezing during the winter months. From age 12 to 26 he was free from asthma. He developed asthma in October 1943, at the age of 26 and thereafter had asthma every year from mid August throughout the autumn.

In December 1957, at age 40, he was admitted to our hospital with dyspnea, wheezing, and tightness in the chest. The present episode had started in August and was marked by many attacks, more or less relieved by medication.

On physical examination the chest was normal. Pulse was 108, blood pressure was 140/100. In the Allergy Clinic ragweed and dust asthma was diagnosed by history and positive skin tests (4+ to ragweed .or TN, 5+ to undiluted dust, and 3+ to 1-10 dust). No evidence of infection was found.

Immunization against dust and ragweed antigens was started. He was discharged after eight days of hospitalization. Soon after discharge the patient developed a cold, which precipitated asthma especially at night. He could work only half the time. By February 1958, he had improved markedly and was free from asthmatic attacks. Immunizing injections were administered weekly for eight months and then monthly until September 1961, a period of nearly four years. Follow-up pulmonary function studies were repeated about once a year. In 1965, he was working full time and usually felt well. At times he used a medihaler preventively. He smoked an occasional cigarette but admitted to feeling better when he did not smoke.

This patient was followed for six years (Fig. 1). His clinical condition unquestionably improved. The pulmonary function studies were similar over the years, a fact which shows that accurate techniques and cooperative patients provide precise, reliable physiological information. Slight functional abnormalities were present from the beginning (FEV₁, RV, TLC, and R/T). They remained unchanged. Δ CO₂ became slightly greater. In this case asthma had started in early childhood; active treatment was initiated at the age of 40, yet it resulted in a comfortable and useful life.

Case No. 2. Asthma with allergy and infection. Immunization with moderate clinical improvement. No functional improvement.

A. G., a colored male, developed pneumonia at age nine, after which he became dyspneic on exertion. While in the Service (1941-45, ages 23-27) he experienced five episodes of "laryngitis with bronchitis". In 1948, at age 30, he was hospitalized for ten days with the diagnosis of "bronchial asthma". He had suffered repeated attacks of asthma, mostly during the autumn, induced by inhalation of pollen, dust, fumes, odor of pine, paint and animal feed.

Wheezing was frequently noted on auscultation in 1954 at which time intradermal skin tests were positive (3+ to 4+) to timothy, plantain, ragweed,

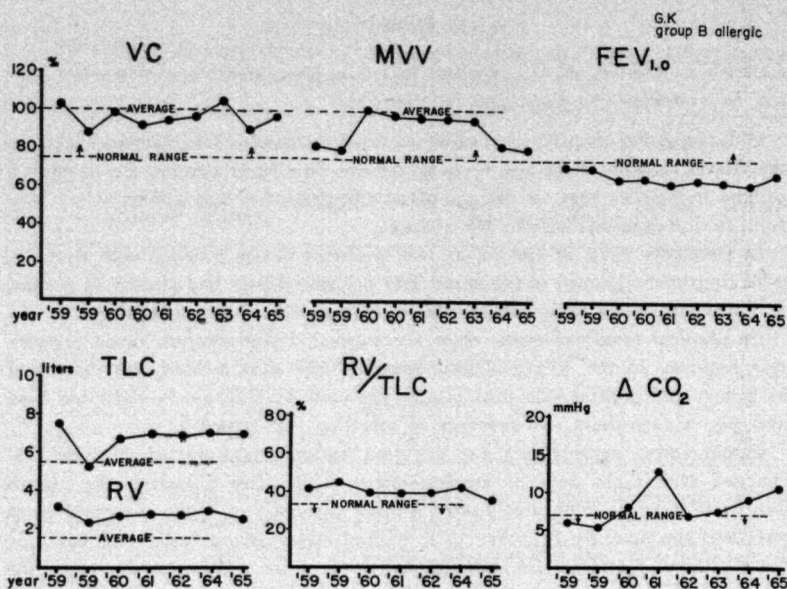


Fig. 1. Case No. 1.

See text for explanation of symbols. Arrows on the dotted line "Normal Range" show if this is the upper or lower limit of the normal range.

feathers, cat, dog, pyrethrum, orris, kapok, tobacco and dust. Abscessed teeth and chronic tonsillitis were treated by dental extractions and tonsillectomy. Immunizing injections against ragweed and dust antigens were started and following these the asthma improved but did not disappear. He was hospitalized several times for asthma, now apparently triggered by infection. In 1957 purulent sinusitis was treated surgically. Abscessed teeth were extracted in 1963. Recurrent sinusitis again was treated by antibiotics in 1966. Immunization has been maintained continuously from 1954 to the present time. The patient works regularly as a truck driver. He has attacks of asthma now and then. His sputum is scanty and white. On a recent physical examination he had prolonged, noisy expiration, an occasional wheeze, but no rales. Electrocardiogram was normal.

Pulmonary function studies obtained in the last six years (Fig. 2) show that the VC has remained normal, MVV and FEV₁ showing slight to moderate obstructive ventilatory insufficiency. Lung volumes, normal at first, became slightly elevated. Distribution of ventilation has been normal most of the time.

In summary, after two decades of asthma with chronic bronchitis and several foci of infection, this patient later developed allergy to pollen and dust. Treatment of allergy and infection enabled the patient to work. Pulmonary function

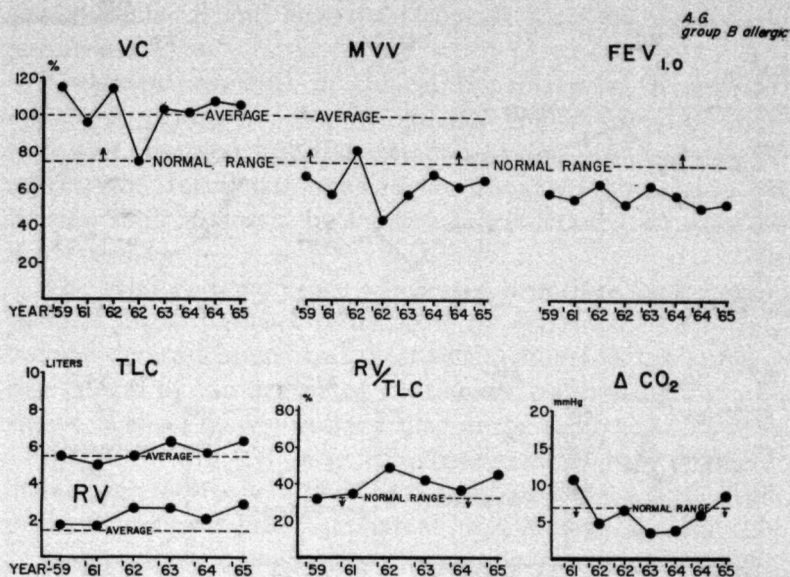


Fig. 2. Case No. 2.

For explanations, see Fig. 1.

tests have not improved; higher RV and R/T may indicate developing emphysema.

Case No. 3. Asthma with infection, chronic bronchitis and emphysema. Clinical improvement without functional improvement.

F.B., a white male, was first admitted to this hospital in 1958 at age 31. Since the age of 21 he had suffered attacks of asthma, more severe in the winter. Smoking cigarettes exacerbated his symptoms. Sputum was usually yellowish.

On physical examination the anteroposterior diameter of the chest was increased. There was hyperresonance on percussion, and the breath sounds were distant. Expiratory whines and wheezes were heard throughout the chest. The heart rate was 80. Skin tests were negative except for a 2+ reaction to undiluted dust.

The diagnosis was chronic bronchitis with asthma and emphysema. Several teeth were removed because of apical abscesses. A tonsillectomy was performed. Thereafter, he had fewer attacks of asthma until 1961, after which time he had none.

In May 1965, he was employed full time as a construction worker. He was

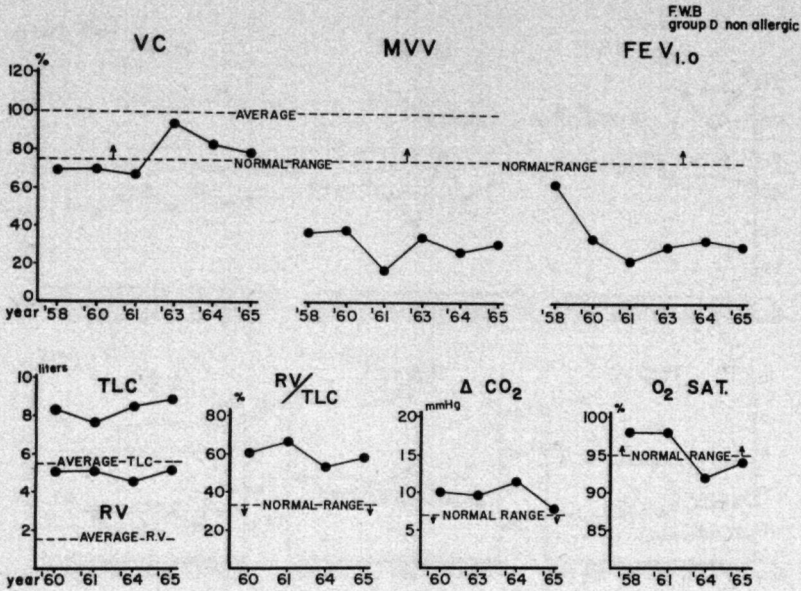


Fig. 3. Case No. 3.

For explanations, see Fig. 1.

occasionally short of breath in the morning. He continued to smoke one pack of cigarettes daily. During the previous winter he had several colds but none severe enough to keep him from work.

The pulmonary function studies from 1958 to 1965, shown in Fig. 3, demonstrate a slight improvement of the vital capacity. The test of distribution of ventilation, Δ CO₂ is closer to normal in 1965 than in 1960. There has been no improvement of the obstructive ventilatory insufficiency, no improvement of RV, TLC, and R/T, and slight worsening of the arterial oxygen saturation.

In summary, contrasted with a remarkable clinical improvement with subsidence of asthma after 13 years of symptoms, only the VC improved. All other tests remained abnormal, and the arterial blood oxygen decreased. Noteworthy are his relative comfort and ability to work, despite the more severe functional disorder.

DISCUSSION

The method of pulmonary function testing was uniform throughout the period of study and the breakdown into five categories is based on results of pulmonary function tests, regardless of clinical condition. Subsequent study indicated

that the clinical and functional courses were not necessarily parallel.

Treatment resulted in clinical improvement in approximately 50 per cent of the 73 patients. Improvement of function was observed in approximately twelve per cent. In the others, the functional impairment remained unchanged, or became slightly worse. In Table 2 more detailed information is presented.

The relative importance of chronic bronchitis and emphysema in these patients is difficult to determine, since lung volume determinations and chest roentgenograms are not precise indices of the degree of anatomical emphysema (2). As shown in the Figures, in particular in the three case histories (Figs. 1, 2 and 3), lung volume determinations remained stable over the years, and in most cases were abnormally high, probably indicating that emphysema was present.

In our series the mortality rate was seven per cent in three and a half years. Comparing our patients with asthma and patients with chronic obstructive pulmonary disease (4, 5) we see that the mortality rate was higher in the latter disease, 53 per cent at four years (5) and 32 per cent after an interval of two to six years (4). Even though it is difficult to compare the cases in different series, it appears that the presence of a treatable factor, allergy and/or infection, improves the prognosis, and Mitchell and Filley made the same observation (4).

SUMMARY

Seventy three veterans suffering from recurrent asthma for 15 years or more were studied for an average period of three and a half years. Repeated tests of pulmonary function showed a general downward trend over the years. The presence of a treatable factor, allergy and/or infection, decreased the patient's clinical disability, often enabling him to become economically self supporting.

Treatment of allergy by hyposensitization after 15 years of asthma, despite alleviation of seasonal symptoms, did not

alter the direction of functional change. Whether hyposensitization early in the course of asthma would have had a more favorable influence is unknown.

Pulmonary function tests repeated over the years were useful in assessing organic and functional damage in recurrent asthma.

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