PAPERS AND ORIGINALS

Pulmonary Emphysema and α_1-Antitrypsin Deficiency

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Summary

Of 72 patients with radiological evidence of pulmonary emphysema, emphysema occurred either alone or in association with bronchitis in 61, and 8 of these (13%) were found to have α_1-antitrypsin deficiency. The main features of this condition are: exertional dyspnoea of relatively early onset (generally between 30 and 45 years of age), severely impaired FEV_1 and T_{LCO}, and radiological emphysema predominantly affecting the lower zones of the lungs. It is probable that any patient with all the above abnormalities has α_1-antitrypsin deficiency. There is evidence to suggest that cigarette smoking may hasten the onset of this type of emphysema.

Introduction

Deficiency of α_1-antitrypsin has been found to be associated with early onset of generalized pulmonary emphysema (Laurell and Eriksson, 1963; Eriksson, 1964). Eriksson (1965) showed that the plasma concentration of α_1-antitrypsin, the major component of the α_1-globulin fraction, is genetically determined and suggested that this level was dependent on a pair of autosomal genes. He found that α_1-antitrypsin is normally responsible for about 90% of the total serum trypsin inhibitory capacity (T.I.C.), the values of which appeared to fall into one of three main groups: normal, "intermediate" (60% of normal), and "low" (10%), corresponding respectively to normal individuals, to heterozygotes, and to homozygotes with α_1-antitrypsin deficiency. The frequency of α_1-antitrypsin deficiency in a Swedish population was estimated by Eriksson (1965) to be about 1 in 1,750.

A number of genetically determined α_1-antitrypsin variants may be detected by starch gel electrophoresis (Fagerhol, 1968). Each allele has been assigned an alphabetical letter on the basis of the electrophoretic mobility of the variant it determines, and the common pattern with normal plasma α_1-antitrypsin and T.I.C. is termed type MM. Individuals with α_1-antitrypsin deficiency are of type ZZ and have a low T.I.C.

A number of cases of α_1-antitrypsin deficiency have now been described, but there has been some disagreement regarding the prevalence of the condition among patients with emphysema, which may perhaps arise from differences in the way that emphysema has been defined. The object of the present investigation was to study only patients with definite radiological evidence of emphysema and to estimate the prevalence of α_1-antitrypsin deficiency in this selected group. We have also measured plasma α_1-antitrypsin in relatives of the propositi, and those found to be deficient have been more fully investigated.

Patients and Methods

We have examined standard posteroanterior chest radiographs of most of the patients investigated in the pulmonary research unit at King's College Hospital during the past eight years. Plasma T.I.C. estimation and starch gel electrophoresis were performed in as many as possible of those patients who were found to have radiological pulmonary emphysema by the criteria of Laws and Heard (1962).

Detailed case histories were obtained by us in person from those patients (Cases 1 to 8) and the sibs of Cases 3 to 5 (Subjects 3b and 5b) who had α_1-antitrypsin deficiency. Particular attention was paid to the age of onset of permanent exertional dyspnoea and of the onset of chronic bronchitis when present (Medical Research Council, 1965). A history of cigarette smoking at all periods of the patient's life was obtained and the quantity of tobacco consumed was estimated in grammes. One cigarette of the most popular size (class B) was considered to contain 1 g of tobacco (0·8 g if tipped) and smaller untipped cigarettes of Woodbine type (class A) to contain 0·8 g (Tomalin, 1969). For those patients who "rolled their own" the weight smoked in ounces was converted into grammes.

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The body weight was expressed as a percentage of the mean value for subjects of equivalent height and age (Society of Actuaries, 1959). In patients who had undergone thoracic surgery the only data considered were the preoperative chest x-ray films and pulmonary function.

Biochemical Methods.—Heparinized blood samples were used throughout. Starch gel electrophoresis was carried out by a modification of the method of Fagerhol (1969). Gels of 14·5% hydrolysed starch (Connaught Laboratories) were run at pH 5 for seven hours at 30 mA. T.I.C. assays were performed by a modification of Eriksson's (1965) method. One millilitre of plasma diluted 1:100 in 0·05 M tris buffer (pH 8) was incubated with 0·04 mg of trypsin (Boehringer) in 0·5 ml of N/1,000 HCl for 10 minutes at 25°C. Then 1·5 ml of 0·002 M N-α-benzoyl-L-arginine ethyl ester hydrochloride (B.D.H.) containing 0·008 M $CaCl_2$ in tris buffer was added and the rate of change in optical density at 25°C was measured in a spectrophotometer at 254μ. The T.I.C. was expressed in mg of trypsin inhibited per ml of plasma. The values obtained in 279 healthy unrelated subjects were used as controls.

Radiology.—Standard 6 ft. posteroanterior and lateral films were taken during full inspiration in the upright position. Whole lung tomograms were obtained in all propositi and one of their sibs with α_1-antitrypsin deficiency. The presence of vascular attenuation, bullae, lung compression or overexpansion, "chronic inflammatory disease" (Fletcher, Jones, Burrows, and Niden, 1964), and any other abnormality was recorded.

Pulmonary Function.—Forced expiratory volume in one second (FEV_1), vital capacity (VC), functional residual capacity (FRC), total lung capacity (TLC), carbon monoxide transfer factor (T_LCO), arterial oxygen and carbon dioxide tensions (Pao_2, $Paco_2$), physiological dead space as a fraction of tidal volume (V_D/V_T), and alveolar-arterial O_2 tension difference ($A\text{-}aDo_2$) were measured by methods given by Pride, Hugh-Jones, O'Brien, and Smith (1970), except that in calculation of T_LCO the alveolar volume was obtained from the simultaneous dilution of helium. Normal values for all the above measurements were obtained from the diagrams of Cotes (1968). kCO, the permeability constant for carbon monoxide (Krogh, 1915), was derived by the formula given by McGrath and Thomson (1959), and in all normal subjects studied in this laboratory was greater than 3·5 min^{-1}. Lobar ventilation was measured at bronchoscopy as described by Hugh-Jones (1967).

Results

Blood samples were obtained from 72 patients who fulfilled the radiological criteria of pulmonary emphysema.

TABLE I—*Plasma Trypsin Inhibitory Capacity (T.I.C.)**

Subjects	No.	T.I.C.* Mean	T.I.C.* S.D.	P Difference of Means
Emphysema alone or with bronchitis:				
α_1-antitrypsin Deficient	8	0·61	0·20	<0·001
α_1-antitrypsin Normal	53	1·86	0·38	
				0·2–0·1
Emphysema associated with asthma or fibrosis	11	2·06	0·28	0·05–0·025
Total No. with emphysema	72			0·01–0·05
Control (unrelated healthy individuals)	279	1·73	0·40	
Sibs with α_1-antitrypsin deficiency	4	0·72	0·15	

*mg Trypsin inhibited/ml plasma.

Emphysema occurred either alone or in association with bronchitis in 61 patients (Table I), of whom eight were homozygous for α_1-antitrypsin deficiency. On starch gel electrophoresis (Fig. 1) the M bands were absent or replaced by faint Z bands and the mean T.I.C. was significantly lower

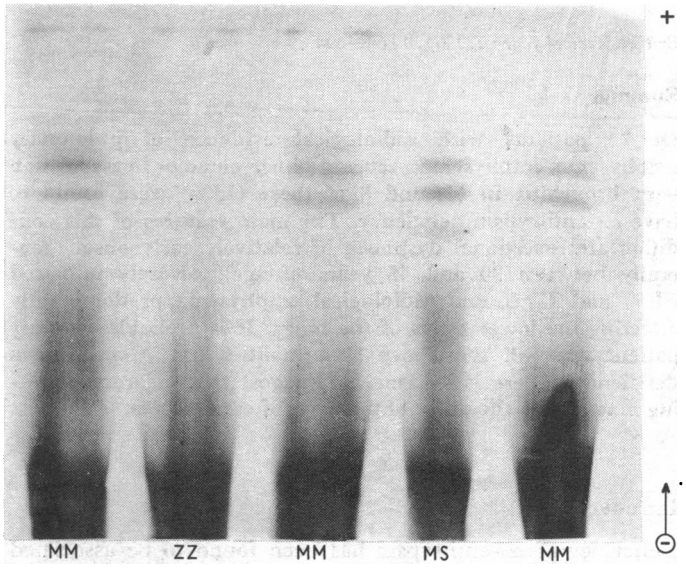

FIG. 1—Starch gel stained with nigrosin showing: (*a*) the normal MM phenotype; (*b*) the ZZ phenotype typical of α_1-antitrypsin deficiency (Case 6); no M bands are visible, and faint Z bands of very slow migration rate are present; and (*c*) the MS phenotype, heterozygous for the "slow" (S) variant; this pattern is present in about 5% of the population of the U.K.

TABLE II—*Patients with α_1-antitrypsin Deficiency: Clinical Data*

Case No.	Sex	Age (Years)	Height (m)	Weight kg	Weight % of Predicted	Dyspnoea on Exertion: Age of Onset (Years)	Chronic Bronchitis: Age of Onset (Years)	Cigarette Smoking: Total in Grammes × 10^3
1	F.	49	1·60	60	91	43	—	2·1
2	M.	41	1·65	68	96	38	38	0·7
3	M.	50	1·68	51	70	36	40	1·0
4	M.	45	1·87	62	70	36	—	0·6
5	M.	48	2·03	97	95	38	32	1·8
6	F.	52	1·65	54	77	42	42	2·7
7	M.	39	1·74	56	74	28	—	1·1
8	M.	46	1·70	64	87	40	36	1·5
Mean		46·2	1·74	64·0	82·5	37·6	37·6	1·44
S.D.		4·5	0·14	14·4	11·0	4·6	3·8 (N=5)	0·73
Subject 3b	M.	73	1·63	72	110	50	50	2·6
„ 4b	M.	50	1·92	96	104	—	—	Nil
„ 5b	F.	44	1·77	62	84	—	—	Nil

Subjects 3b, 4b, and 5b are sibs of Cases 3, 4, and 5 respectively.

than that of the 53 other patients in this group ($P<0.001$). The mean T.I.C. of these 53 was slightly greater than that of the controls ($0.05>P>0.025$). In the remaining 11 patients, all of whom had normal plasma α_1-antitrypsin concentrations, emphysema was associated with bronchial asthma (six patients) or with severe forms of localized or generalized fibrosis (five patients).

The patients with α_1-antitrypsin deficiency had a total of 17 full sibs, of whom 14 survived. One, a female, was stated to have died at the age of 38 from "chest trouble." Starch gel electrophoresis and T.I.C. estimations were performed in 12 of the surviving sibs, of whom four were found to have α_1-antitrypsin deficiency. There was no significant difference between the mean T.I.C. of these four subjects and that of the eight propositi ($0.5>P>0.4$).

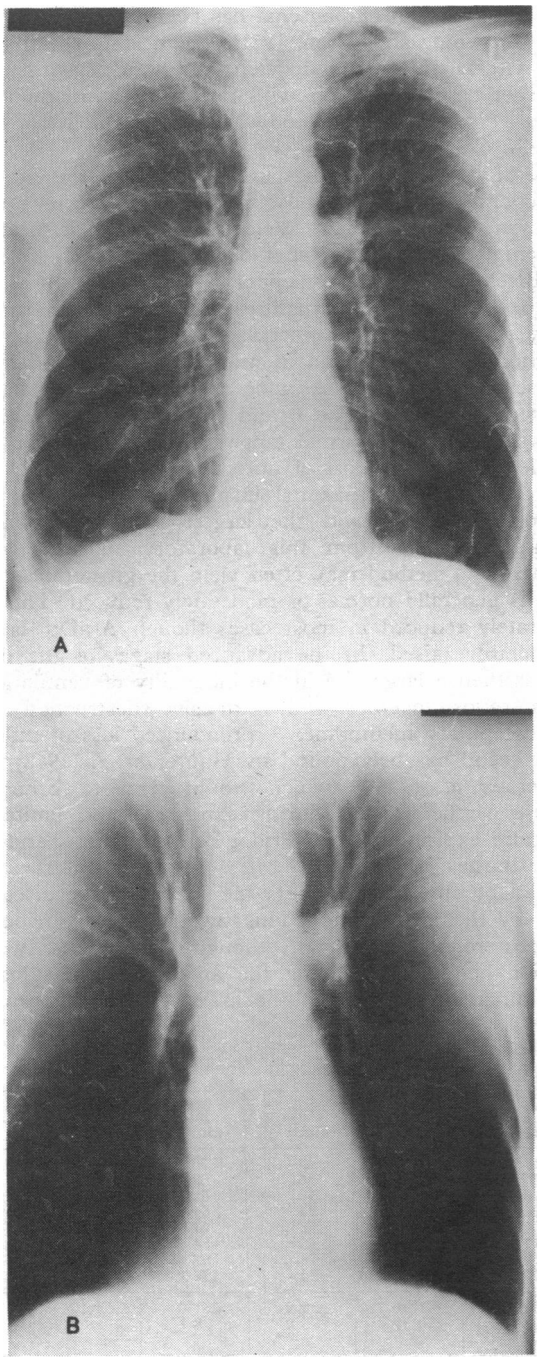

FIG. 2—Case 4. A, posteroanterior chest in full inspiration. B, whole lung tomogram (13 cm cut). The lungs are overexpanded with severe vascular attenuation at both bases. The left upper zone is also affected.

CLINICAL FEATURES

The most prominent symptom in all eight patients was shortness of breath on exertion, the mean age of onset being 37.6 years (S.D. 4.6) (Table II). Two (Cases 1 and 5) complained that the chest became "blown up" on exertion after which they had difficulty in deflating their lungs. Five patients had chronic bronchitis and in two (Cases 5 and 8) this preceded the onset of exertional dyspnoea. Two (Cases 4 and 7) first became aware of exertional dyspnoea immediately after an acute respiratory infection. Cases 6 and 7 stated that, in retrospect, they believed that they had been unduly short of breath on exertion since childhood, though pronounced deterioration and interference with the way of life did not occur until some years later (see Table II). Case 5 also gave a history of intermittent wheeziness from the age of 32 and was regarded as having bronchial asthma; two near relatives were also stated to be asthmatic. All eight had been moderate or heavy cigarette smokers (with inhalation) for a number of years. Four were substantially below the expected body weight for their height and age, though actual weight loss had occurred in only two (Cases 4 and 7). Two (Cases 3 and 6) had maintained a relatively low body weight for some years; Case 3 had undergone a partial gastrectomy.

Three of the four sibs with α_1-antitrypsin deficiency underwent further investigation. Subjects 3b, 4b, and 5b were the sibs of Cases 3, 4, and 5 respectively. Subject 3b was an elderly man with a history of over 20 years of sputum production. Subjects 4b and 5b were healthy subjects with no respiratory symptoms. Subject 4b was a pipe smoker (who did not inhale) with a current tobacco consumption of 1 oz (28.3 g) per week; his maximum past consumption was of the order of 2 oz (56.7 g) per week, and he had never smoked more than 10 cigarettes in a year. Subject 5b had never smoked.

RADIOLOGICAL FEATURES

Gross vascular attenuation was seen in the standard posteroanterior radiographs and in tomograms in all eight propositi (Cases 1 to 8), the lower zones being the most severely affected in all. The typical appearances are shown in Fig. 2 A and B. Less severe vascular attenuation was also seen in one upper zone in four patients (Cases 2, 4, 5, and 7). There was evidence of "chronic inflammatory disease" in Case 6. None of the sibs (Subjects 3b, 4b, and 5b) had evidence of emphysema.

In five subjects (Cases 1, 3, 6, and 8 and Subject 3b) unusual horizontal linear striations were observed in one or

TABLE III—*Patients with α_1-antitrypsin Deficiency: Radiological Data*

Case No.	Vascular Attenuation	Bullae	Other Findings
1	LLZ+	Nil	Faint linear striations: R. and L.
2	LUZ+ R and LLZ ++	Anterior LZ (Lateral view only)	Mediastinal shift to R.
3	R and LLZ++	R and LLZ	Dense linear striations: L. Compression L. lower lobe
4	LUZ+ R and LLZ++	R and LLZ	—
5	LUZ+ R and LLZ++	Nil	—
6	R and LLZ++	R and LLZ	Dense linear striations: R. and L. "Chronic inflammatory disease"
7	LUZ+ R and LLZ++	R and LLZ	Enlargement of R. and L. pulmonary arteries
8	RLZ+ and LLZ++	Nil	Faint linear striations: R. and L.
3b	Nil	Nil	Dense linear striations: R. and L.
4b	Nil	Nil	—
5b	Nil	Nil	—

LZ Lower zone. UZ Upper zone.
+ Moderate. ++ Severe.
Linear striations: visible in costophrenic angles on posteroanterior view (see text).

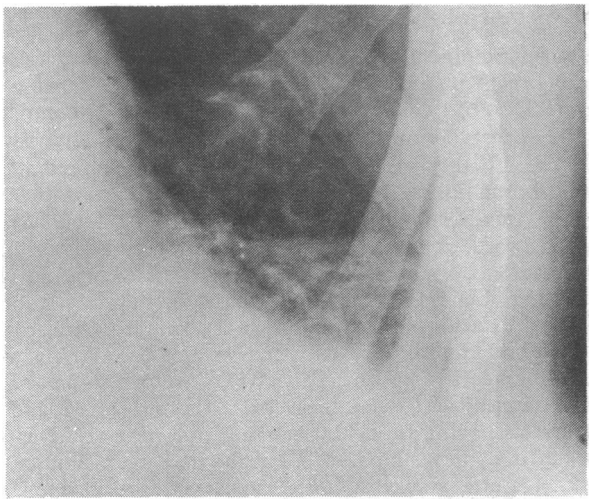

FIG. 3—Enlargement (×1·14) of the left lower zone of Subject 3b showing dense horizontal striations in the costrophrenic angle (see text).

both costophrenic angles. In some patients these were of considerable density (Fig. 3).

RESPIRATORY FUNCTION

In all eight propositi the FEV_1 and $FEV_1/VC\%$ were severely reduced (Table IV); there was no significant increase in FEV_1 after inhalation of isoprenaline aerosol. VC was within normal limits in all. TLC was normal or raised and FRC was considerably raised in all but one. T_{LCO} and kCO were severely reduced in all. $Paco_2$ was reduced or normal in all but one (Case 7). There was a reduction in Pao_2 in all patients, though in some instances this was relatively slight; the $A\text{-}aDo_2$, however, was severely raised in all those in whom it was measured. V_D/V_T was raised in three.

In Subject 3b the FEV_1, VC, T_{LCO}, and kCO were all moderately reduced. In Subjects 4b and 5b the values for VC were greater than those predicted. T_{LCO} was at the lower limit of normal in both these subjects, and kCO was moderately reduced.

Measurement of the ventilation of individual lobes at bronchoscopy indicated that the main abnormalities were in the lower and middle lobes in five of the six patients in whom the test was performed. In case 2 the left upper lobe and right lower lobe appeared to be the lobes mainly affected.

Discussion

Eriksson (1964), in his report of the first few cases of α_1-antitrypsin deficiency, drew attention to its association with severe generalized pulmonary emphysema, presenting with shortness of breath at a relatively early age, commonly between 30 and 40 years. Though Talamo, Allen, Kahan, and Austen (1968) found that there was no evidence of early bronchitis in the majority of such patients, Eriksson (1965) reported that over half suffered from recurrent attacks of bronchitis with sputum production. In a number of his patients bronchitis preceded the onset of exertional dyspnoea, though the latter eventually became the most prominent feature in all. Similar results were obtained by Briscoe, Kueppers, Davis, and Bearn (1966), by Hunter, Pierce, and LaBorde (1968), by Tarkoff, Kueppers, and Miller (1968), and by Welch, Reinecke, Hammarsten, and Guenter (1969), and in the present report five of the eight patients had a history of chronic bronchitis.

Loss of body weight has been described in a number of patients with α_1-antitrypsin deficiency (Eriksson, 1965; Welch *et al.*, 1969) and occurred in two of our cases. An association of weight loss with emphysema has been recognized for some years (Browning and Olsen, 1961). There is no specific association with α_1-antitrypsin deficiency as patients with a similar degree of emphysema but with normal α_1-antitrypsin have a similar distribution of body weight (Hutchison, Barter, Martelli, Cook, and Hugh-Jones, 1970).

The physiological findings in the present series of patients are generally similar to those reported by previous workers (Eriksson, 1965; Guenter, Welch, Russell, Hyde, and Hammarsten, 1968; Hunter *et al.* 1968; Tarkoff *et al.*, 1968; Hepper, Black, Gleich, and Kueppers, 1969; Welch *et al.*, 1969). One of the main abnormalities is a gross impairment of FEV_1, with little or no increase following inhalation of a bronchodilator aerosol and in most cases T_{LCO} and kCO are also severely reduced. A wide variation in VC has been reported by Eriksson (1965) and by Welch *et al.* (1969), but this was within the normal range in all our patients. It may be relevant that in most of our cases the VC was measured both during a slow maximal inspiration and during a slow maximal expiration and the largest values were selected. Unpublished data from this laboratory suggests that the "inspiratory" method may often yield the greater results. The $Paco_2$ is generally normal or moderately reduced. The Pao_2 is moderately reduced in most cases though $A\text{-}aDo_2$ is always considerably raised. In the advanced stages of the disorder there is then a large rise in the inequality of ventilation-perfusion ratios together with extensive destruction of the alveolo-capillary membrane. A pronounced loss of pulmonary elastic recoil has been found by Hunter *et al.* (1968) and by Hepper *et al.* (1969), which would tend to bring about collapse of the airways during expiration and limitation of maximum expiratory flow (Pride, Permutt, Riley, and Bromberger-Barnea, 1967).

In all of our eight patients the brunt of the disease was borne by the lower zones. This was generally obvious from the posteroanterior views, though tomograms were on occasion helpful in defining the area of vascular loss. The predominant destruction of the lower zones has been amply

TABLE IV—*Patients with α_1-antitrypsin Deficiency: Measurements of Pulmonary Function*

Case No.	FEV_1 (% Predicted)	VC (% Predicted)	FEV_1/VC (%)	FRC (% Predicted)	T_LC (% Predicted)	T_{LCO} (% Predicted)	kCO (Min^{-1})	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)	$A\text{-}aDo_2$ (mm Hg)	V_D/V_T (%)
1	19	89	20	127	89	17	1·1	42	78	28	28
2	21	95	18	193	147	25	1·2	36	82	31	43
3	35	95	28	67	92	40	2·0	40	69	38	31
4	22	98	18	192	152	24	1·2	34	61	50	53
5	21	107	14	247	143	37	1·6	30	77	30	30
6	19	103	17	152	135	17	0·9	45	64	40	40
7	15	79	15	150	128	10	0·6	58	62	—	—
8	36	81	34	130	115	45	2·3	34	75	—	—
Mean	23·5	93·4	20·5	157·2	125·1	26·9	1·36	39·9	71·0	36·2	37·5
S.D.	7·7	9·9	6·9	54·0	24·3	12·5	0·57	8·8	8·1	8·3	9·6
3b	48	75	46	—	—	64	2·3	—	—	—	—
4b	103	126	60	137	122	71	2·4	—	—	—	—
5b	87	122	61	—	—	71	2·4	—	—	—	—

described by previous authors. Eriksson (1965), Briscoe *et al.* (1966), Guenter *et al.* (1968), Hepper *et al.* (1969), Kowalyshyn and Sataline (1969), and Welch *et al.* (1969) have demonstrated by *x*-ray examination or lung scan that the main abnormalities were situated in the lower zones in practically every case. The horizontal linear striations (Fig. 3) observed in five subjects also deserve some comment. These opacities were in some cases of considerable density and, so far as we are aware, have not been previously described. They bear no resemblance to Kerley's B lines, nor to the linear opacities described by Laws and Heard (1962), and their precise nature remains uncertain.

Pathological details are available in relatively few cases, but in all those reported emphysema was of the panacinar type and the lower lobes were more severely affected (Eriksson, 1965; Schleusener, Talamo, Paré, and Thurlbeck, 1968; Tarkoff *et al.*, 1968).

PREVALENCE

The frequency of the ZZ phenotype in the general population has been estimated at about 1 in 1,750 by Eriksson (1965) in a survey of a Swedish community of 6,995 persons. We have found no examples of the ZZ phenotype among 1,250 unrelated, apparently healthy Europeans mainly from the United Kingdom. The frequency among patients with emphysema, however, is in dispute, a matter which may be due to differences in selection criteria. Kueppers, Briscoe, and Bearn (1964), for instance, could find only one such subject among 99 patients attending an emphysema clinic, while in a later publication (Kueppers, Fallat, and Larson, 1969) 5 were found out of 103 patients classified as having chronic obstructive pulmonary disease. Lieberman (1969) found seven patients (10·4%) with α_1-antitrypsin deficiency among 66 patients with emphysema, the frequency rising to 47·8% when patients under the age of 50 were considered alone. Hepper *et al.* (1969), found that 5 out of 14 patients with chronic obstructive lung disease under the age of 40 had α_1-antitrypsin deficiency, and if the selection had been confined to a homogeneous group of five males under the age of 40 with radiological evidence of lower zone emphysema, then all would have had the deficiency. In these investigations, however, precise selection criteria have not been stated, and so a direct comparison with each other and with our own study is not possible.

All patients described in the present report did, in fact, have definite radiological evidence of emphysema by well-established criteria, and 8 out of 72 (11·1%) had α_1-antitrypsin deficiency. This group may not, however, be representative of the distribution and type of emphysema in the population as a whole. If the selection of patients is based on radiological criteria alone some of the milder cases will not be included. Furthermore, some of the patients were referred for assessment for surgical treatment, and so there may have been further selection in favour of younger patients and those in whom the disorder seemed relatively localized. Whatever the true position, a particularly high incidence of α_1-antitrypsin deficiency is found when the characteristics of our younger patients are examined more closely. If we consider a group of patients with relatively severe emphysema ($T_LCO<45\%$ of the predicted value), who developed permanent exertional dyspnoea between the ages of 30 and 45 inclusive, then 7 out of 11 (64%) have the deficiency. This figure rises to 100% if the group is still more narrowly defined to include only those with emphysema confined to or predominantly involving the lower zones.

CIGARETTE SMOKING

Not all subjects with α_1-antitrypsin deficiency develop emphysema at this early age, however, and an unknown proportion may escape altogether or develop the disease late in life. The only relevant study is the population survey of Eriksson (1965) where two of the four deficient subjects detected had definite evidence of emphysema though the numbers are clearly too small for any accurate conclusion to be drawn. Nevertheless, the onset of emphysema may be precipitated by certain additional factors, one of which may be cigarette smoking, though the evidence is conflicting. The patients of Briscoe *et al.* (1966), Hunter *et al.* (1968), Tarkoff *et al.* (1968), and Hepper *et al.* (1969) were all cigarette smokers, while among those of Guenter *et al.* (1968) were two non-smokers—one with no symptoms and one who did not develop shortness of breath until the age of 58. Similarly, in the present study all eight of the propositi had smoked cigarettes for some years, and it may be of importance that the only two symptom-free individuals with the deficiency (Subjects 4b and 5b) were non-smoking sibs, though kCO was suspiciously low in both.

In contrast, only half of Eriksson's (1965) larger series of deficient subjects with emphysema were smokers, and Talamo *et al.* (1968) reported among their patients two non-smokers who developed symptoms suggestive of emphysema before the age of 35. Our own cases include one, subject 3b, with a relatively high cigarette consumption yet who has no definite evidence of emphysema at the age of 72, unless the horizontal linear striations described above can be so regarded. The total life-time cigarette consumption of the eight deficient subjects reported here was found to be considerably smaller than that of patients with a similar degree of emphysema but with normal α_1-antitrypsin levels in their blood (Hutchison, Cook, and Barter, 1970), suggesting that the deficient patients may be particularly sensitive to cigarette smoke. On balance, therefore, it seems reasonable to incriminate cigarette smoking as a possible precipitating factor in this type of emphysema, as indeed was suggested by Guenter *et al.* (1968).

The manner in which cigarettes could bring about these harmful effects, however, is not at present clear. It is established that smoking is closely associated with bronchitis (Higgins, 1959). Kueppers and Bearn (1966) observed that α_1-antitrypsin inhibits proteolytic enzymes produced by human leucocytes and suggested that, in its absence, any inflammatory process may bring about structural damage to the lung. Many patients do in fact have some degree of bronchitis, and Hepper *et al.* (1969) found that patients with α_1-antitrypsin deficiency were more likely to suffer from recurrent infections than patients with other types of chronic obstructive lung disease. Among our own patients, however, were to be found individuals who brought up sputum on every day of the year others who had occasional attacks of acute bronchitis, and one who had never produced sputum at any time. In two cases chronic bronchitis developed before the onset of dyspnoea, but the incidence of chronic bronchitis in these eight patients was no different from that found in similar patients without α_1-antitrypsin deficiency (Hutchison, Barter, Martelli, Cook, and Hugh-Jones, 1970). Some evidence in favour of the hypothesis is provided by those who develop permanent shortness of breath immediately after an attack of acute bronchitis. Such a history was obtained from two of our patients.

With regard to the predilection for the lower zones, it is known that the blood flow per unit volume of lung tissue is considerably greater at the bases (West, 1962). Welch *et al.* (1969) therefore suggested that if proteolytic enzymes were released in the lung by blood-borne leucocytes the lower zones would be the most severely affected. An alternative explanation (Hutchison, Cook, and Barter, 1970) is that in the upright posture the hydrostatic pressure at the base of the human lung is some 15 cm H_2O greater than at the apex; it again follows that if a blood-borne agent is postulated a given degree of damage to the pulmonary vascular bed would have more serious effects on the lower zones.

HETEROZYGOTES

It is clearly of importance to determine whether heterozygous individuals are also more liable to develop pulmonary emphysema. The present divergence of opinion on this question may possibly be related to differences in the methods used to detect heterozygosity. Using the "intermediate" level of T.I.C. as an indicator, Eriksson (1965) could find no evidence of an increased incidence of chronic obstructive pulmonary disease among heterozygotes. Welch *et al.* (1969), with the same method, found that the pattern of lung disease in the heterozygotes was completely different from that found in homozygotes, and that the prevalence of the heterozygous state among 146 chest clinic patients was no different from that in the general population. The results obtained by Lieberman (1969) in 66 patients with emphysema point to the same conclusion.

The mean T.I.C. in 14 proved heterozygotes investigated by us (parents or children of confirmed homozygotes for the deficiency) was 1·21 mg trypsin inhibited/ml plasma (S.D. ± 0·16), very significantly lower than the values obtained in normal controls or in non-deficient patients with definite radiological emphysema. The mean T.I.C. of the emphysematous patients was in fact slightly greater than that of the controls, and the variances were not significantly different (variance ratio = 1·05; $P > 0·05$), suggesting that even if these two populations contain heterozygous individuals there is no apparent excess in patients with emphysema. It can be argued, however, that no definite conclusion on the issue can be reached with T.I.C. estimations alone, since the presence of chronic infection may raise the T.I.C. of heterozygotes into the normal range (Kueppers 1968). By crossed antigen-antibody electrophoresis, on the other hand, Kueppers, Fallat and Larson (1969) obtained a very different result, reporting that no fewer than 25 out of 103 patients classified as having "chronic obstructive pulmonary disease" were heterozygotes, a frequency significantly greater than that of their control group (14 out of 100). The latter figure, however, is also considerably greater than that found by other investigators, and would be associated with a general population frequency for α_1-antitrypsin deficiency of over 10 times that observed by Eriksson (1965). Moreover, as Lieberman (1970) pointed out, no family data were presented to confirm the genetic status of the postulated heterozygotes. At present there does not appear to be definite evidence linking emphysema with the heterozygous state.

TREATMENT

Curative treatment of this type of emphysema is clearly not possible other than by some form of transplant or prosthesis. If we assume that there is a direct relationship between emphysema and the biochemical disorder, it would be desirable to replace the missing plasma fraction before the lung has suffered irreversible damage. In view of the short (four days) half-life of α_1-antitrypsin (Kueppers and Fallat, 1969) such an approach would require a long-lived synthetic antitryptic substance with similar biochemical properties, as suggested by Eriksson (1970). At present, therefore, therapy (whether aimed at preventing the onset of emphysema or at preventing further deterioration) can consist only of the immediate administration of suitable antibiotics in the event of chest infection, strenuous efforts to persuade the patient to abandon cigarette smoking, and a change of occupation or environment if these seem likely to exacerbate pulmonary disease. It must be admitted, however, that there is little information on how effective such measures are likely to be in slowing the advance of this type of emphysema.

It seems of considerable importance to detect subjects homozygous for α_1-antitrypsin deficiency at the earliest possible stage, but unless some form of health screening programme is in operation a family carrying the gene is not likely to be detected until at least one member has developed serious emphysema. Once such a family has come to light, however, it would be desirable to measure α_1-antitrypsin levels in sibs of affected patients, who would be the only relatives likely to be homozygous for the deficiency. It could well be argued that this estimation should now form part of the investigation of any patient with severe pulmonary emphysema, particularly in the younger age group.

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