Results of investigation of patients with positive test results

	Patients not taking non-steroidal anti-inflammatory drugs (n=405)	Patients taking non-steroidal anti-inflammatory drugs (n=50)
No disease	276	40
Total No (%) with neoplasia (carcinoma or adenoma >1 cm)	129 (32)	10 (20)
No (%) with carcinoma	23 (5.7)	3 (6)
No (%) with adenoma (>1 cm)	106 (26.1)	7 (14)

Discussion

Although treatment with non-steroidal anti-inflammatory drugs may cause upper gastrointestinal bleeding, any blood loss will be subject to digestion during its passage through the proximal gut to the colon. The pseudoperoxidase activity of the haematin necessary to render the Hemoccult test positive and the immunological properties of the haemoglobin molecule required for the Feca EIA may thereby be reduced or lost completely.

The number of carcinomas detected in our study was similar in both groups. The group taking non-steroidal anti-inflammatory drugs had fewer adenomas than the non-treatment group; nevertheless, there were enough patients with adenomas in the treated group to warrant appropriate investigation.

A positive faecal occult blood test result in patients taking non-steroidal anti-inflammatory drugs cannot safely be attributed to upper gastrointestinal bleeding and should be followed by a thorough colorectal examination.

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Deoxyribonucleic acid (DNA) polymorphism of the α_1 -antitrypsin gene in chronic lung disease

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Abstract

Specific gene probes were used to study restriction fragment length polymorphisms of the human α_1 -antitrypsin gene. A polymorphism due to loss of a recognition site for the restriction enzyme Taq I was identified in eight of 42 patients with bronchiectasis and nine of 49 patients with pulmonary emphysema, none of whom had α_1 -antitrypsin deficiency. Among a control group without lung disease the polymorphism was significantly less frequent, being found in only five of 101 apparently healthy blood donors. The deoxyribonucleic acid (DNA) polymorphism was also present in two of 14 unrelated patients with α_1 -antitrypsin deficiency, indicating a lack of association with any specific α_1 -antitrypsin protein phenotype.

The polymorphism identified in this study may be a new marker for genetic predisposition to chronic lung disease.

Introduction

People with substantially reduced concentrations of α_1 -antitrypsin in serum (<35% of normal) are predisposed to developing pulmonary emphysema.^{1,2} Hitherto, some 30 variants of the proteins have been defined conventionally by isoelectric focusing.³ People with two common variants have reduced concentrations in serum and are at risk of developing disease; ZZ homozygotes have about 20% and SZ heterozygotes about 40% of the mean serum concentrations found in normal MM homozygotes. This risk is greatly increased if the subject also smokes.⁴

Fewer than 5% of patients with emphysema have α_1 -antitrypsin deficiency.⁵ With specific deoxyribonucleic acid (DNA) probes we have identified DNA variants of the human α_1 -antitrypsin gene that are not detected by isoelectric focusing and defined one potentially useful DNA polymorphism in relation to pulmonary emphysema.⁶ This paper examines whether the frequency of this DNA polymorphism is increased in patients with pulmonary emphysema and bronchiectasis.

Subjects and methods

Four groups were studied: 101 healthy white blood donors (49 women, 52 men aged 18-59 (mean 31) years); 49 patients with pulmonary emphysema unrelated to α_1 -antitrypsin deficiency (13 women, 36 men aged 38-80 (mean 56) years); 14 patients with pulmonary emphysema due to homozygous deficiency (eight women, six men aged 24-68 (mean 42) years); and 42 patients with bronchiectasis (20 women, 22 men aged 36-73 (mean 56) years). All the patients were white and assessed by physical examination, chest radiography, and physiological tests of lung function.

All 63 patients with pulmonary emphysema (14 with α_1 -antitrypsin deficiency) had features compatible with emphysema with or without evidence of chronic bronchitis. Eighteen of these patients were smokers, 42

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had a long past history of smoking (5-60 cigarettes a day for at least 10 years), and three patients with α_1 -antitrypsin deficiency had never smoked. The radiological criteria used to diagnose pulmonary emphysema included hyperinflated lung fields, a paucity of vascular markings at the lung periphery, and enlarged pulmonary arteries. The physiological criteria used to support a diagnosis of emphysema were a reduced transfer factor for carbon monoxide in the presence of a decrease in forced expiratory volume in one second and a reduction in the ratio of the forced expiratory volume to the forced vital capacity when compared with predicted values (table 1).

used as probes to search for restriction endonuclease cleavage sites in and around the α_1 -antitrypsin gene in the four groups of subjects. DNA was extracted from peripheral blood leucocytes by standard techniques⁹ and digested with the restriction enzyme *Taq* I. The fragments of DNA were separated by electrophoresis on 1% agarose gels and transferred to nitrocellulose filters by Southern blotting.¹⁰ The conditions for hybridisation were as described.⁶

Serum α_1 -antitrypsin concentrations were measured by automated kinetic immunonephelometry and α_1 -antitrypsin typing performed by

TABLE 1—Mean lung function values (SD) in patients with pulmonary emphysema and bronchiectasis

	Pulmonary emphysema (n=49)		α_1 -Antitrypsin deficiency (n=12)†		Bronchiectasis (n=42)	
	Absolute values	% Of predicted*	Absolute values	% Of predicted*	Absolute values	% Of predicted*
Forced expiratory volume (l)	0.94 (0.57)	40 (20)	1.70 (0.94)	61 (27)	1.46 (0.74)	57 (29)
Forced vital capacity (l)	2.34 (0.78)	66 (20)	3.48 (1.08)	85 (17)	2.88 (0.91)	78 (19)
Forced expiratory volume/forced vital capacity (l)	39.12 (10.91)	58 (17)	46.30 (19.91)	69 (29)	49.11 (17.19)	72 (29)
Total lung capacity (l)	6.88 (2.36)	120 (18)	5.93 (1.16)	104 (15)	5.75 (1.99)	99 (20)
Uptake of carbon monoxide (mmol/min/kPa)	4.11 (1.24)	53 (17)	6.55 (2.19)	71 (29)	6.53 (2.21)	79 (14)

*Percentage of predicted values expected from patient's age, sex, and height²¹ expressed to nearest whole number.

†Two subjects with α_1 -antitrypsin deficiency did not have lung function tests.

FIG 1—Autoradiograph showing 2.4 kbp (kilobase pairs) polymorphism of α_1 -antitrypsin gene detected with restriction enzyme *Taq* I.

The group of patients with bronchiectasis included 23 lifetime non-smokers and 10 ex-smokers who had smoked 20-40 cigarettes a day for seven to 45 years; these patients had quit the habit some four to 26 years previously. The diagnosis was supported by bronchography and clinical assessment. No patient had immune deficiency or the immotile cilia syndrome.

Genomic (α_1 pAT 6.5)⁷ and complementary DNA (α_1 pNJ)⁸ clones were

isoelectric focusing in agarose.¹¹ The functional activity of α_1 -antitrypsin was measured by the ability of serum to inhibit porcine pancreatic elastase in a kinetic assay and expressed as units of enzyme inhibited per ml serum.¹²

Statistics—Frequencies of the *Taq* I polymorphism in patients and the normal group were compared by χ^2 2×2 contingency tables, except that the comparison between α_1 -antitrypsin deficient patients and the normal group was by Fisher's exact probability test. Log odds ratios and 95% confidence intervals were also estimated for the polymorphism in patients with bronchiectasis and pulmonary emphysema.

Results

TAQ I POLYMORPHISM

Figure 1 shows the α_1 -antitrypsin fragments detected by Southern blotting and autoradiography when genomic DNA from a normal subject and a heterozygote and a homozygote was digested with *Taq* I and probed with α_1 pAT 6.5. The normal subject showed three bands of 5.7, 1.5, and 1.0 kilobase pairs (kbp). In the heterozygote there was an additional band of 2.4 kbp and in the homozygote a band of 2.4 kbp and loss of the band of 1.5 kbp.

Figure 2 shows a limited restriction endonuclease map of the human α_1 -antitrypsin gene with the predicted recognition sites for the enzyme *Taq* I. Eight *Taq* I sites were normally present in and around the α_1 -antitrypsin gene. In addition to the bands shown in figure 1, there were five *Taq* I fragments that should have been detected by α_1 pAT 6.5, which range from 0.08 to 0.69 kbp. These fragments, however, were too small to be seen by Southern blotting. The 2.4 kbp variant allele was due to loss of a recognition sequence for *Taq* I (fig 2). The complementary DNA probe which spans exon V also detected the 2.4 kbp variant allele in addition to the invariant allele at 1.5 kbp, confirming the location of this polymorphism. A further *Taq* I polymorphism was present in the gene (fig 2) and has been

FIG 2—Human α_1 -antitrypsin gene. Black areas represent coding sequences (exons II-V; exon I not translated). Restriction enzyme sites: *Bam* HI (B); *Taq* I (T). ▼=Loss of *Taq* I site resulting in 2.4 kbp (kilobase pairs) band. ★=Likely position of extra *Taq* I restriction site producing polymorphism described previously.¹³

described previously.¹³ There was no difference in the frequency of 30% for the second polymorphism between the normal subjects and patients (results not shown).

Table II shows the frequencies of the 2.4 kbp Taq I polymorphism in the controls and patients. The polymorphism was present in patients with

TABLE II—Frequency of 2.4 kbp Taq I polymorphism in α_1 -antitrypsin gene in control population and patients with pulmonary emphysema and bronchiectasis. (Figures in parentheses are numbers of homozygotes)

	Taq I polymorphism	
	Present	Absent
Controls	5	96
Pulmonary emphysema with α_1 -antitrypsin deficiency	2	12
Pulmonary emphysema without α_1 -antitrypsin deficiency	9* (2)	40
Bronchiectasis	8* (1)	34

*Compared with controls $p < 0.01$ (χ^2 test).

pulmonary emphysema but who were not α_1 -antitrypsin deficient at a frequency of 3.7 times that in normal people ($\chi^2 = 7.13$; $p < 0.01$). This gave a mean log odds ratio of 1.415 with a 95% confidence interval of 0.302 to 2.527. The polymorphism was also present at a significantly higher frequency in patients with bronchiectasis ($\chi^2 = 7.435$; $p < 0.01$), giving a log odds ratio of 1.449, 95% confidence interval 0.351 to 2.635. The frequency of the polymorphism in patients with α_1 -antitrypsin deficiency was not significantly different from that in the normal group.

α_1 -ANTITRYPSIN PROTEIN TYPES

Table III shows the mean serum α_1 -antitrypsin concentrations and mean serum elastase inhibitory capacities in subjects with and without the polymorphism. The mean serum concentration for homozygous MM

TABLE III— α_1 -Antitrypsin types, mean serum α_1 -antitrypsin concentrations (SD), and mean units of elastase inhibited (SD) by serum α_1 -antitrypsin in subjects with and without 2.4 kbp Taq I polymorphism ($n = 206$)

	Taq I polymorphism									
	Present					Absent				
	MM	MS	MZ	FM	ZZ	MM	MS	MZ	FM	ZZ
α_1 -Antitrypsin type	17	1	2	2	2	138	22	7	3	12
Mean α_1 -antitrypsin (g/l) [1.46 (0.64)]*	1.53 (0.51)	1.20	1.15	1.50	0.30	1.74 (0.57)	1.31 (0.29)	0.95 (0.21)	1.53	0.41
Units of elastase inhibited/ml serum [13 (4)]*	13.20 (3.78)	12.11	10.90	13.60	2.61	15.12 (3.91)	11.71 (3.15)	7.91 (2.54)	14.15	3.15 (1.06)

*Figures in square brackets are means (SD) of reference ranges.

phenotypes was higher than the mean of our reference range. This was probably due to the "acute phase" response which occurs after inflammation and results in a rise in the serum concentration of α_1 -antitrypsin.¹⁴ The polymorphism did not appear to have a strong association with any particular α_1 -antitrypsin protein type (table IV). The functional activity, measured by the capacity of serum to inhibit porcine pancreatic elastase, was compatible with the serum concentration of α_1 -antitrypsin, suggesting that there were no functionally abnormal α_1 -antitrypsin variants related to the polymorphism.

TABLE IV— α_1 -Antitrypsin types in controls and patients with 2.4 kbp Taq I polymorphism, excluding patients with classical α_1 -antitrypsin deficiency

	MM	FM	MS	MZ
Controls	2	1	1	1
Pulmonary emphysema	7	1	—	1
Bronchiectasis	8	—	—	—

PATIENTS WITH TAQ I POLYMORPHISM

None of the subjects were related and only two came from the same locality. The nine patients with pulmonary emphysema (table II) were aged between 42 and 80 at the time of diagnosis and all had been long-standing cigarette smokers. Each had appreciable airways obstruction and radiological features of emphysema. The nine patients had generalised emphysema, and two of the patients with α_1 -antitrypsin deficiency had typical basal emphysema. There were no clinical features that separated them from the remaining patients with emphysema. The patients with bronchiectasis who had the polymorphism included four non-smokers and four ex-smokers.

The three patients who were homozygous for the polymorphism could not be distinguished clinically from heterozygotes. Furthermore, all were of the MM protein type with appropriate serum α_1 -antitrypsin concentrations and functional activity (results not shown).

Discussion

We have identified a polymorphism in a flanking sequence of the α_1 -antitrypsin gene which occurred at significantly higher frequency in a group of patients with chronic lung disease. The frequency of the Taq I polymorphism in our control population was nearly identical with that in a North American white population.¹⁵ One report, however, has suggested that the Taq I polymorphism is present in about 10% of M alleles but it was not stated whether the population sample included patients with lung disease.¹⁶ Probably the frequency of the polymorphism is constant in white people, and population differences are unlikely to have accounted for the higher frequency of the polymorphism in our group of patients with chronic lung disease.

The mean log odds ratios were equivalent to odds of 26:1 for developing pulmonary emphysema and 28:1 for developing bronchiectasis if a subject carried the polymorphism. A larger study is required to improve the confidence intervals.

The polymorphism was not associated with classical α_1 -antitrypsin

deficiency and not strongly associated with any specific α_1 -antitrypsin protein type. Furthermore, we were unable to detect a reduction in the concentration or function of α_1 -antitrypsin in serum. The mean serum concentrations were in fact higher than expected. This suggests that the increase was likely to have been related to the underlying inflammatory process,¹⁴ but there is no way of knowing whether this increase was appropriate for the degree of inflammation.

We did not investigate whether the α_1 -antitrypsin in these subjects was more susceptible to oxidative inactivation at the methionine residue of its active site, an unlikely possibility as the polymorphism does not appear to occur in association with a specific protein type. The DNA sequence at the site of the polymorphism may have a role in expressing the α_1 -antitrypsin gene during inflammation, a possibility that can be investigated only when the gene with the variant allele has been cloned. Preliminary DNA sequencing data of the normal gene at the site of the Taq I polymorphism show a potential alternative polyadenylation signal roughly 25 base pairs away (unpublished observations), which may

serve to regulate gene expression during inflammation. This signal may be deleted in people with the Taq I polymorphism or the polymorphism may be silent.

If the polymorphism is silent and associated with chronic lung disease the lack of a strong association with any particular protein type for α_1 -antitrypsin suggests that there may be other closely linked genes which contribute to chronic lung disease. The Taq I polymorphism may be coinherited with an abnormal gene. Of potential importance, for example, are a gene related sequence¹⁷ and α_1 -antichymotrypsin,¹⁸ which by in situ hybridisation shows similar chromosomal locations to α_1 -antitrypsin on chromosome 14. Little work has been done on the genetics of α_1 -antichymotrypsin and the gene related sequence has not been characterised. The importance of abnormalities in these genes and as yet undescribed genes on chromosome 14 in the pathogenesis of chronic lung disease merits further investigation.

The association of α_1 -antitrypsin deficiency and pulmonary emphysema is related to the lack of protection against neutrophil elastase in the lower respiratory tract, and there is a suggestion that similar mechanisms may operate in bronchiectasis. Proteolytic enzymes have been implicated in the pathogenesis of bronchiectasis.¹⁹ Additionally there are isolated reports of bronchiectasis in patients with α_1 -antitrypsin deficiency.²⁰ The unexpected association of the polymorphism with both diseases suggests that there may be more than one genetic determinant in common related to the control of proteinases.

Clearly there are people in the general population with the restriction fragment length polymorphism who do not have any evidence of lung disease. We do not know if all people with the polymorphism have an increased risk of developing pulmonary emphysema or bronchiectasis. Long term prospective studies in a large population group would be required to investigate the relative risk in this group. People at risk should be strongly discouraged from smoking.

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100 YEARS AGO

The long spell of dry, hot weather which set in during the first week of June, and has since prevailed throughout the whole country, is almost without a parallel within the last twenty years, especially when account is taken of the fact that the whole of the present year has been marked by an exceptionally small rainfall. During the past week some few welcome showers have fallen in various parts of the country with beneficial results, but more rain is needed, and that soon, to arrest the evils that have accompanied the drought. On June 1st, agriculturists were complaining that, owing to the cold spring and the delay in the appearance of summer weather, the crops generally were terribly backward, and the harvest would be late and poor; but before the end of the month they had occasion to complain that the great heat had brought the corn prematurely into ear. At the present time some of the crops are suffering much, the grass is bare and scorched, and the cattle are distressed from want of water. One immediate result has been a decrease in our milk-supply, with the prospect of a further failure. From a sanitary point of view, the drought has brought its lessons. A scarcity, if not a failure, in the domestic water-supplies has been very generally experienced throughout the country, and it is to be feared that doubtfully pure sources of supply have very frequently been resorted to without due precaution, such as boiling the water before use. We have already recently referred to the misfortunes of the 100,000 inhabitants of Swansea, who, after an expenditure of about £300,000 on waterworks, have been afflicted with a veritable water-famine, owing to a defect in the main reservoir. For some time the water was turned on only once every three days; water was pumped from disused colliery workings and from old wells that years ago had been closed as polluted;

numbers of workmen were thrown out of employment by the closing of works that could not be carried on without water; and there was no water for extinguishing fires. Kidderminster, on the other hand, has been reaping the benefits of the Town Council's action in constructing a new covered reservoir and improving the water-supply. It is to be hoped that the hardships and dangers of the present season will lead to the construction of works for the storage of water where they have been found to be needed. The flushing of sewers is a matter of supreme importance to the public health, but we fear it has been much neglected in many cases during the past few weeks, although a little trouble and temporary expense might have overcome the difficulty. Thus, at Kidderminster the steam fire-engine has been made use of for pumping water from the River Stour for street-watering and such like purposes; whilst towns on the sea-coast might with great advantage have adopted more generally the system of sewer-flushing and street-watering with sea-water, which has been put into practice with good results at Yarmouth, Bournemouth, and other towns. Another evil which the dry weather has intensified is the pollution of many of our rivers and streams by crude or insufficiently purified sewage and filth, and on this ground there have been loud complaints as to the state of the Irwell, the Thames, and many other important rivers. It is to be hoped that sanitary workers will not overlook these and the many other lessons taught by the recent drought, and that they will use the opportunity to urge reforms in these directions. It will be interesting to note the effect which the rain, when it comes, will have on the public health.

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