Lower-zone emphysema in young patients without α_1-antitrypsin deficiency

NESTOR A. MARTELLI, ERNESTO GOLDMAN, and AQUILES J. RONCORONI

Centro de Rehabilitación Respiratoria 'María Ferrer', Finochietto 849, Buenos Aires, Argentina

Martelli, N. A., Goldman, E., and Roncoroni, A. J. (1974). *Thorax*, **29**, 237–244. **Lower-zone emphysema in young patients without α_1-antitrypsin deficiency.** Three young patients with radiographic pulmonary emphysema predominantly in the lower zones are reported. The clinical and physiological features were those observed in severe pulmonary emphysema. Predominance of the main lesions in the lower zones was confirmed in two cases by selective pulmonary angiography. One of the patients died and extensive panlobular emphysema was found at necropsy. Although the similarities between our patients and those with emphysema and α_1-antitrypsin deficiency were remarkable, the latter condition was ruled out.

Shortness of breath in patients with pulmonary emphysema usually starts in the fifth or sixth decades. Occasionally, it begins at a much earlier age and there are reports of severe emphysema occurring before or soon after the age of 30 (Burke, 1937; Carasso, Maheux, and Gregoire, 1955; Seebohm and Bedell, 1963).

We now know that a proportion of young patients with pulmonary emphysema have an inherited deficiency of the serum globulin α_1-antitrypsin (Laurell and Eriksson, 1963). A remarkably constant feature exhibited by these patients is a symmetrical loss of pulmonary vessels in the lower zones (Eriksson, 1965; Guenter *et al.*, 1968; Hutchison *et al.*, 1971; Jones and Thomas, 1971). In fact, the association between lower-zone emphysema, young age, and α_1-antitrypsin deficiency is so strong that some authors (Hepper, Black, Gleich, and Kueppers, 1969; Hutchison *et al.*, 1971) were unable to find other than α_1-antitrypsin deficiency among patients with early onset of dyspnoea and lower-zone emphysema.

We report three young patients who, despite showing the clinical, radiological, and functional characteristics present in patients with α_1-antitrypsin deficiency, proved to be non-deficient.

METHODS

Chronic bronchitis was diagnosed according to the criteria established by the Medical Research Council Committee on the Aetiology of Chronic Bronchitis

(1965). The total life-time cigarette consumption was expressed in grammes, as described by Hutchison *et al.* (1971).

Trypsin inhibitory capacity (TIC) assays were performed by a modification of the method of Homer, Katchman, and Zipf (1963). A mixture of 0·8 ml of trypsin (0·06mg) in 0·0025 N HCl and 0·2 ml of diluted serum was prepared. An aliquot (0·2 ml) of this mixture was added to 3 ml of 0·5 mmol N-α-benzoyl-L-arginine ethyl ester hydrochloride in 0·1 M phosphate buffer (pH 7) and the rate of change in optical density was measured in a spectrophotometer at 253 μ. A 1 : 10 dilution of serum in 0·1 M phosphate buffer (pH 7) was used routinely but deficient sera were diluted 1 : 5, 1 : 2 or measured undiluted. Sample assays and controls were carried out in triplicate consecutively at 28°C and the mean result was expressed in milligrammes of trypsin inhibited per millilitre of plasma.

PULMONARY FUNCTION TESTS Forced expiratory volume in one second ($FEV_{1.0}$), slow vital capacity (VC), inspiratory capacity (IC), and maximal mid-expiratory flow rate (MMFR) were measured on a Collins 13·5-litre spirometer before and after 300 μg of salbutamol administered by means of a pocket nebulizer. The values shown are those obtained after salbutamol as these were essentially the same as before the inhalation. Functional residual capacity (FRC) was measured by the method of DuBois *et al.* (1956) using a volume displacement body plethysmograph (Mead, 1960); total lung capacity (TLC) was calculated using measured IC. In case 3 the FRC was measured by the closed-circuit helium-

dilution technique (Gilson and Hugh-Jones, 1949). Airways resistance (Raw) and thoracic gas volume (Vtg) were measured near FRC by the method of DuBois, Botelho, and Comroe (1956). Specific conductance (SGaw) was calculated as the ratio of 1/Raw to Vtg. The static elastic recoil pressure of the lung (Pst (1)) was measured by the oesophageal balloon technique (Milic-Emili, Mead, Turner, and Glauser, 1964) at different points in the expiratory vital capacity. From this pressure-volume curve static compliance (Cst) was measured over the tidal volume range. Dynamic compliance (Cdyn) during quiet breathing was measured at points of zero flow at the beginning and end of expiration. Measurements of arterial blood tensions of oxygen (Pao$_2$) and carbon dioxide (Paco$_2$) were made by means of Radiometer electrodes. All volumes are expressed at BTPS. Normal values for FEV$_{1.0}$, VC, MMFR, TLC, and FRC were obtained from Cotes (1968). Normal values for Pst (1) at 90% TLC were obtained from Turner, Mead, and Wohl (1968).

PATIENTS

CASE 1   B. S., a 22-year-old man first seen at this hospital in November 1970, had complained of dyspnoea on exertion and a dry cough since the age of 19. At age 20, he noted shortness of breath after climbing one flight of stairs and at 21 this forced him to leave his job on a farm. He never produced any sputum. He started to smoke at the age of 7 and still smokes 10 cigarettes a day. His 60-year-old father complained of shortness of breath but we were unable to interview him.

On examination the chest was barrel-shaped and hyperresonant. Breath sounds were greatly diminished, especially over both lower zones of the lungs. The pulmonary component of the second heart sound was accentuated. Blood pressure was 120/80 mmHg. A chest radiograph (Fig. 1) showed pulmonary hyperinflation, a marked reduction in the peripheral vascular pattern in the lower lobes, and prominence of the main pulmonary artery. Bronchography showed a normal bronchial tree without dilatation of bronchial glands. A selective pulmonary arteriogram showed that the arteries to both lower lobes were thin and deprived of most of their lateral branches (Fig. 2); the arteries to the upper zones were engorged. An electrocardiogram showed right ventricular hypertrophy and right bundle-branch block. The α$_1$-globulin band on cellulose acetate electrophoresis was normal. The TIC was 0·81 mg of trypsin inhibited per millilitre of plasma. Tests of overall lung function showed severe airways obstruction, marked pulmonary hyperinflation, loss of elastic recoil, low SGaw, and slight lowering of Pao$_2$. Clinical data, lung function tests,
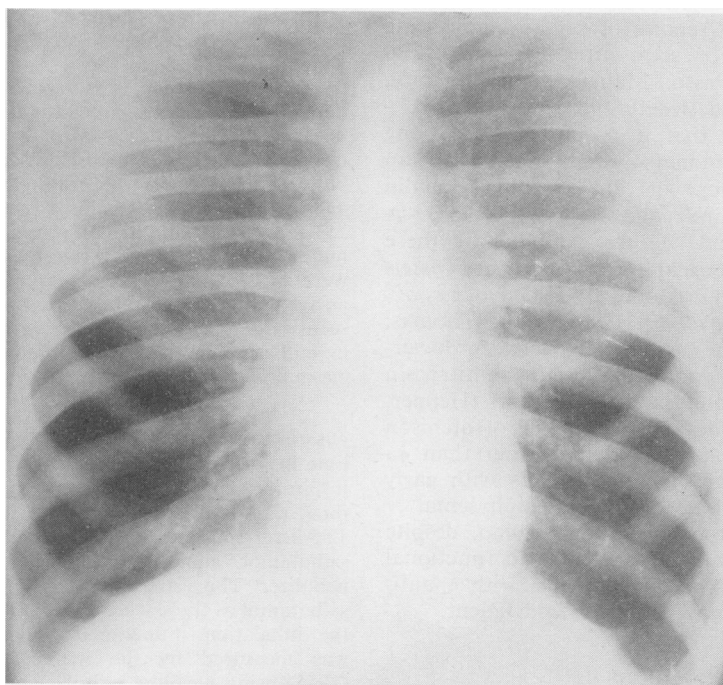

FIG. 1. *Case 1. Posteroanterior chest radiograph in full inspiration showing predominantly lower-zone emphysema. The pulmonary artery is prominent.*
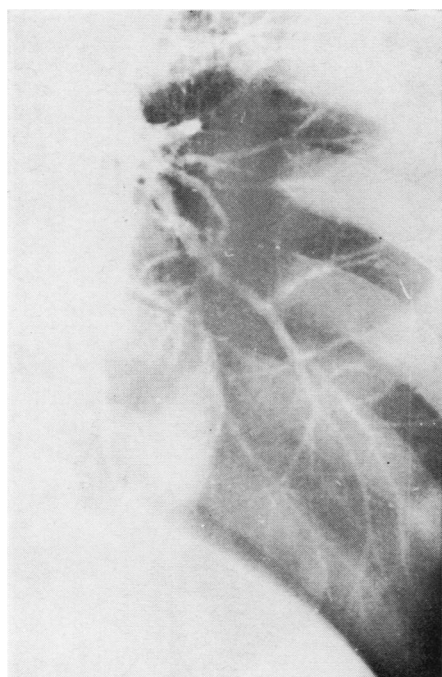
and blood gases are presented in Tables I and II.

In view of the severe incapacity of this patient it was thought that resection of right lower lobe bullae might re-expand the compressed upper and middle lobes and improve elastic recoil. At operation the whole right lung had the appearance usually seen in severe diffuse emphysema, but no gross bullae were visible. Partial resection of an enormously enlarged lower lobe was carried out. During a stormy postoperative course, in which the patient was assisted with a respirator, a bronchocutaneous fistula developed and persisted at the time of discharge from hospital 45 days after admission, only to close a few weeks later. Reassessment three years later showed no improvement in lung function.

CASE 2 P. F., a 30-year-old agricultural labourer, was referred to this hospital in October 1972, because of breathlessness when walking on the level. Dyspnoea on exertion had started at age 28 and progressed steadily. He had smoked cigarettes from the age of 7 until 23 when he stopped after an episode of acute bronchitis. After this he developed a chronic cough and white sputum which persisted up to now. There was no history of lung disease among his relatives.

Physical examination revealed enlargement of the anteroposterior diameter of the thorax and hyperresonance on percussion. Breath sounds were nearly absent over both lower lung fields. Cardiac sounds were distant. Blood pressure was 130/90 mmHg. There was neither oedema nor cyanosis. The normal nail-bed angle was obliterated. A chest radiograph (Fig. 3) showed overexpanded lungs, a small cardiac silhouette, and severe vascular attenuation in both lower zones and the left upper zone. A selective pulmonary arteriogram (Fig. 4 a and b) confirmed these findings. Pulmonary artery pressure was 35/15 (mean 23) mmHg. The ECG was normal. Serum cellulose acetate electrophoresis showed a normal α₁-globulin band and the TIC was 1·89 mg of trypsin inhibited per millilitre of plasma. Pulmonary function tests and blood gases were similar to those of case 1. Clinical data, lung function tests, and blood gases results are shown in Tables I and II. The patient was treated with bron-

TABLE I
CLINICAL DATA AND PLASMA TRYPSIN INHIBITORY CAPACITY (TIC)

Case	Age	Sex	Height (m)	Weight (kg)	Dyspnoea on Exertion: Age of Onset (yr)	Chronic Bronchitis: Age of Onset (yr)	Cigarette Smoking: Total (g × 10⁶)	TIC (mg trypsin inhibited/ml plasma)
1	22	M	1·70	59	19	—	0·58	0·81
2	30	M	1·58	46	28	23	1·10	1·89
3	34	F	1·68	46	31	32	0·46	1·74

TABLE II
PULMONARY FUNCTION TESTS

Case	$FEV_{1.0}$ (l.)	VC (l.)	MMFR (l./sec)	TLC (l.)	FRC (l.)	Cst (l./cmH₂O)	Cdyn (l./cmH₂O)	Pst(l.) at 90%TLC (cmH₂O)	Raw (cmH₂O/ l./sec)	SGaw (cmH₂O/ sec)	Pao_2 (mmHg)	$Paco_2$ (mmHg)
1	1·07(26)¹	2·91(61)	0·38(7)	9·40(152)	7·00(189)	0·53	0·15	3·8(20)	1·80	0·08	75	44
2	0·90(27)	2·81(70)	0·15(3)	7·43(143)	5·83(162)	0·60	0·12	2·9(17)	2·21	0·08	78	30
3	0·60(19)	1·60(47)	0·33(8)	6·52(120)	5·34(172)	—	—	—	—	—	46	42

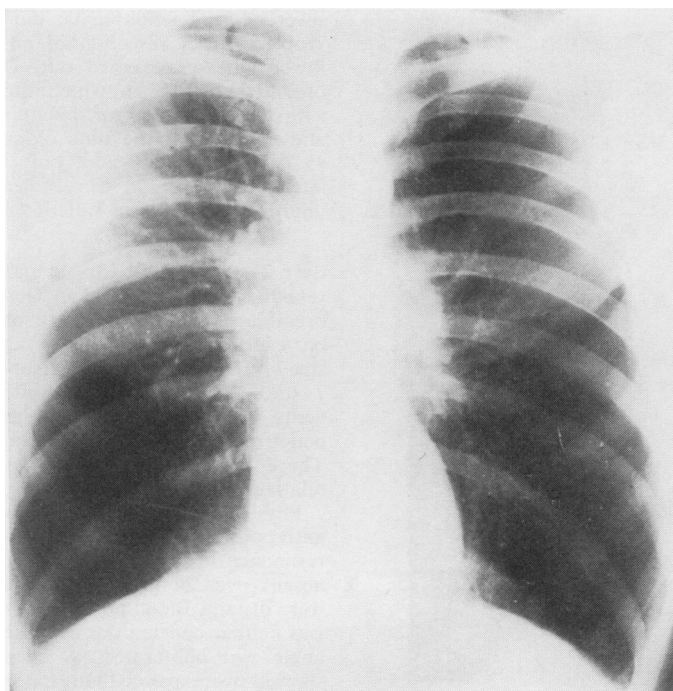¹ Figures in parentheses are percentages of predicted values.

FIG. 3. *Case 2. Chest radiograph showing hyperinflation and predominantly lower-zone emphysema.*

chodilators and physiotherapy but there was no objective improvement at the time of discharge.

CASE 3   M. S., a 34-year-old woman clerical worker, was referred to this hospital in May 1972 complaining of severe dyspnoea at rest. Her illness had begun at the age of 31 when, after an influenza-like illness, she found she could not walk more than 50 metres without feeling breathless. Two years later a chronic cough productive of green sputum developed. After a right middle lobe pneumonia in June 1971, even minimal effort would bring about severe dyspnoea. A bronchoscopy performed at another hospital was reported as normal. She was put on steroids without relief. Seven days before admission she noticed oedema of the legs. She started to smoke only two years before the onset of dyspnoea and gave up after the pneumonic episode. Her family history was non-contributory.

Examination showed a thin woman with laboured breathing. There was cyanosis, clubbing of the fingers and toes, and obvious right heart failure. The chest was overexpanded and hyperresonant; breath sounds were diminished throughout but especially over both lower zones. A parasternal heave suggested right ventricular hypertrophy. Cardiac sounds were distant. Blood pressure was 120/80 mmHg. There was a normal α_1-globulin band on serum cellulose acetate

electrophoresis and the TIC was 1·74 mg of trypsin inhibited per millilitre of plasma. A chest radiograph (Fig. 5) showed severe pulmonary hyperinflation, a prominent main pulmonary artery, and peripheral vascular attenuation, more marked over both lower zones. A whole lung tomogram (Fig. 6) confirmed the latter. The ECG showed right atrial and ventricular hypertrophy. Overall lung function tests showed severe airways obstruction, pulmonary hyperinflation, and severe hypoxaemia. Clinical data, lung function tests, and blood gases results are shown in Tables I and II. The clinical course was marked by episodes of severe CO_2 retention. Considering that the patient had reached the final stage of a severe and rapidly progressive emphysema, it was felt that, despite her young age, ventilation with a respirator was not indicated and she died 74 days after admission.

Necropsy   The lungs were distended with formalin for 96 hours and then cut into sagittal slices. The amount of emphysema was estimated by naked eye. There was severe panlobular emphysema involving 95% of the lung substance. Microscopically there was emphysema and acute and chronic inflammatory changes in large and small bronchi. Despite these changes the calibre of the small airways was not reduced. The Reid index (Reid, 1960) was 0·45. The heart showed moderate right ventricular hypertrophy.
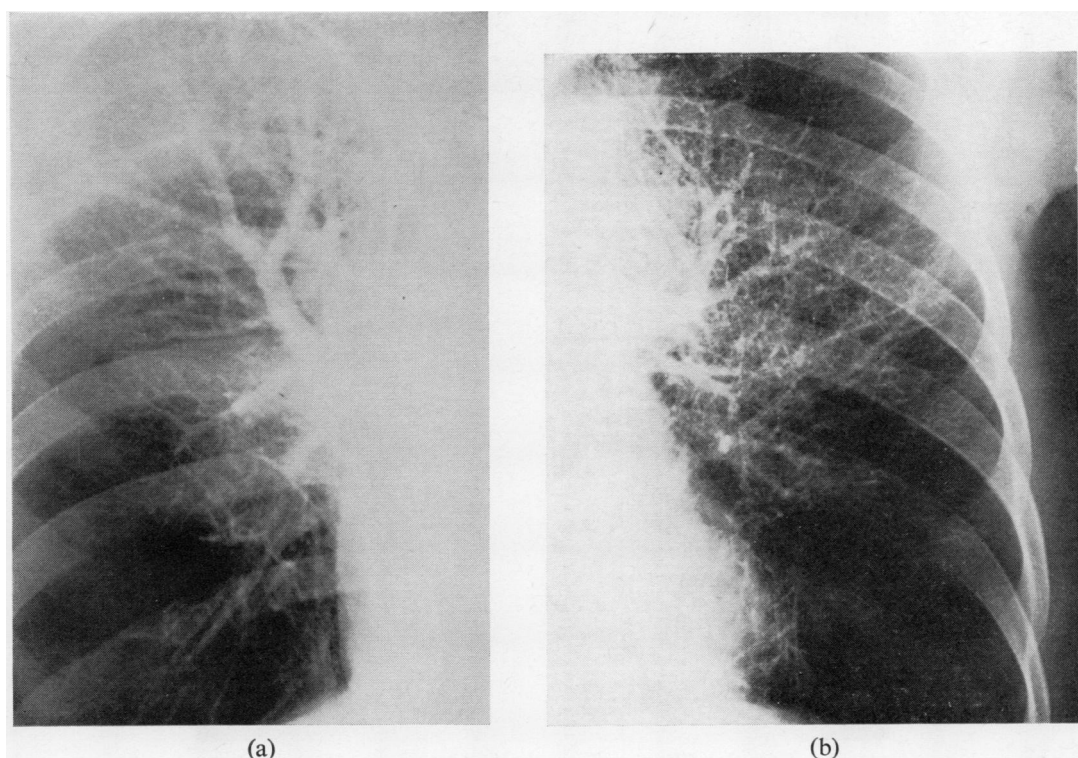
FIG. 4. *Case 2. Selective right (a) and left (b) pulmonary arteriograms showing vascular attenuation at both bases and left upper zone.*

DISCUSSION

Pulmonary emphysema is probably produced, and certainly aggravated, by a number of factors, among which cigarette smoking and chronic bronchitis rank first. These factors must be present over a long period of time before they inflict severe damage to the lungs. Dyspnoea does not usually present before the age of 50 although most emphysematous patients started smoking before 20. For those cases in which dyspnoea begins earlier in life, an inherent tissue defect was proposed (Seebohm and Bedell, 1963). This has never been proved but some have recently been shown to have an α_1-antitrypsin deficiency. Serum α_1-antitrypsin is genetically determined by a pair of codominant alleles and, although several phenotypes have been identified (Fagerhol and Laurell, 1970), only those homozygous for the deficient gene Pi^z (ZZ phenotype) show a definite predisposition to develop pulmonary emphysema (Hutchison *et al.*, 1972). In this situation the TIC is very low (Talamo, Allen, Kahan, and Austen, 1968; Tarkoff, Kueppers, and Miller, 1968; Jones

and Thomas, 1971). The clinical picture is similar to that of non-deficient patients except for two distinguishing features already mentioned—permanent dyspnoea on exertion starts at an earlier age (mean age 37·6 years in the series of Hutchison *et al.* (1971)) and the chest radiograph shows in every case that the lower zones are predominantly affected. This distribution is significantly different from that of non-deficient patients in whom upper zone predominance is more commonly observed (Hutchison *et al.*, 1972).

These features so constantly shown by α_1-antitrypsin deficient patients were also present in our cases. Dyspnoea on exertion started at a very young age and the radiological lesions predominated in the lower pulmonary zones. The latter was confirmed by pulmonary angiography in two cases and by tomography in the third. Assessment of pulmonary vasculature loss in emphysema by tomography and by angiography provides similar information (Bentivoglio *et al.*, 1963).
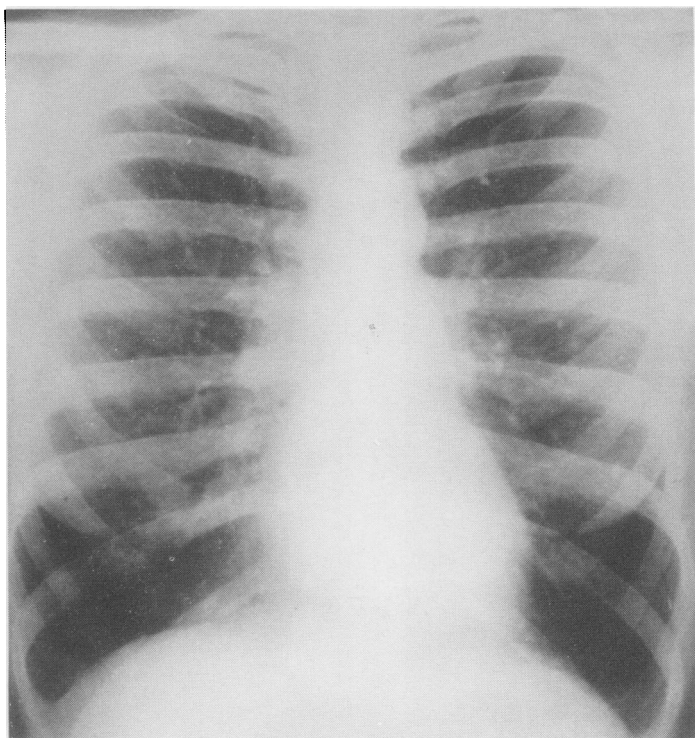
Radiological emphysema in patients with

FIG. 5. *Case 3. Chest radiograph showing severe hyperinflation, prominent pulmonary arteries, and peripheral vascular attenuation, most marked in the lower zones.*

normal α_1-antitrypsin globulin can either predominate in the upper or lower zones or can be diffuse and show no predominance. Since lower-zone emphysema is the rule in α_1-antitrypsin deficient patients it would be interesting to know how often it occurs in young non-deficient patients. Few reports have dealt with this matter. Hepper *et al.* (1969) studied 12 patients in whom a diagnosis of 'chronic obstructive lung disease' was made at 40 years or younger and found four with radiological pulmonary peripheral vascular attenuation. Lower zone predominance was observed in three, all of whom were α_1-antitrypsin deficient; the fourth, who was non-deficient, had upper zone predominance. Hutchison *et al.* (1971), in a large number of patients with relatively severe emphysema selected by radiological criteria (Laws and Heard, 1962), found that all those with lower zone predominance whose dyspnoea had started between the ages of 30 and 45 years, were α_1-antitrypsin deficient. Although the number of observations is not large, it seems likely that predominant lower-zone emphysema in young, non-deficient patients must be uncommon.

None of our patients was homozygous for α_1-antitrypsin deficiency. All showed a normal α_1-globulin peak on cellulose acetate electrophoresis, a finding which rules out the ZZ phenotype, in which the peak is either absent or forms a flat plateau (Lieberman, Gaidulis, Garoutte, and Mittman, 1972). The TIC values were normal in two and although low in the third, it was two to three times greater than the values for two proven ZZ homozygotes studied in this laboratory.

It is now established that there is considerable overlapping of TIC values between the normal homozygous MM phenotype and several other homo- and heterozygous phenotypes including MZ heterozygotes (Lieberman *et al.*, 1972). It is conceivable therefore that any of our patients could in fact be a heterozygote. Evidence that the heterozygous state predisposes to emphysema is still lacking (Hutchison *et al.*, 1972) but even if the association does in fact exist we must em-
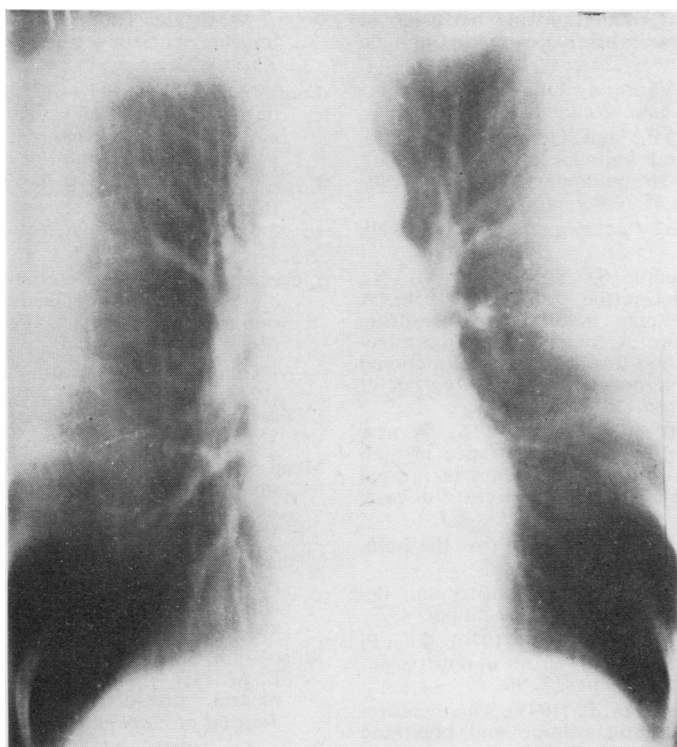
FIG. 6. Case 3. *Whole lung tomogram showing vascular attenuation involving predominantly the lower zones.*

phasize that Lieberman (1969) and Stevens, Hnilica, Johnson, and Bell (1971) found that their heterozygotes with pulmonary emphysema were older than the homozygotes, whereas our patients were actually younger.

The similarity between α_1-antitrypsin deficient and non-deficient patients with lower-zone emphysema and the possibility that the latter might also have a biochemical disorder have already been suggested by Hutchison *et al.* (1972). Our three cases might lend further support to this hypothesis since they were even younger than the average patient with α_1-antitrypsin deficiency.

The role played by cigarette smoking in cases 1 and 2 is difficult to assess. They both started to smoke at the rather unusual age of 7 years. Whether cigarette smoking at a time when alveoli are still developing (Dunnill, 1962) can provide changes that will end up as emphysema later in life seems a remote possibility. On the other hand, the total life-time cigarette consumption of our patients was less than the average found by Hutchison *et al.* (1971) in patients with α_1-

antitrypsin deficiency in whom early onset of emphysema might be related to cigarette smoking (Hutchison *et al.*, 1971; Jones and Thomas, 1971). This might indicate either an increased susceptibility or simply that our patients had smoked less because they were younger. On the other hand, cigarette smoking was probably not relevant in case 3 as this woman started to smoke two years before the onset of dyspnoea.

Our three cases emphasize that young patients with lower-zone emphysema are not necessarily α_1-antitrypsin deficient and that present knowledge about the aetiology of emphysema is, at best, incomplete.

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Requests for reprints to: Dr. N. A. Martelli, Centro de Rehabilitación Respiratoria 'María Ferrer', Finochietto 849, Buenos Aires, Argentina.