Alpha₁ antitrypsin deficiency and pulmonary emphysema

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An association between a genetically determined deficiency of the serum enzyme α_1 antitrypsin and pulmonary emphysema is now well established. Serum antitryptic activity was measured in 103 patients suspected of having emphysema. Eighty-seven fulfilled the diagnostic criteria for emphysema and, of these, 16 had deficient levels, 5 had intermediate levels, and 66 had normal levels. The results of clinical, radiographic, and physiological studies in each group were then compared. Characteristic features noted in the deficient group included onset of dyspnoea during the third or fourth decades and uniformly symmetrical radiographic lower zone involvement. Other factors such as sex distribution, cigarette smoking, and chronic bronchitis are discussed.

Sixty-eight relatives of the 16 patients with deficient levels were also studied. The findings in these are compatible with an autosomal recessive mode of inheritance although difficulties in identifying the heterozygous state were encountered. Six relatives had deficient levels and of these three had emphysema.

Emphysema is most commonly diagnosed in men with chronic bronchitis in the fifth or sixth decades (Talamo, Blennerhassett, and Austen, 1966). Cigarette smoking and recurrent pulmonary infection have been suggested as important aetiological factors, but although the occurrence of emphysema in families has been recognized since the early nineteenth century (Louis, 1837) there has, until recently, been little direct evidence about genetic factors.

Laurell and Eriksson in 1963 and Eriksson in 1965 first described an association between chronic obstructive pulmonary disease and a genetically determined deficiency of α_1 antitrypsin, the chief component of α_1 globulin. Family studies revealed a trimodal distribution of α_1 antitrypsin serum levels with normal, intermediate (approximately 60% of normal), and deficient (less than 15% of normal) levels, compatible with the hypothesis of an autosomal recessive mode of inheritance. The homozygotes for the deficiency gene were found to have a high incidence of emphysema, while the heterozygotes, classed as those with intermediate levels, did not show this association. These findings have since been confirmed both in the United States and in Europe, though the exact role of the heterozygous state is undecided.

This paper presents the findings in a selected series of patients attending the Brompton Hospital

with chronic respiratory disease in whom levels of serum antitryptic activity were estimated.

DIAGNOSIS OF EMPHYSEMA

Emphysema is defined on an anatomical basis as a disease characterized by structural changes in the lung causing increase, beyond the normal range, in the size of air spaces distal to terminal bronchioles (Scadding, 1969). In life, however, histopathological specimens are not usually available and therefore the diagnosis depends on clinical, radiological, and physiological criteria. For the purpose of this study the following radiological and physiological criteria were adopted, the former having been shown to be strongly correlated with moderate to severe emphysema (Reid and Millard, 1964):

1. Radiological (Simon, 1964).
 - (a) Low flat diaphragm
 - (b) Large retrosternal translucent zone
 - (c) Attenuation of the larger intrapulmonary vessels
 - (d) Dilated hilar arteries
2. Physiological
 - (a) Decrease in forced expiratory volume in one second (FEV_1) and $FEV_1/FVC\%$ ($<60\%$)

- (b) Increase in residual volume (RV), total lung capacity (TLC), and RV/TLC% (>45%)
 (c) Impaired gas transfer (TLco).

DIAGNOSIS OF CHRONIC BRONCHITIS

Simple chronic bronchitis is defined as a chronic or recurrent increase in the volume of mucoid bronchial secretion sufficient to cause expectoration (*Lancet*, 1965). For the purpose of this study the diagnosis was applied to any patient who had coughed up sputum on most days during at least three consecutive months for more than two successive years.

MATERIAL

Serum antitryptic activity was measured in the following:

CONTROLS Eighty-seven subjects consisting of 39 healthy blood donors, 35 members of the hospital staff, and 13 patients who had non-respiratory disease.

PATIENTS One hundred and three selected patients attending the Brompton Hospital between 1966 and 1969 and suspected of having emphysema. Eighty-seven of these fulfilled the diagnostic criteria for emphysema. The remaining 16 patients comprised nine with chronic bronchitis, four with asthma, one with obliterative bronchiolitis, one with pulmonary hypoplasia, and one with systemic lupus erythematosus.

RELATIVES Sixty-eight relatives of the 16 patients found to have deficient α_1 antitrypsin levels were studied. Brief clinical details were obtained in each case.

METHODS

LABORATORY The following investigations were performed:

(a) Cellulose acetate serum electrophoresis was performed on all samples from patients.

(b) The serum antitryptic activity was measured in all cases by the trypsin inhibitory capacity (T.I.C.) method described by Eriksson (1965) using benzoyl-arginine-*p*-nitroanilide as a synthetic substrate. The *p*-nitroaniline released by tryptic hydrolysis is measured colorimetrically. The inhibitory action of serum on this reaction is expressed as milligrams of trypsin inhibited per millilitre of serum. The T.I.C. results were classified according to Eriksson's criteria as follows:

Deficient	< 0.4 mg/ml
Intermediate	0.4–0.8 mg/ml
Normal	> 0.8 mg/ml

In 39 of the 68 relatives α_1 antitrypsin levels were also measured by agar gel immunodiffusion (Mancini, Vaerman, Carbonara, and Hermans, 1964) using

rabbit anti- α_1 antitrypsin antiserum (Behringwerke). The following criteria were adopted:

Deficient	< 100 mg%
Intermediate	100–200 mg%
Normal	> 200 mg%

CLINICAL The following investigations were performed on all patients with emphysema:

(a) Postero-anterior and lateral chest radiographs. Tomography was used in some cases for the identification of bullae and the study of blood vessel distribution.

(b) Detailed pulmonary function tests including static lung volumes, spirometry (before and after bronchodilator aerosol), and gas transfer factor (TLco). The latter was measured by the steady state method (MacNamara, Prime, and Sinclair, 1959) or, in a few cases, by the single breath technique (Ogilvie, Forster, Blakemore, and Morton, 1957). Approximately half the patients also had arterial blood gas estimations and regional lung function studies using xenon 133 (Mannell, Prime, and Smith, 1966).

RESULTS

LABORATORY RESULTS (Table I and Fig. 1)

TABLE I
TRYPSIN INHIBITORY CAPACITY (T.I.C.)

Group	No.	Mean Age	T.I.C. (mg/ml)		
			Range	Mean	S.D.
Controls	87	43.7	0.63–2.06	1.13	±0.30
Deficient	16	41.1	0.12–0.33	0.32	±0.03
Intermediate	5	60.6	0.61–0.79	0.72	±0.06
Non-deficient	66	53.0	0.81–1.94	1.25	±0.30

FIG. 1. Distributions of T.I.C. levels.

Controls T.I.C. levels ranged from 0.63 to 2.06 mg/ml with a mean of 1.13 mg/ml (S.D. $\pm$ 0.30 mg/ml). Among these were three subjects who were pregnant (T.I.C. levels 2.06, 1.82, and 1.6 mg/ml) and three others with non-pulmonary carcinoma (T.I.C. levels 1.56, 1.54, and 1.20 mg/ml). Pregnancy and malignant disease are known to increase the serum α_1 antitrypsin levels and therefore if these six are omitted, the mean T.I.C. becomes 1.09 mg/ml (S.D. $\pm$ 0.25 mg/ml) which corresponds with Eriksson's results (mean 1.07 ± 0.12 mg/ml). Seven subjects had levels in the intermediate range; these were included in the calculation of the mean level for controls.

Patients Sixteen patients without emphysema all had T.I.C. levels of 0.85 mg/ml or above.

Eighty-seven patients with emphysema were divided according to their T.I.C. levels:

(a) Deficient group: sixteen patients came into this category with levels between 0.12 and 0.33 mg/ml (mean 0.32 mg/ml; S.D. $\pm$ 0.03). All had a greatly diminished or absent α_1 globulin zone on electrophoresis.

(b) Intermediate group: five patients had T.I.C. levels ranging from 0.61 to 0.79 mg/ml (mean 0.72 ± 0.06). These showed a diminished α_1 globulin zone on electrophoresis.

(c) Non-deficient group: the remaining 66 patients had levels between 0.81 and 1.94 mg/ml (mean $1.25 \text{ mg/ml} \pm 0.30$) with normal electrophoretic strips.

Relatives of patients in deficient group (Table II) Sixty-eight relatives consisted of 9 parents, 9 spouses, 15 siblings, and 35 children. The latter included 21 children of index cases plus 6 children of two siblings also found to be α_1 antitrypsin deficient and 8 children of two other siblings with intermediate T.I.C. levels.

Assuming from previous evidence (Eriksson, 1965) that the gene for α_1 antitrypsin deficiency is

transmitted as an autosomal recessive, the nine parents and 27 of the children examined may be regarded as 'genetic heterozygotes' unless any of the spouses of index cases also 'carry' the gene when some of the children might then be deficient homozygotes. In fact two children of case 4 had T.I.C. levels of 0.25 mg/ml and 0.35 mg/ml respectively, indicating that the spouse was probably a heterozygote despite a T.I.C. level of 0.82 mg/ml. The T.I.C. levels in the remaining 34 subjects ranged from 0.49 to 0.87 mg/ml with a mean of 0.73 mg/ml (S.D. $\pm$ 0.115). (One parent with a level of 1.00 mg/ml was excluded because he was receiving oestrogen therapy.) Eight of the 34 genetic heterozygotes had levels between 0.80 and 0.87 mg/ml (included in a separate column in Table II) but in four of these α_1 antitrypsin levels were estimated and found to be less than 200 mg% (105 mg%, 180 mg%, 180 mg%, and 195 mg%).

Among the eight remaining children three had intermediate and five non-deficient T.I.C. levels. One of the latter had a level of 0.82 mg/ml, but an α_1 antitrypsin level of 110 mg% (intermediate).

Of the 15 siblings, four had deficient, five intermediate, and six non-deficient levels. Two of the six non-deficient siblings had T.I.C. levels of 0.87 and 0.89 mg/ml. Both, however, had α_1 antitrypsin levels of 170 mg% (intermediate range). If these two siblings are regarded as heterozygotes, the findings became compatible with a recessive mode of inheritance with four deficient homozygotes, seven heterozygotes, and four normal subjects corresponding to the predicted ratio of 1:2:1.

The nine spouses all had non-deficient T.I.C. levels.

Thirty-nine relatives had both T.I.C. and α_1 antitrypsin levels estimated. A good degree of correlation was found in 32 subjects, 3 with deficient, 15 with intermediate, and 14 with non-deficient levels recorded by each method. In the

TABLE II
T.I.C. LEVELS IN RELATIVES OF PROBANDS

Relatives of Probands	No.	T.I.C. Levels (mg/ml)			
		< 0.4	0.4-0.8	0.8-0.87	> 0.87
Parents	9	0	7	1	1 ¹
Children	27	2	18	7	0
Spouses	9	0	0	0	9
Siblings	15	4	5	2	4
Children of siblings with intermediate T.I.C. levels	8	0	3	2	3
Total	68	6	33	12	17

¹On oestrogens.

remaining seven relatives, referred to in the text above, four of whom were considered to be genetic heterozygotes, T.I.C. levels exceeded 0.80 mg/ml (range 0.82–0.89 mg/ml) whereas α_1 antitrypsin levels were less than 200 mg% (range 105–195 mg%). This discrepancy merely highlights the difficulty in identifying the heterozygous state.

CLINICAL DETAILS OF EMPHYSEMA PATIENTS

Sex (Table III) There were 76 male and 11 female patients (ratio 7:1). This ratio was the same in both the deficient (14 males and 2 females) and non-deficient (57 males and 9 females) groups. All five patients with intermediate levels were males.

Age (Table III) The mean age at presentation, i.e., when first referred to hospital, was appreciably lower in the deficient group of patients (41.1 years) than in the intermediate (60.6 years) or non-deficient (53.0 years) groups. Dyspnoea, based on the patient's history, developed on average three to five years before presentation in each group. Dyspnoea started at a mean age of 35.6 years in the deficient group of patients, all of whom were dyspnoeic before the age of 50 years (range 29–49 years). The mean age at onset of dyspnoea in the intermediate and non-deficient groups was 56.6 and 50.4 years respectively. Only 29 of these latter 71 patients were dyspnoeic before the age of 50.

Sixty per cent of the emphysema patients whose dyspnoea began before the age of 40 years, 16% of those in whom it began between 40 and 49 years, and none of those in whom it began later were α_1 antitrypsin deficient (Table IV). All five patients in the intermediate group became dyspnoeic after the age of 50 years.

Cigarette smoking (Table III) In the deficient group of patients only one was a non-smoker.

He did not develop dyspnoea until the age of 49 years, over 13 years above the mean age and 7 years later than any other patient in that group. There were 11 non-smokers (7 male and 4 female) in the non-deficient group and none in the intermediate group.

Chronic bronchitis (Table III) Sixty-eight of the 87 patients with emphysema had chronic bronchitis and all were cigarette smokers. In the deficient group 12 (75%) had chronic bronchitis, symptoms of cough and sputum preceding dyspnoea in some cases. Excepting the non-smoker in this group, there was no difference in the age at onset of dyspnoea or presentation between those with and those without chronic bronchitis.

Peptic ulcer (Table III) Evidence of peptic ulceration, based on recent or previous barium studies, was obtained in 12 (13.7%) of all 87 patients, none being in the deficient group.

Radiographic findings (Table V and Fig. 2) In the deficient group the radiographic features of emphysema were marked. The distribution in every case was symmetrical, involving predominantly the lower zones. Bullae were seen in six (37.5%), always in the lower zones. In the other groups the appearances were more variable, symmetry was less evident, and upper zone involvement was common. Bullae were present in 29 (40.8%).

TABLE IV
AGE AT ONSET OF DYSPNOEA IN EMPHYSEMA PATIENTS
RELATED TO α_1 ANTITRYPSIN DEFICIENCY

Age at Onset of Dyspnoea (yr)	No. of Patients		% Deficient
	Total	Deficient	
< 40	20	12	60
40–49	25	4	16
> 50	42	0	0

TABLE III
CLINICAL DETAILS OF EMPHYSEMA PATIENTS

Group	No.	Sex	Age at Onset		Age at Presentation		Smoker	Chronic Bronchitis	Peptic Ulcer
			Range	Mean	Range	Mean			
Deficient	16	14 M 2 F	29–49	35.6	33–59	41.1	15	12	0
Intermediate	5	5 M	47–62	56.6	50–64	60.6	5	2	2
Non-deficient	66	57 M 9 F	23–64	50.4	31–73	53	55	54	10

TABLE V
RADIOLOGICAL DISTRIBUTION OF EMPHYSEMA

Group	No.	Emphysema					Bullae		
		Widespread			Limited		Random	U.Z.	L.Z.
		Mainly U.Z.	Mainly L.Z.	Both	U.Z.	L.Z.			
Deficient	16	0	7	2	0	5	0	0	6
Intermediate	5	0	2	1	0	2	0	0	1
Non-deficient	66	5	17	36	6	2	3	12	13

U.Z.=upper zone; L.Z.=lower zone.

FIG. 2. Chest radiograph of a deficient homozygote showing symmetrical, predominantly lower zone emphysema.

Pulmonary physiology The results in the 16 deficient patients are summarized in Table VI. In general the findings were similar in all groups.

Relatives The 68 relatives consisted of 36 males and 32 females whose ages ranged from 3 to 72 years. Of the 59 blood relatives 6 were α_1 antitrypsin deficient. Three aged under 35 years (16, 18, and 34 years) were symptom free while the

three aged over 35 years (36, 42, and 49 years) had undoubted emphysema. Three of the 33 relatives with intermediate levels and one of the 20 with non-deficient levels had chronic bronchitis. A history of extrinsic asthma was found in two relatives aged under 30 years—one with intermediate (son of case 5—IV³ in Fig. 3), the other with a normal T.I.C. level. The remaining 47 relatives were free from respiratory disease.

TABLE VI
PULMONARY PHYSIOLOGY IN α_1 ANTITRYPSIN DEFICIENT PATIENTS

Patient	FEV ₁ /FVC %	RV/TLC %	TLco (rest)		Pao ₂ (mmHg)	Paco ₂ (mmHg)
			Pred.	Obs.		
1	22	71.5	23.2	9.3	64	40
2	37	52	22.8	10.6	—	—
3	32	80.6	19.6	9.1	72	33
4	42	72	16.5	6.0	41	61.5
5	50	65.2	34.4	17.3 ¹	88	28
6	24	56	16.7	11.2	—	—
7	31	72	17.2	5.3	47	42
8	32	57	20.0	9.9	—	—
9	43.8	78.2	17.5	11.6	72	40
10	33	57	18.9	4.0	—	—
11	40	72	20.0	11.9	67	38
12	33	67	16.7	8.8	75	38
13	35.4	53	20.4	4.9	88	35
14	23	54	20.0	11.2	87	37
15	33.4	55	14.0	6.0	92.8	33.5
16	35	78	20.0	5.6	40	46

¹Single breath method.

Brief clinical details of cases 5, 9, and 13 are given together with their respective family pedigrees (Figs. 3, 4, and 5).

CASE HISTORIES

CASE 5 C.K., male aged 38.

History Well until 11 years previously when he developed extrinsic allergic asthma. Later noticed cough and sputum which improved after he stopped smoking 40 cigarettes per day. Four years ago noticed dyspnoea on exertion without wheezing. Asthma well controlled with corticosteroids and disodium chromoglycate.

Family history See Figure 3.

Examination Well-built man. Diminished breath sounds with faint expiratory wheeze. No other abnormality.

Investigations Chest radiograph shows low flat diaphragms, large retrosternal translucent zone, and attenuation of mid-lung vessels to lower zones. Pulmonary physiology (predicted values in parentheses): FRC 10,400 ml (4,250 ml); TLC 13,800 ml (7,620 ml); RV/TLC 65.2% (30%); FVC 4,400 ml (5,300 ml); FEV₁ 2,200 ml (4,240 ml); FEV₁/FVC 50% (80%); TLco (rest) 17.3 ml CO/min/mmHg—single breath method. Arterial blood gases: Pco₂ 28 mmHg; Po₂ 88 mmHg. Protein electrophoresis: absence of α_1 globulin fraction. α_1 antitrypsin level 23 mg%.

Diagnosis Emphysema and extrinsic allergic asthma.

Pedigree (α_1 antitrypsin levels in parentheses)

- I₁ d. aged 54 [Carcinoma of the larynx
- I₂ d. aged 83 No known respiratory disease
- I₃ d. aged 70 No known respiratory disease
- I₄ d. aged 89 No known respiratory disease

- II₁ aged 66 Well (110 mg %)
- II₂ aged 61 Well (115 mg %)
- III₁ Wife of proband (400 mg %)
- III₂ aged 38 Proband (23 mg %)
- III₃ aged 40 Well (110 mg %)
- III₄ aged 34 Symptom-free when seen (35 mg %)¹
- III₅ aged 36 Emphysema, mainly basal; disability minimal; smoked 15 cigarettes per day (22 mg %)
- III₆ Wife of III₅ (230 mg %)
- IV₁₋₄ aged under 15; IV₅ has extrinsic asthma; others well (125 mg %; 115 mg %; 135 mg %; 135 mg %)
- IV₅₋₈ aged under 15 both well (115 mg %; 135 mg %)

CASE 9 G.P., female aged 36.

History Progressive dyspnoea with cough and mucoid sputum for six years. Smoked 50 cigarettes per day.

Family history See Figure 4.

Examination Thin. Overinflated chest with diminished breath sounds.

Investigations Chest radiograph shows low flat diaphragms and large retrosternal translucent zone. Widespread attenuation of mid-lung vessels with lower zone bullae. Pulmonary function tests (predicted values in parentheses): VC 1,950 ml (3,760 ml); FRC 7,630 ml (3,140 ml); TLC 8,930 ml (5,510 ml); RV/TLC 78.2% (31.8%); FVC 1,600 ml (3,760 ml); FEV₁ 700 ml (3,020 ml); FEV₁/FVC 43.8% (80%); TLco (rest) 11.6 ml CO/min/mmHg at minute volume of 13.8 l/min; (17.5 ml CO/min/mmHg); % extraction CO 32% (47%). Arterial blood gases: Pco₂ 40 mmHg; Po₂ 72 mmHg. Protein electrophoresis: absent α_1 globulin fraction. T.I.C. 0.28 mg/ml.

Diagnosis Emphysema and chronic bronchitis.

¹III₄ has recently developed dyspnoea.

Pedigree (T.I.C. levels in parentheses)

I ₁	aged 73	Mild chronic bronchitis (0.86 mg/ml)
I ₂	aged 73	On oestrogen therapy (1.09 mg/ml)
I ₃	aged 67	On oestrogen therapy (1.00 mg/ml)
II ₁	aged 40	Husband of proband (0.93 mg/ml)
II ₂	aged 36	Proband (0.28 mg/ml)
II ₃	aged 40	Well (0.85 mg/ml)
III ₁	aged 2	Well
III ₂	aged 9	Well (0.70 mg/ml)
III ₃	aged 10	Well (0.70 mg/ml)
III ₄	aged 6	Well (0.78 mg/ml)
III ₅	aged 12	Well (0.82 mg/ml)

CASE 13 J.E., male aged 39.

History Cough, sputum, and progressive dyspnoea for six years. Unable to continue work as a professional dancer. Smoked 30 cigarettes per day.

Family history See Figure 5.

Examination Thin man with hyperinflated chest and diminished breath sounds.

Investigations Chest radiograph shows low flat diaphragm, large retrosternal translucent zone, narrow vertical heart, large main pulmonary vessels and attenuated mid-lung vessels, particularly in the lower zones. Pulmonary function tests: FRC 5,400 ml (4,250 ml); TLC 7,950 ml (7,620 ml); RV/TLC 53.0% (30.4%); FVC 3,400 ml (5,300 ml); FEV₁ 1,200 ml (4,240 ml); FEV₁/FVC 35.4% (80.0%); TLco (rest) 4.9 ml CO/min/mmHg at minute volume of 6.65 l/min (20.4 ml CO/min/mmHg); % extraction CO 30.2 (46%). Arterial blood gases: Pco₂ 35 mmHg; Po₂ 88 mmHg. Protein electrophoresis: diminished α₁ globulin fraction. T.I.C. 0.18 mg/ml.

Progress Had a plication of right lower lobe with minimal improvement. Losing weight.

Diagnosis Emphysema and chronic bronchitis.

Pedigree (T.I.C. levels in parentheses)

I ₁ d.	aged 74	No known respiratory disease
I ₂ d.	aged 72	No known respiratory disease
I ₃ d.	aged 66	No known respiratory disease
I ₄ d.	aged 64	No known respiratory disease
II ₁ d.	—	Cerebral tumour
II ₂	—	Well
II ₃	aged 71	Chronic bronchitis (0.79 mg/ml)
II ₄	aged 72	Well (0.79 mg/ml)
II ₅₋₁₆	—	Two sisters had pulmonary tuberculosis; no other evidence of respiratory disease
III ₁	aged 39	Proband (0.18 mg/ml)
III ₂	aged 49	Emphysema; 12-year history of progressive dyspnoea; severely incapacitated and losing weight; smokes 30 cigarettes per day (0.38 mg/ml)
III ₃	aged 46	Wife of III ₂ (1.0 mg/ml)
IV ₁	aged 23	Well (0.84 mg/ml)
IV ₂	aged 13	Well (0.84 mg/ml)
IV ₃	aged 20	Well (0.83 mg/ml)

DISCUSSION

Alpha₁ antitrypsin forms the major component of the α₁ globulin fraction seen on serum electrophoresis. First isolated by Schultze, Heide, and Haupt (1962), its physical characteristics are now well described (Schultze *et al.*, 1963). It is responsible for approximately 90% of the total serum T.I.C., the remaining 10% being mainly in the form of an α₂ macroglobulin. The role of α₁ antitrypsin in healthy subjects is as yet unknown. Raised levels have been reported in association with malignant disease (Clark, Clifton, and Newton, 1948), pregnancy (Faarvang and

Lauritsen, 1963), and in response to a variety of stimuli including infections (Jacobsson, 1955), typhoid vaccine (Kueppers, 1968), oestrogens (Schumacher and Pearl, 1968), surgical stress, and corticosteroids (Faarvang and Lauritsen, 1963).

This study has confirmed the association between a genetically determined deficiency of α_1 antitrypsin and pulmonary emphysema. Sixteen (18.4%) of the 87 patients with clinical, radiological, and physiological evidence of emphysema had absent α_1 globulin fractions on serum electrophoresis and unequivocally deficient T.I.C. levels of 0.33 mg/ml or less, 11 to 30% of the mean level in controls. This incidence of 18.4% in a highly selected group of patients is greater than that found in other series. However, methods of selection and investigation have differed widely, making comparisons difficult. The previous highest incidence was 11% of 55 individuals with severe airways obstruction reported by Pedersen, Weeke, and Georg (1969) whose criteria most closely matched those of this study. It is probable, as these authors implied, that the more stringent the criteria used the higher the incidence obtained is likely to be, an observation that would apply particularly to this study. Local environmental factors cannot be implicated as the patients came from many different geographical areas both urban and rural.

The clinical picture of emphysema in patients with α_1 antitrypsin deficiency is well documented (Talamo, Blennerhassett, and Austen, 1966) and shows certain features not seen with emphysema in general. The most consistent difference is the much earlier age at which dyspnoea develops, usually in the third decade. The youngest recorded case is 22 years (Makino, Chosy, Valdivia, and Reed, 1970). In the present series the mean age at onset of dyspnoea was only 35 years; four-fifths of the patients in the deficient group were dyspnoeic before the age of 40 years and all before the age of 50 years. Considering all 87 emphysema patients, the younger the age at which symptoms developed, the higher was the incidence of α_1 antitrypsin deficiency: among the 20 patients who became dyspnoeic before the age of 40 years, 60% were α_1 antitrypsin deficient.

Similar observations were made in the six relatives also found to be α_1 antitrypsin deficient. Three, aged 38 to 49 years, had undoubted emphysema while the other three, all under 35 years of age, were symptom-free though not fully investigated. Recent evidence (Levine, Talamo, Shannon, and Kazemi, 1970) suggests that detailed physiological evaluation of lung function may

detect abnormalities in asymptomatic patients with α_1 antitrypsin deficiency and that altered distribution of pulmonary perfusion using xenon 133 is the earliest detectable defect. Thus, it appears that the majority of subjects with α_1 antitrypsin deficiency, approximately 90% according to Eriksson (1965), are likely to develop emphysema before the age of 50 years.

Kowalyszyn and Sataline (1969) stated that emphysema associated with α_1 antitrypsin deficiency occurs predominantly in females, but this has not been confirmed in most series. Although 10 of 13 α_1 antitrypsin deficient patients with emphysema reported by Welch, Reinecke, Hammersten, and Guenter (1969) were women, these authors commented that this might not be a true representation of sex distribution, as young women with emphysema were sufficiently unusual to prompt referral for consultation. In the present series a great excess of men was found among deficient and non-deficient emphysema patients, the sex ratio being 7:1 in both groups.

Eriksson (1965) found emphysema in 88% of men with α_1 antitrypsin deficiency but in only 50% of women. This suggests that either α_1 antitrypsin deficient females are protected against the development of emphysema or that exogenous factors, affecting men predominantly, are important.

The importance of cigarette smoking to the early development of symptoms in patients with emphysema and α_1 antitrypsin deficiency has been emphasized (Kueppers, Fallat, and Larson, 1969). This may have been relevant in the case mentioned by Townley, Rynning, Lynch, and Brody (1970); this was a 46-year-old male non-smoker who, though a deficient homozygote, showed no evidence of emphysema. In the present study the mean age at onset of dyspnoea in the deficient group was 35.6 years, yet symptoms did not develop until the age of 49 years in the only non-smoker in the group. Among non-deficient patients no such difference between smokers and non-smokers was apparent.

It has been reported (Talamo, Allen, Kahan, and Austen, 1968) that chronic bronchitis occurs infrequently in association with emphysema in α_1 antitrypsin deficient subjects. However, a review of the literature shows that the majority of patients do have the features of chronic bronchitis, though clinical details are often sparse and evaluation difficult. Sixteen (70%) of Eriksson's (1965) 23 patients had produced sputum for five years or more while 10 (77%) of 13 patients reported by Welch *et al.* (1969) were said to have

bronchitis. In the present study 75% of the α_1 antitrypsin deficient patients and 78% of all patients gave a history of chronic bronchitis.

It is of interest to note that a history of extrinsic allergic asthma, a disease in which genetic factors are probably important, was found in case 5 and in one of his sons who was a heterozygote. A similar family history of extrinsic allergic asthma was recorded in two of Eriksson's deficient homozygotes (1965) and in four members of the family reported by Townley *et al.* (1970).

A high incidence of peptic ulcer has been reported in patients with a variety of chronic bronchopulmonary diseases (Mitchell and Filley, 1964). Eriksson (1965) found an incidence of 30% in deficient homozygotes with emphysema and similar results have since been obtained (Lieberman, 1969). By comparison, in this study, though 15% of non-deficient patients gave a history of peptic ulcer none of the deficient group did so.

The radiographic appearances of emphysema in α_1 antitrypsin deficient patients have been described in detail (Welch *et al.*, 1969) and agree closely with those seen here. Involvement was invariably symmetrical and maximal in the lower zones. Bullae were common. These changes differed from those seen in non α_1 antitrypsin deficient patients in whom symmetry was infrequent and upper zone distribution common. However, a clear-cut distinction was not always apparent; 19 (28.8%) of the non-deficient group of patients also exhibited lower zone predominance. Nevertheless, it is evident that α_1 antitrypsin deficiency should be suspected in patients presenting before the age of 50 years with progressive dyspnoea and radiographic evidence of symmetrical lower zone emphysema.

Radioxenon studies confirmed the impairment of ventilation and perfusion to the lower zones in the α_1 antitrypsin deficient group of patients. Other tests of pulmonary function differed little between the three groups.

Whereas the homozygous deficient state was readily identified on the basis of T.I.C. levels alone, using Eriksson's criteria, no such precise correlation existed between the heterozygous state and intermediate T.I.C. levels. Family studies indicated that several 'genetic heterozygotes' had T.I.C. levels of between 0.8 and 0.87 mg/ml. Lieberman (1969) and Kueppers (1967), using similar techniques, have also recorded T.I.C. levels of 0.85 mg/ml or greater in true heterozygotes. It has been shown that heterozygotes, unlike deficient homozygotes, are capable of increasing their T.I.C. levels to within the normal

range in response to certain stimuli (Kueppers, 1968). This was probably the case in the male parent of the homozygous patient who had a T.I.C. level of 1.00 mg/ml and who was being treated with oestrogens for carcinoma of the prostate.

In view of the possible overlap in T.I.C. levels in a proportion of heterozygotes and normal subjects, accurate distinction between the two is difficult and leads to an underestimate of the frequency of the heterozygous state. Eriksson (1965) found a frequency of 4.7% in a Scandinavian population and Kueppers, Briscoe, and Bearns (1964) 2.1% in a small white population in Georgia, U.S.A. Using similar techniques in the present study, we found that 10% of controls had intermediate T.I.C. levels, the number rising to 14% if the upper limit is raised to 0.9 mg/ml. Kueppers, Fallat, and Larson (1969), in a follow-up study using 'antigen antibody crossed electrophoresis', a technique based on qualitative rather than quantitative differences in globulins which, they claim, distinguishes reliably between heterozygotes and normal individuals, found an incidence of 9 to 14% of heterozygotes in their controls.

Due partly to the difficulties in recognizing the heterozygous state, its role in the development of pulmonary disease has remained in dispute. Eriksson (1965) and other workers failed to find any evidence to associate the heterozygous state with lung disease in general or emphysema in particular. However, using antigen antibody crossed electrophoresis, Kueppers *et al.* (1969) found that 25.5% of their patients with 'obstructive lung disease' compared to 9 to 14% of their controls were heterozygotes whereas, when T.I.C. estimations alone had been used in an earlier series, they had found no heterozygotes among 99 patients with emphysema. Lieberman (1969) measured the T.I.C. levels of 66 patients with emphysema and found 15.2% of heterozygotes and 10.6% of deficient homozygotes. These authors did not have a control group but regarded a T.I.C. level of 0.85 mg/ml as the upper limit of normal.

Unfortunately, assessment of these findings is complicated by the fact that the terms emphysema and particularly chronic obstructive lung disease, so commonly used, are often not precisely defined. In the present series there was no evident association between the heterozygous state and either chronic bronchitis or emphysema.

The relationship between α_1 antitrypsin deficiency and the pathogenesis of emphysema is

still conjectural and it remains to be proved whether this deficiency is causally related to the development of emphysema or merely acts as a genetic marker. It is possible that α_1 antitrypsin normally protects alveolar septa against enzymatic digestion. Gross *et al.* (1965) showed that in rats panacinar emphysema could be produced by intratracheal instillation of the proteolytic enzyme papain and this has recently been confirmed in dogs (Pushpakom *et al.*, 1970). The α_1 globulins inhibit not only trypsin but also chymotrypsin, plasmin, thrombin and elastase (Rimon, Shamash, and Shapiro, 1966; Turino *et al.*, 1969). Kueppers and Bearns (1966) observed that α_1 antitrypsin inhibits the proteolytic enzymes released by human leucocytes. It seems possible that these enzymes are being continually released in the alveoli by macrophages and other phagocytic cells and that failure to inhibit them may lead to increased breakdown or disturbed re-synthesis of alveolar connective tissue proteins. The continual physical stress of the lung during normal breathing might be sufficient to precipitate the structural defects in this organ leading to emphysema.

Although curative treatment is not possible, early detection is important so that factors such as cigarette smoking and infection, which may increase lung destruction, can be eliminated. Fortunately the clinical presentation and the pattern of serum electrophoresis in affected individuals appears to be sufficiently characteristic to suggest the diagnosis which can be readily confirmed by α_1 antitrypsin estimation. Should the heterozygous state also be shown to predispose to pulmonary emphysema and to occur commonly in the population, then identification of all affected persons might become necessary.

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ADDENDUM

Since this paper was submitted for publication a further article on this subject has been published [Hutchinson, D. C. S., Cook, P. J. L., Barter, C. E., Harris, H., and Hugh-Jones, P. (1971). Pulmonary emphysema and α_1 antitrypsin deficiency. *British Medical Journal*, **1**, 689]. They studied 72 patients with radiographic evidence of pulmonary emphysema, using criteria similar to those described in this paper but found a lower incidence (11.1%) of α_1 antitrypsin deficiency. The T.I.C. levels which they reported were appreciably higher, both in the controls and in the patients classified as 'deficient', than those found in this investigation and those recorded by other workers.

The clinical and radiological features in their eight patients with α_1 antitrypsin deficiency are similar to those described in this article. However, the horizontal striations at the costophrenic angles which they observed in the chest radiographs were not evident in the present series.