Lung distensibility and airway function in intermediate α_1 -antitrypsin deficiency (Pi MZ)

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ABSTRACT We examined the role of intermediate α_1 -antitrypsin deficiency in predisposing to abnormalities of lung distensibility and airway function in 20 heterozygotes (Pi MZ) who were individually matched with a control Pi M subject of similar age, height, and smoking habits drawn from the same male, working population. There were no significant differences between the heterozygotes and their controls in the results of spirometry, maximum expiratory flow-volume curves (breathing air), single breath nitrogen test, arterialised capillary blood oxygen pressure, or single breath carbon monoxide transfer.

Additional studies were made in 12 of the pairs of Pi MZ and Pi M subjects. Comparison of maximum expiratory flow-volume curves breathing air and 80% helium-20% oxygen showed no differences between the Pi MZ and Pi M subjects. Although airway function was similar in the two groups, four of 12 Pi MZ subjects showed abnormalities of the pressure-volume curve of the lung (reduction in lung recoil pressure, abnormal shape factor, increase in functional residual capacity). Abnormalities of washout of a helium-sulphur hexafluoride gas mixture, of a type previously described as characteristic of emphysema, were found in two of the men with abnormal pressure-volume curves.

The results suggest that Pi MZ subjects have an increased susceptibility to alveolar abnormalities without increased abnormalities of airway function; this may explain the increased frequency of emphysema at necropsy despite many studies showing no predisposition to abnormal airway function in life. The functional changes we observed would be unlikely to cause symptoms. The risk of disablement from chronic lung disease appears to be only slightly enhanced by intermediate α_1 -antitrypsin deficiency.

The association between low serum α_1 -antitrypsin levels and pulmonary emphysema was first recognised by Laurell and Eriksson in 1963. Since then it has been established that several α_1 -antitrypsin variants exist in the population and that the inheritance of protease inhibitor (Pi) type is by a system of autosomal codominant alleles. Most of the population have Pi M* and normal serum α_1 -antitrypsin levels, while a small minority have Pi Z, very low serum levels of α_1 -antitrypsin, and high risk of developing severe panacinar emphysema in early adult life

(Eriksson, 1965). Several other phenotypes exist, most of which have not been reported to be associated with emphysema. The homozygous deficiency (Pi ZZ) state is rare, occurring in 1 in 1750 of the Swedish population and in 1 in 3460 people in England and Wales (Cook, 1974). The Pi MZ heterozygous state is much more common, occurring in 3 to 4% of the British population (Cook, 1974; Blundell *et al*, 1974/5), and it is therefore of considerable interest whether or not these subjects have an increased risk of developing emphysema.

Several types of investigation have examined the role of the heterozygous state as a factor predisposing to chronic airflow obstruction and emphysema, but their results have been conflicting.

* Occasionally there may be a gene deletion (—) and it is not possible to distinguish between MM and M— subjects or ZZ and Z— subjects by Pi typing. The vast majority of Pi M subjects will be homozygotes (Pi MM) (First International Workshop on the Pi system, 1975).

In many of the early reports serum α_1 -antitrypsin levels or trypsin inhibitory capacity were used to identify heterozygotes, but these methods cannot clearly distinguish Pi MZ subjects from those with other variants such as Pi types MS, SZ, and some with Pi type M (Talamo *et al.*, 1972; Webb *et al.*, 1973). Most, but not all studies have found that the incidence of Pi MZ in patients with chronic airflow obstruction is somewhat higher than that in the general population (Shigeoka *et al.*, 1976; Camara and Martin, 1978). Studies of Pi MZ subjects detected by studying relatives of those Pi Z subjects who present with disease have shown mild abnormalities in pulmonary function suggesting premature loss of elasticity of the lungs (Stevens *et al.*, 1971; Ostrow and Cherniack, 1972; Cooper *et al.*, 1974). Not all Pi Z subjects develop disease, and emphysema still has a familial aggregation after allowing for Pi type (Cohen *et al.*, 1975) so obligatory heterozygotes (those who are relatives of Pi Z subjects) may also have other inherited factors predisposing them to the development of emphysema. To avoid some of these problems recent studies have been based on heterozygous subjects identified from epidemiological surveys. In general such studies agree in finding no differences in spirometry between subjects with Pi type MZ and those with Pi M, but a variety of abnormalities in other tests of lung function have been found.

During a study of the use of tests of peripheral lung function in 1974 we detected 20 men having Pi type MZ, and we have compared their lung function to that of 20 men with Pi type M drawn from the same population and closely matched for age, height, and smoking habit. We have used a wide variety of tests of lung function and particularly have examined tests thought to reflect the functional changes of emphysema as well as the more usual tests of airway function.

Methods

The subjects were drawn from a sample of 492 working men in West London who had pulmonary function testing and α_1 -antitrypsin phenotyping performed (Tattersall *et al.*, 1978). Phenotyping was performed on a 10 ml sample of blood from each subject which was allowed to clot, and the serum was separated by centrifugation and frozen at -20°C . α_1 -antitrypsin phenotyping was undertaken by starch gel electrophoresis (Fagerhol, 1968) at pH 5.0 and antigen antibody crossed electrophoresis. An automated immunoprecipitin technique using a Technicon autoanalyser II was

used to measure the α_1 -antitrypsin levels (Blundell *et al.*, 1974/5). Twenty Pi type MZ heterozygotes were detected, and their α_1 -antitrypsin levels are shown in fig 1. Each of the 20 Pi MZ heterozygotes was matched for age (usually within one year), height (within 4 cm), and smoking habits (within five cigarettes/day) with a Pi M subject drawn from the rest of the population under study. Among the Pi MZ subjects there were four life-long non-smokers, one ex-smoker, four light smokers (up to 10 cigarettes daily), and 11 heavy smokers (20 or more cigarettes daily). Their ages ranged from 22 to 54, 14 men being 43 or older. All the subjects had normal chest radiographs and normal haemoglobin levels.

Spirometry was performed using a dry spirometer (Garw Electronic Instruments Ltd). The best of five attempts at one second forced expiratory volume (FEV_1) and the best of three measurements of slow vital capacity (VC) were recorded. Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were measured in an integrated flow, pressure-corrected body plethysmograph (Leith and Mead, 1974). Maximum expiratory flow-volume (MEFV) curves were recorded with the subject seated in the plethysmograph and breathing out to atmosphere through a Fleisch No 4 pneumotachograph coupled to a Sanborn 270 differential pressure transducer. Flow and change in thoracic gas volume were displayed on a Tektronix storage oscilloscope with hard copy unit, and from the tracings flow at 50% and 25% of VC ($V_{\text{max}_{50}}$ and $V_{\text{max}_{25}}$) and at 60% of TLC ($V_{\text{max}_{60 \text{ TLC}}}$) was

Fig 1 Distribution of serum α_1 -antitrypsin levels among Pi M and Pi MZ subjects in 492 men from whom present subjects were selected. Expected range for homozygous deficient subjects (Pi ZZ) is marked with arrows.

read. Closing volume (CV) was measured using a single breath nitrogen dilution technique (Anthonisen *et al*, 1969/70) and read as recommended by the National Heart and Lung Institute (1973). The results were expressed as the ratio of CV to VC (CV/VC%) and closing capacity (CC=CV+RV) to TLC (CC/TLC%). The slope of the alveolar plateau (nitrogen slope) was recorded as per cent change in expired nitrogen concentration per litre of expired volume. Each subject performed three single-breath test manoeuvres in the seated position and the mean of three values was used. Single breath carbon monoxide transfer (DLCO) was measured by the technique of Ogilvie *et al* (1957). The mean of two measurements was taken and the result expressed as carbon monoxide transfer per litre of alveolar volume (DLCO/VA). Alveolar volume was calculated from the single breath dilution of helium and expressed at BTPS. Arterialised capillary oxygen tension (P_{aO_2}) was measured on duplicate samples of capillary blood taken from the ear lobe five minutes after applying a vasodilator cream (Godfrey *et al*, 1971) with the patient in the supine position.

Twelve of the pairs of men were able to attend for further study, using tests thought to be particularly sensitive for the detection of emphysema or minor changes in airway function. Static expiratory pressure-volume (PV) curves were recorded with the subject sitting in a constant pressure plethysmograph using an oesophageal balloon to record lung recoil pressure (Milic-Emili *et al*, 1964). Each curve was preceded by three slow vital capacity breaths to ensure a constant volume history. Balloon volume (0.5 ml) was checked several times during the procedure. Mean PV curves were constructed by drawing a line of best fit by eye through the points from at least three, and usually five to seven expirations. Generally, pressures at a given volume were in agreement to ± 0.1 kPa. Static lung recoil pressure (Pst (1)) was plotted against per cent predicted TLC (Cotes, 1975) to allow for differences in height between different pairs of subjects. The results were expressed as expiratory compliance over the volume range from FRC to (FRC+500 ml) and as specific compliance (compliance/FRC). In addition an exponential function was fitted to the pressure-volume curve by an iterative least-squares technique using a computer and the shape factor, k , of the pressure-volume curve was obtained (Glaister *et al*, 1973; Gibson *et al*, 1979). Maximum lung recoil pressure was taken as the greatest pressure that was sustained for two or three seconds at full inflation. In seven subjects it was measured 50–

150 ml below TLC because oesophageal spasm occurred when full inflation was maintained. Maximum flow-static recoil pressure curves were constructed from the PV curve and the MEFV curves breathing air (Mead *et al*, 1967).

MEFV curves while the subjects breathed a mixture of 80% helium and 20% oxygen were recorded with the subject seated in the plethysmograph. Flow was measured with the Fleisch pneumotachograph that had been calibrated for the expired gas mixture. After a three minute wash-in with an occasional deep breath, a series of MEFV curves were obtained and three of the curves breathing He-O₂ were matched (± 100 ml) for vital capacity with three curves breathing air. The three curves breathing each gas mixture were then superimposed at RV and the mean value of flow at 50% of the largest VC ($V_{max_{50}}$) was calculated. From the mean values of the air and the helium curves, the increase in $V_{max_{50}}$ when breathing helium expressed as a percentage of the original $V_{max_{50}}$ breathing air ($\Delta V_{max_{50}}$) and the volume over which the two curves coincided expressed as a percentage of the VC (Viso V) were calculated (Dosman *et al*, 1975).

Fig 2 Schematic washout curves for helium (○) and sulphur hexafluoride (●). End-tidal concentration of each gas is expressed as a percentage of concentration at start of washout. Cross-over point is shown by arrow, and volume expired to this point (cross-over volume, COV) is calculated from record of tidal volume. In addition cumulative expired volume to point where end-tidal concentration of each gas is 1% of initial concentration (CEV 1%) is calculated from washout curves.

Simultaneous multiple breath washout of two gases of widely differing density, helium (He) and sulphur hexafluoride (SF₆), was performed (von Niding *et al*, 1977). With the subject seated the

Table 1 Characteristics of the 20 Pi MZ and 20 Pi M men

	Pi MZ mean	(SE)	Pi M mean	(SE)
Age (yr)	41.2	(2.6)	41.6	(2.6)
Height (m)	1.77	(0.02)	1.77	(0.01)
Smoking history (cigs/day)	16.7	(2.7)	17.4	(2.9)
Alpha ₁ -antitrypsin level (g/l)	1.65	(0.03)	2.49	(0.05)

wash-in of a mixture of 10% SF₆ and 5% He in air was continued until the difference between the inspired and the end-tidal He and SF₆ concentrations was small and constant. The subject was then allowed to inspire room air via a gas meter. Volume from the gas meter and end-tidal concentrations of He and SF₆ (measured using a mass spectrometer MS4X, AEI Scientific Apparatus) were recorded. The He and SF₆ concentrations were recorded as a percentage of the end-tidal concentration at the end of the wash-in period. Tidal volume was monitored throughout the procedure and maintained nearly constant. Washout curves were analysed by measuring the cumulative expired volume to the point at which the helium concentration equalled the SF₆ concentration (He-SF₆ cross-over volume, COV) (fig 2) and to the point at which the SF₆ concentration reached 1% (cumulative expired volume to 1%, CEV 1%) of the value at the end of wash-in. Both volumes were also expressed as a ratio of the functional residual capacity (FRC) so allowing for differences in lung size.

Results

The mean ages, heights, smoking habits, and alpha₁-antitrypsin levels for the 20 M and 20 MZ subjects are shown in table 1. The only significant difference between the two groups was the serum

alpha₁-antitrypsin level. Results of the tests of pulmonary function applied to the whole group are shown in table 2. There were no significant differences ($p > 0.10$) between the heterozygotes and their controls using the paired *t* test, although the mean value for most tests was very slightly worse in the heterozygotes than in their controls.

As the 20 heterozygotes varied in age and smoking habit, this analysis may have concealed abnormalities in a few individuals. Because older, heavily smoking heterozygotes would be expected to show the greatest effect of antiprotease deficiency we examined the results for the six pairs of subjects aged more than 40 and smoking 20 or more cigarettes a day. Although there was again a trend for the mean values of most tests to be slightly worse in the heterozygotes than in the controls, these differences were hardly more pronounced in this subgroup than for the original 20 pairs, except for the ratio FRC/TLC, the mean value of which was 55.5% (SE 2.0) in the six Pi MZ subjects and 46.5% (SE 1.4) in the Pi M control subjects (*p* for paired *t* test < 0.01).

The matching of the 12 pairs of subjects who returned for additional tests for age, height, and smoking habit was extremely close. Comparison of the standard pulmonary function tests listed in table 2 showed only minor differences, although mean TLC was 7.37 l in the 12 Pi MZ subjects and only 6.86 l in the 12 Pi M subjects. Some of

Table 2 Results of pulmonary function testing in 20 heterozygotes and 20 control subjects

	Pi type MZ Mean	(SE)	Pi type M Mean	(SE)
Spirometry				
FEV ₁ (l)	4.0	(0.2)	4.1	(0.2)
FEV ₁ /VC (%)	76.1	(1.5)	77.8	(1.9)
Lung volumes				
TLC (l)	7.1	(0.2)	7.0	(0.2)
RV/TLC (%)	22.2	(2.0)	24.6	(1.8)
FRC/TLC (%)	51.2	(1.5)	51.4	(1.4)
MEFV curves (breathing air)				
V max ₅₀ (l/s)	5.3	(0.4)	5.6	(0.4)
V max ₂₅ (l/s)	1.6	(0.2)	1.8	(0.2)
V max ₅₀ TLC (l/s)	4.8	(0.5)	5.0	(0.5)
Single breath nitrogen test				
CV/VC (%)	20.3	(1.8)	19.9	(1.8)
CC/TLC (%)	37.0	(2.0)	38.6	(2.2)
Nitrogen slope (%/l)	0.9	(0.1)	1.0	(0.2)
Gas exchange				
Dlco/VA (mmol/min/kPa/l)	1.6	(0.06)	1.6	(0.08)
Pao ₂ (kPa)	10.9	(0.2)	11.1	(0.3)

Table 3 Results of helium-oxygen flow-volume curves, static pressure-volume curves, and helium-sulphur hexafluoride washout curves in 12 pairs of men

	Pi MZ Mean	(SE)	Pi M Mean	(SE)	P value for paired <i>t</i> test (Pi MZ vs Pi M)
Helium vs air maximum flow-volume curves					
$\Delta V_{\max 50}$ (%)	44.7	(2.7)	48.1	(3.3)	NS
V iso V (% VC)	14.2	(2.0)	16.0	(1.8)	NS
Pressure-volume curves					
TLC (l)	7.37	(0.31)	6.86	(0.18)	NS
(% pred)	106.2	(2.4)	98.7	(2.2)	NS
FRC/TLC (%)	52.8	(2.0)	52.3	(2.1)	NS
Exp compliance (l/kPa)	4.28	(0.61)	3.82	(0.27)	NS
Specific compliance (kPa ⁻¹)	1.12	(0.14)	1.12	(0.10)	NS
Pst (l) at TLC (kPa)	2.53	(0.21)	2.50	(0.17)	NS
Pst (l) at 90% pred TLC (kPa)	1.11	(0.08)	1.54	(0.11)	0.014
----- 80% pred TLC (kPa)	0.80	(0.08)	1.13	(0.07)	0.027
----- 70% pred TLC (kPa)	0.58	(0.06)	0.84	(0.05)	0.017
----- 60% pred TLC (kPa)	0.44	(0.04)	0.59	(0.04)	0.019
----- 50% pred TLC (kPa)	0.25	(0.04)	0.41	(0.04)	0.013
k (kPa ⁻¹)	1.46	(0.48)	1.14	(0.25)	0.075
Helium-SF ₆ washout curves*					
Cross-over volume (COV) (l)	5.54	(1.9)	2.88	(0.6)	NS
COV/FRC (%)	1.30	(0.4)	0.90	(0.2)	NS
CEV 1% (SF ₆) (l)	38.6	(4.0)	30.7	(2.8)	0.060
CEV 1%/FRC (SF ₆) (%)	9.79	(0.7)	9.34	(0.7)	NS

NS = $p > 0.10$.

*9 pairs only available.

the additional tests, however, showed abnormalities in the Pi MZ subjects (table 3). In four of the Pi MZ subjects the PV curves were displaced to lower values of pressure at a given volume (fig 3). Detailed analysis of these curves showed that specific compliance near FRC and maximum lung recoil pressure at (or close to) TLC were not different between Pi MZ and Pi M subjects. Lung recoil pressures between 90% and 50% of the predicted TLC were significantly lower in Pi MZ subjects. One of the Pi MZ subjects showed much lower pressures than any of the other subjects, but significant differences ($p < 0.05$) in these pressures persisted when this subject and his Pi M control were removed from the analysis. When lung recoil pressures were analysed at standard percentages of the actual TLC, pressures were consistently lower in the Pi MZ subjects at all volumes but the differences were not significant ($p > 0.10$ for paired *t* test), indicating that the larger TLC in the Pi MZ subjects was in part responsible for the difference in PV curves. The shape factor for the PV curves (*k*) also tended to be higher in the Pi MZ subjects, although this was not significant at the 5% level ($p = 0.075$). The Pi MZ subjects with abnormal PV curves tended to have a slightly higher maximum expiratory flow rate at a given static recoil pressure (figs 4a and b).

Although helium-SF₆ washout curves were ob-

tained in the 12 pairs of subjects, the comparison in table 3 is confined to nine pairs because in three Pi M subjects the results were technically unsatisfactory. The three Pi MZ subjects paired with these three Pi M subjects all had normal values (< 4.0 l) of COV. Although in the remaining nine pairs there was a large difference in mean COV, this was accounted for by high values in two Pi MZ subjects who had COV values of 12.4 and 17.8 l.

Comparisons of the change in maximum flow rates when breathing a He-O₂ mixture instead of air failed to show any significant differences between Pi MZ and Pi M subjects.

When the full range of tests of pulmonary function was considered it was apparent that the abnormalities found were predominantly in three of the four middle-aged, heavily smoking Pi MZ subjects studied, but the numbers were too small to permit statistical analysis of this trend.

Discussion

Despite many recent investigations, the precise role of intermediate α_1 -antitrypsin deficiency in predisposing to chronic lung disease remains uncertain. A slight excess of Pi MZ subjects has been found among patients with chronic airflow obstruction attending hospital clinics (Shigeoka

Fig 3 Static expiratory pressure-volume curves of lung for (a) 12 Pi M subjects and (b) 12 Pi MZ subjects. In (b) shading indicates range of values found in Pi M subjects. $Pst(1)$ =Static lung recoil pressure, volume expressed as a percentage of predicted total lung capacity to allow for differences in size of subjects.

et al, 1976; Camara and Martin, 1978); such studies are inevitably biased and in some comparisons control groups have been drawn from inappropriate populations. A random post-mortem study has shown an increased frequency of emphysema in Pi MZ subjects, although there was no tendency for this to be associated with a lower age at death (Eriksson *et al*, 1975). Early studies of obligatory heterozygotes of symptomatic Pi Z subjects showed abnormalities in lung recoil pressures and maximum flow rates (Stevens *et al*, 1971; Ostrow and Cherniack, 1972; Cooper *et al*, 1974), but such studies will be influenced by other co-existing factors. Recently, several epidemiological studies have been made in which control subjects have been from the same population (table 4); these studies have consistently failed to show any difference in spirometry in adults but abnormalities of other tests of pulmonary function have been detected in several of the studies, particularly in

Table 4 Studies comparing lung function in Pi MZ and Pi M subjects identified in epidemiological surveys

Place	Authors	Pi MZ Subjects No	Male	Age* (yr)	Smokers	Controls	FEV ₁	MEFV _{air}	MEFV _{He-O₂}	Single breath N _A	Lung function tests CO transfer	Pao _a	TLC and sub- divisions	Static lung recoil	Dynamic compliance	Resistance
USA, Rochester	Webb, <i>et al</i> (1973)	18	?	>21	7	Population	NS	NS	NS	NS	NS	NS	NS	NS	Abn§	Abn§
USA, Rochester	Hall <i>et al</i> (1976)	15	8	47	0	Matched	NS	Abn	NS	NS	NS	NS	NS	NS	NS	NS
USA, Rochester	Vance <i>et al</i> (1977)	16	?	15	0	Matched	Abn	NS	NS	NS	NS	NS	NS	NS	NS	NS
USA, Tucson	Morse <i>et al</i> (1977)	88	?	42	?	Population	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
USA, Tucson	Lebowitz <i>et al</i> (1978)	29	?	25-54	?	Matched	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
USA, Tucson	McDonagh <i>et al</i> (1979)	24	10	50	16	Population	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
USA, Tucson	Cole <i>et al</i> (1976)	73	48	35-70	?	Population	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
United Kingdom	Present study	20	20	41	15	Matched	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Sweden	Larsson <i>et al</i> (1977)	39	39	41	24	Matched	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
France	Girard <i>et al</i> (1978)	24	24	39	19	Matched	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Yugoslavia	Kozarevic <i>et al</i> (1978)	21	21	55	?	Population	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

*Mean age indicated by bar over number.
†Abnormalities in smokers only.
‡Increased RV/TLC ratio.
§Abnormal frequency dependence of resistance.
Abn = Abnormality found in Pi MZ subjects.
NS = No significant abnormality found in Pi MZ subjects.

smoking men. Although epidemiological studies would appear to be the ideal method, loss of disabled subjects from the population sampled would bias them in the opposite direction to studies based on hospital clinics.

In our study we have tried to combine the advantages of the epidemiological approach with a detailed assessment of lung function with particular emphasis on lung distensibility and airway function. Our Pi MZ subjects were identified during a survey of pulmonary symptoms and function in working men in West London (Tattersall *et al*, 1978); in this survey the prevalence of Pi MZ subjects (4.1%) was similar to that found in previous studies in Britain (Cook, 1974; Blundell *et al*, 1974/5), and there was no suggestion of loss of older Pi MZ subjects. Although our sample was small, it consisted only of men (who have a higher risk of developing chronic airflow obstruction and emphysema), was biased towards middle-aged smokers, and each Pi MZ man was individually matched for age, height, and smoking habit with a Pi M subject identified in the survey. Our results agree with all previous studies in adults in showing no tendency to greater abnormalities in FEV₁ in Pi MZ subjects (table 4). Function of peripheral airways, as indicated by V max₂₅ breathing air, comparison of maximum flow breathing air and helium-oxygen, closing volume, and residual volume, was similar in Pi MZ and Pi M subjects. Nevertheless, several Pi MZ subjects showed abnormalities in the PV curve (reduction in lung recoil pressure at 90–50% of predicted TLC, an increase in shape factor (k), rise in FRC). All these changes occur in patients diagnosed as having emphysema (Finucane and Colebatch, 1969; Gibson *et al*, 1979). The changes were subtle and did not affect all Pi MZ subjects or lead to significant differences in all measurements from the PV curve. In part they were due to a slightly larger TLC in the Pi MZ subjects, although the shape factor (k) was also abnormal in several subjects. Reduction in lung recoil pressure in some Pi MZ subjects has been described previously by Stevens *et al* (1971), Ostrow and Cherniack (1972), and Cooper *et al* (1974), and in a well-controlled study of 50-year-old smoking men by Larsson *et al* (1977). A recent study (McDonagh *et al*, 1979), however, failed to confirm this abnormality in a group of 24 Pi MZ subjects of a wide age range, both sexes, and varying smoking history.

We sought other functional evidence of emphysema in the Pi MZ subjects, particularly those with abnormal PV curves. A reduced co transfer

appears to be a sensitive indicator of moderate emphysema that was not suspected clinically (Gelb *et al*, 1973). However, values of co transfer were similar in our 20 Pi M and 20 Pi MZ subjects (as in all previous studies, table 4) and co transfer was not consistently reduced in the four Pi MZ subjects with abnormal PV curves. A slight reduction in co transfer occurs in male smokers aged 20–30 years (Tattersall *et al*, 1978) and has been reported to be more pronounced at this age in women smokers (Enjeti *et al*, 1978). These findings imply that processes other than emphysema must contribute to early reduction in co transfer because emphysema is rare at such an early age (except in Pi Z subjects), and is at all ages less common in women than men (Anderson *et al*, 1972). In contrast to these negative results two middle-aged Pi MZ subjects showed an abnormality in the He-SF₆ washout curves—a delayed cross-over point and large cross-over volume—which has been claimed to be a feature of “chronic obstructive emphysema” but not of individuals with disease confined to the airways (von Nieding *et al*, 1977). Both these men also had abnormal PV curves. Von Nieding and colleagues interpret a large cross-over volume as indicating an impaired diffusive mixing of gas in the periphery of the lung. They reason that during the washout procedure the lighter gas (He) will be washed out faster as it will be more effectively mixed with the inspired air. At the beginning of the washout it will therefore appear in relatively higher concentrations in the expirate than the denser gas (SF₆). As the washout proceeds He will be washed out more rapidly and its relative concentration in the expirate will fall more rapidly than that of SF₆ so that the curves for the two gases will cross. If there is enlargement of peripheral air spaces, as in emphysema, peripheral gas mixing will be impaired, and this will delay washout of the denser gas more than that of the lighter gas and increase cross-over volume. In addition to this differential behaviour of the two gases, the washout of both gases will be delayed by airway disease. Abnormalities of airway function were mild and of similar severity in our Pi M and Pi MZ subjects and the volume (CEV 1%/FRC) required to washout SF₆ to 1% of the equilibrated wash-in concentration was similar in the two groups, confirming the similarities in other tests of airway function. While the large cross-over volumes in two of our patients are of interest, theoretical analysis of the washout of helium and SF₆ in normal lungs is complex (Kawashiro *et al*, 1976), and in practice it is sometimes difficult to

identify the cross-over point, so further studies are required to assess whether this technique can reliably distinguish different functional patterns in abnormal lungs.

Because of the relation between lung recoil pressure and maximum expiratory flow (Mead *et al*, 1967), a reduction in lung recoil pressure would be expected to reduce maximum expiratory flow. In the four Pi MZ subjects with abnormal PV curves, however, maximum expiratory flow rates were maintained so that flow was large at a given lung recoil pressure and upstream conductance (Mead *et al*, 1967) was increased (fig 4); similar preservation of maximum flow despite loss of lung recoil has been reported by Demedts *et al* (1978). Maximum flow might be maintained if loss of lung recoil pressure was offset by a peripheral movement of equal pressure points and shortening of the airway segments contributing to upstream con-

ductance on forced expiration. If this was the mechanism maintaining maximum flow then the flow response to breathing helium should be disproportionately reduced (Dosman *et al*, 1975), but this was hardly evident in the subjects with abnormal PV curves. Alternatively, the loss of lung recoil pressure might be offset by changes in airway distensibility so allowing airways to be larger at a standard lung recoil pressure. Such a change has been thought to be the cause of the increase of upstream conductance with aging (Mead *et al*, 1967). Whatever the precise mechanism preserving maximum flow in our subjects, we suspect it would be inadequate to prevent loss of airway function when loss of lung recoil pressure is more pronounced.

In summary therefore, some of the Pi MZ subjects showed changes compatible with emphysema (loss of lung recoil pressure, delayed cross-over volume for helium, and SF₆ washout) while there was no evidence of an increased susceptibility to deterioration in airway function as judged by maximum flow-volume curves, single breath N₂ test, maximum flow response to breathing helium-oxygen, or measurement of upstream conductance. These changes suggest that intermediate alpha₁-antitrypsin deficiency enhances the risk of developing emphysema but of a form or severity that does not significantly impair airway function. Although this hypothesis challenges much recent work that emphasises the close linkage between loss of lung recoil pressure and decline in airway function, it is compatible with the post-mortem finding of increased risk of emphysema but not of premature death (Eriksson *et al*, 1975), with numerous epidemiological studies denying an increased tendency to loss of airway function (table 4) and most other studies of lung distensibility in Pi MZ subjects. If this hypothesis is correct it suggests that although lung abnormalities are indeed somewhat more common in Pi MZ individuals than in Pi M controls, the changes are unlikely to lead to disabling chronic lung disease in the majority of individuals.

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Fig 4 Relation between static lung recoil pressure ($P_{st}(1)$) and maximum expiratory flow in (a) 12 Pi M subjects and (b) 12 Pi MZ subjects. In (b) shading indicates range of values found in Pi M subjects.

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