

FIVE YEAR FOLLOW-UP STUDY OF LUNG FUNCTION
IN
PATIENTS WITH RHEUMATOID ARTHRITIS

Elizabeth Annie HILLS

M.D.

St. Mary's Hospital Medical School, London

ABSTRACT

Respiratory function in 99 patients with rheumatoid disease was compared with that in 60 matched normal subjects. Vital capacity and exercise transfer factor were significantly lower in rheumatoid patients.

Mean dynamic compliance was not significantly different in rheumatoid patients. High C_{dyn} was slightly more common than low C_{dyn} and in males was associated with nodules ($p < .001$). Frequency dependence of compliance (FDC) was more common in rheumatoid patients, significantly more prevalent ($p < .05$) over the age of 50. Exposure to dusts and fumes was similar in rheumatoid and control groups, but more exposed rheumatoid patients showed FDC.

Capillary volume (V_c) was significantly lower in male rheumatoid patients (smokers) compared with male volunteers ($p < .05$) and in rheumatoid female smokers compared with rheumatoid female non-smokers ($p < .01$). V_c was significantly lower ($p < .05$) in patients with nodules, in those not receiving corticosteroids ($p < .05$) and in patients known to have persistently low T_L ($p < .05$).

FDC and low V_c are newly described abnormalities in rheumatoid patients and are compatible with disturbed function of bronchioles and pulmonary blood vessels, both known to be affected by inflammatory changes in rheumatoid pneumonitis.

Over a 5 year period 76, 65, 56 and 60 patients attended at succeeding visits. The incidence of abnormal lung function in 60 patients attending for 5 years was 90%. Abnormal findings were usually persistent, frequently multiple.

A significantly higher proportion of patients with nodules ($p < .05$), arteritis ($p < .02$) and the sicca syndrome ($p < .05$) had abnormal T_L . Patients with nodules also showed a significantly greater fall in FEV_1 over the 5 years ($p < .02$).

Respiratory symptoms and signs were associated with significantly greater change in compliance over 5 years ($p < .01$). T_L was significantly lower at visits where respiratory symptoms and signs ($p < .02$) and clubbing ($p < .05$) were present, but changes were not related to change in radiographic appearances.

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AIMS OF THE STUDY

- 1a. To compare a randomly selected group of patients with rheumatoid disease with a group of matched control subjects to establish the prevalence of abnormal lung function.
- b. To compare the prevalence of abnormal lung function with that found by other investigators.
2. To study this group of patients with rheumatoid disease at intervals over a 5 year period:
 - (a) to see if abnormal lung function persists.
 - (b) to discover if repeated tests of lung function expose new abnormalities.
 - (c) to relate changes in lung function to features of the rheumatoid disease, to the presence of respiratory symptoms and clinical or radiological signs of lung involvement.
3. To perform additional tests, not repeated annually, to look for physiological abnormalities which might be expected from the known histological changes in the lungs of rheumatoid patients with fibrosing alveolitis:
 - (a) measurement of dynamic compliance at increasing respiratory rates to see if frequency dependence would provide evidence of involvement of small airways.
 - (b) measurement of the membrane component of diffusion (D_m) and capillary volume (V_c) to look for evidence of disease in the small pulmonary blood vessels.

INTRODUCTION:

It is possible that the first observation of pulmonary fibrosis in association with rheumatoid arthritis was made by Charcot¹ who in 1881 described 'chronic pneumonia' in cachectic patients with chronic articular rheumatism. Some cases of chronic pneumonia would probably be infective and it has been suggested that bronchiectasis is more common in patients with rheumatoid disease², but interstitial pulmonary fibrosis would present a similar clinical picture.

In 1948 Ellman and Ball³ described 3 patients with clinical and radiological evidence of generalised pulmonary disease in association with rheumatoid arthritis. The patients all had productive cough, 2 were reported to be short of breath and in 2 the presence of crepitations was noted. All had diffusely abnormal chest radiographs. Two patients died and were found to have interstitial pneumonitis. Ellman and Ball³ discussed the similarity of the lung lesions to those seen in rheumatic fever and the relation between rheumatoid disease and other rheumatic diseases with lung involvement such as systemic lupus erythematosus or polyarteritis nodosa.

A patient presenting a similar clinical picture was also described by Hart⁴ in 1948. The patient died in 1954 and he and McKenzie⁵ reported the post mortem findings and were unconvinced that the lung lesion was related to rheumatoid disease.

Yardumian and Kleiner⁶ in 1949, discussing the pathogenesis of 'Collagen Disease', included 2 patients with rheumatoid arthritis. They described the post mortem finding of 'chronic rheumatic pneumonitis' and including rheumatoid disease with polyarteritis nodosa, systemic lupus erythematosus and systemic sclerosis

suggested that the diseases had a common vascular component.

In 1950 Bloom and Rubin⁷ reported a patient who first had a pleural effusion and subsequently had a very abnormal chest radiograph with widespread mottling in both lung fields. These radiological changes had completely cleared by the following year without any treatment. Following this Katz and Auerbach⁸ (1951) reported the clinical progress and post mortem findings in a patient with fibrosing pneumonitis, but the clinical picture might have been attributable to systemic sclerosis rather than rheumatoid disease. There was no mention of joint erosions or description of the histological changes in the joints. Stolte⁹ in 1952 described a patient with rheumatoid disease and patchy fibrosis complicated by the development of an oat cell carcinoma. Following further reports of diffuse pulmonary disease by Harris¹⁰ (1954), Christie¹¹ (1954) and Spence¹² in 1955 there were 2 papers in 1955 presenting conflicting opinions about the relation of lung disease to rheumatoid arthritis.

Rubin¹³ reported 3 patients with rheumatoid-type arthritis and related diffuse lung disease, but all these patients had drug rashes. No LE cells were found, but the clinical histories were suggestive of systemic lupus erythematosus. Rubin reported them as rheumatoid lung disease. On the other hand Aronoff, Bywaters and Fearnley¹⁴ reviewed 253 patients seen between 1939 and 1948 and followed to the time of the report. They felt that there was no evidence of any specific lung disease related to rheumatoid arthritis, but they described 1 patient who first had pleural effusions, then widespread reticulation on his chest radiograph, then like the patient of Stolte, carcinoma. In this case it was

squamous. They compared chest radiographs of 130 rheumatoid patients with 130 non-rheumatoid patients. Emphysema, 'bronchitis', including pneumonitis, and bronchiectasis were all noticed more commonly in the rheumatoid patients. Reticulation and honeycombing were only seen in rheumatoid patients, although in 1 case this was due to leukaemia and in 2 the diagnosis of histiocytosis X was probable. They also considered 42 post mortem examinations. Bronchiectasis was found in 5 patients and in no control case.

Pleural disease had also been described by Charcot¹, Hart⁴ and Bloom and Rubin⁷ and in 1953 Caplan¹⁵ had described characteristic radiographic changes in coal miners suffering from rheumatoid arthritis.

In addition to continuing reports of pleural disease there were further reports of the clinical picture of breathlessness, cough, clubbing of the finger nails, crepitations and abnormal chest radiographs by Price and Skelton¹⁶ (1956), Edge and Rickards¹⁷ (1957) and Mason and Steinberg¹⁸ (1957).

Also in 1957 Gardner et al¹⁹ described a patient with rheumatoid disease who developed pulmonary hypertension. At post mortem severe fibrous hyperplasia of the intima of arterioles was associated with thrombosis and recanalisation. The vascular changes seemed to have occurred without any significant inflammation of the lung parenchyma.

In an investigation of the prevalence of pleural or lung changes in rheumatoid disease Horler and Thompson²⁰ (1959) in 180 patients found 9 cases of pleural effusion, 1 patient who had a pleural effusion and lung nodules also had a diffuse lung lesion and 2

other patients, both coal miners, had bilateral diffuse radiological changes, 1 with honeycombing.

In the same year Cruickshank²¹ described pathological findings in 8 patients with rheumatoid disease and interstitial pneumonia or interstitial fibrosis.

Locke²² (1963) compared the chest radiographs of 54 patients with rheumatoid arthritis with 54 controls, but they included patients with systemic lupus erythematosus, ankylosing spondylitis and polyarteritis nodosa. They found the basal pattern abnormal in 15 rheumatoid patients but in no controls.

Brannan et al²³ reported abnormal chest radiographs in patients with a diagnosis of rheumatoid arthritis. Of 47 patients with radiographic evidence of interstitial pulmonary fibrosis, 27 had definite rheumatoid arthritis, 8 probable. Also in 1964 Sievers et al²⁴ examined chest radiographs in 260 patients with rheumatoid arthritis (114 sero-negative) and in 94 patients with non-rheumatoid joint disease. There was extensive parenchymal shadowing with pleural thickening or effusion in 7.1% of the sero-positive rheumatoid patients and no similar abnormality in the sero-negative patients or non-rheumatoid group.

Subsequent large series of radiographic investigations were reported. Stack and Grant² in 1965 found abnormalities of the lung fields in 45 of 117 rheumatoid patients compared with 34 of 117 neurological patients, the difference not being significant. Walker and Wright²⁵ (1969) found 8 chest radiographs compatible with interstitial fibrosis in 516 patients with classical or definite rheumatoid arthritis and none in 301 patients with degenerative joint disease.

The Pathological Findings

The pathological changes in the lungs of the 2 patients described by Ellman and Ball³ differed slightly. In both cases there was fibrosis between alveoli and infiltration with inflammatory cells. In the first case fibrinoid degeneration of the muscular coat of the blood vessels was present; in the second case there seemed to be more alveolar change, some alveoli being lined with cuboidal epithelium, but the blood vessels were not affected.

In the patient reported by Hart and McKenzie⁵ the lungs had a cystic appearance, the cysts were lined with granulation tissue and infiltrated with lymphocytes, plasma cells and histiocytes. They felt that the changes were similar to those described as 'honeycomb lung' by Hepplestone²⁶ who suggested that the cystic changes were commonly secondary to bronchiolar disease.

The lungs of the patient described by Katz and Auerbach⁸ contained all the changes described in the previous patients. The bronchi and bronchioles were irregularly dilated and trabeculated. The findings in the 3 patients reported by Christie¹¹ showed fibrosis affecting small air passages and the adventitia of the pulmonary blood vessels in all 3 cases. In one case the alveoli were plugged with fibrin casts. The two biopsies reported in Rubin's patients showed predominant changes in the alveoli. Price and Skelton¹⁶ in post mortem material from their patient distinguished between newer lesions with thickening of alveolar septa and fibrinoid necrosis of arteries and older lesions with thickening or fibrosis of bronchioles and the intima and media of blood vessels. In the two cases described by Edge and Rickards¹⁷ arterial changes did not seem prominent.

Cruickshank²¹ reporting the pathological findings in 8 patients, found that there was often a mixed picture of the various changes described by previous authors.

Ognibene²⁷ (1960) reported 2 patients with rheumatoid disease. In one a lung biopsy showed arterial occlusions, but the pulmonary artery pressure was normal. The other patient had pulmonary hypertension. The alveoli were almost completely replaced by fibrous tissue, but there was no particular evidence of vasculitis.

Anderson and Foraker²⁸ (1960) describing morphological aspects of interstitial pulmonary fibrosis stated that small foci of fibrosis could be found in the lungs of most mature adults. Talbot and Colkins²⁹ (1964) performed post mortem examination of the lungs of 50 patients with rheumatoid arthritis comparing them with 50 patients matched for sex and decade of age. They found a slight excess of pleural change in the rheumatoid group, but no difference in alveolar appearances.

Biopsy specimens were obtained in 5 patients of Brannan et al³. There were inflammatory changes in peribronchial tissue and the alveolar walls and also slight vascular changes. In a series of 76 post mortem examinations they found only one case of interstitial pulmonary fibrosis which could not be attributed to a cause other than rheumatoid disease.

In recent years patients have been described with prominent and progressive bronchiolar disease. Geddes et al³⁰ reported the post mortem findings in 2 patients who showed widespread disease in bronchioles with no involvement of alveoli.

It is clear that all components of lung tissue are affected by

inflammatory and fibrotic changes and it scarcely seems appropriate to refer to the disease as 'fibrosing alveolitis' when bronchioles and blood vessels are also involved. Ellman and Ball's³ original description of penumonitis would encompass all these changes and perhaps 'fibrosing pneumonitis' would be acceptable.

Pulmonary Function Tests

With the first reports of lung involvement there was no assessment of pulmonary function. Katz and Auerbach⁸ recorded a vital capacity (VC) of 1400 mls in their patient, this being 35% predicted normal. The arterial oxygen saturation was low at 65%. Spence¹² reported the response of his patient to corticosteroid treatment; VC rose from 1350 mls to 2450 mls. In one of Rubin's¹³ patients restrictive ventilation was recorded.

Cudowicz et al³¹ (1961) reported a patient whose transfer factor (T_L) was 77 mls/min/mm Hg. in association with restricted ventilation and increased residual volume. The patient had a pleural effusion, but open biopsy showed in addition to pleural rheumatoid nodules, inflammatory changes in the alveoli, bronchioles and small arteries.

One of the 2 patients described by Doctor and Snider³² (1962) had a slightly reduced total lung capacity (TLC) and the arterial oxygen saturation fell from 90.1% at rest to 78% on exercise. Transfer factor was recorded as low in 2 of 3 patients reported by Lee and Brain³³ in 1962. They also referred to restrictive ventilation in 1 patient and 'impaired mechanical function'.

Table 1, shown on pages 13, 14 and 15, summarises the published reports of lung function measurements in series of patients.

Specific investigation of lung function in 13 patients was reported by Newcomer et al³⁴ in 1964. VC was low in 7, residual volume (RV)

increased in 10 and maximal mid-expiratory flow rate (MMEFR) low in 6. This finding suggestive of airways disease was followed by a report from Huang and Lyons³⁵ who studied 11 patients with rheumatoid arthritis. Forced expiratory volume in 1 second (FEV_1) was reduced in 3 patients and maximum voluntary ventilation (MVV) $<50\%$ predicted in 3 patients. Mean RV was 156% predicted normal and mean diffusing capacity (T_L) 79% predicted normal. They found poor correlation between clinical, radiological and physiological findings. Gray and Gray³⁶ investigated 14 patients with rheumatoid disease with no clinical evidence of lung disease. They found the lowest levels for ventilatory capacity, arterial oxygen tension and T_L below the expected levels, but individual results were not published. They assessed the response of 7 patients to cortisone treatment. VC and MVV improved with treatment and declined after it was discontinued. Two female patients were seen over a 16 year period and showed a slow steady fall in VC and MVV more than expected from prediction formulae.

Walker and Wright²⁵ reported reduction of T_L in all 9 patients tested because the chest radiographs suggested lung disease. VC was reduced in 1 patient. In 1970 Loddenkemper, Bach and Carton³⁷ found restrictive ventilation in 7 of 9 patients and low transfer factor in all. Five of the 9 patients had diffusely abnormal chest radiographs.

Morère et al³⁸ (1972) measured airways resistance and dynamic lung compliance in addition to lung volumes and transfer factor. They included very disabled patients who were unable to sit upright for the tests. This is likely to have affected compliance and T_L measurements. Attinger et al³⁹ (1956) showed that compliance was

lower in the supine position in patients with various types of respiratory disease. The prevalence of specific compliance of <0.150 litres/cm H_2O in 45% of Morere's patients may therefore be rather higher than would have been found if all the patients had been able to sit upright. Knowles et al⁴⁰ suggested that the increased pressure changes recorded supine were due to oesophageal compression. Transfer factor is also changed by body position and will be higher in supine patients (Bates and Pearce⁴¹ 1956), so that the prevalence of low transfer factor found may be an underestimation. They also found a high prevalence of increased airways resistance. Although they excluded patients presenting with lung disease, 43% of the patients had abnormal chest radiographs, including 4 with a honeycomb appearance. They found the triad of low oxygen tension, reduced lung compliance and low transfer factor significantly related to a positive Rose Waaler titre of 1/640 or greater.

The following year Popper, Bogdonoff and Hughes⁴² compared 32 patients, 7 of whom had diffusely abnormal chest radiographs, with classical or definite rheumatoid arthritis, with 33 patients with degenerative joint disease. There were no patients with anaemia. FEV_1 , VC and T_L were lower in the group of patients with abnormal chest radiographs or clinical evidence of interstitial pulmonary disease.

Davidson, Brooks and Bacon⁴³ selected a group of 42 patients, all less than 65 years of age, with no dyspnoea and no clinical or radiological evidence of lung disease. They excluded patients with anaemia, with heart disease or patients taking corticosteroids. Unusually they found 10 females of these very selected patients to have $T_L < 80\%$ predicted normal; males were all normal. This reduction

in T_L was not significantly related to any features of the rheumatoid disease, but was significantly related to smoking and chronic cough.

A further series of 41 patients compared with 40 retrospective normal controls was reported from Frank et al⁴⁴ (1973). They compared the 'abnormal' group of patients with low T_L with a 'normal' group with normal T_L and found a history of pleurisy, pneumonia or bronchitis more commonly in the 'abnormal' group. They found that 33% of the females and 57% of the males had some abnormality of lung volumes, T_L or blood gases. An obstructive pattern of ventilation was common in the smokers, but compared with non-rheumatoid patients referred for investigation of chronic bronchitis, T_L was lower. Over the course of 2 years some patients showed a fall in T_L . Eight lung biopsies were performed in patients with abnormal lung function. In all cases the histology was abnormal. In 4 patients with abnormal chest radiographs lung function was normal. These authors stated that they measured D_m and V_c but no results were reported.

Collins et al⁴⁵, in an investigation designed to look for small airways disease, found a prevalence of 71% of abnormal respiratory function in 43 patients all treated with aspirin. The prevalence of low MMEFR was high in smokers (76%), but a similar rate (75%) was found in a control group of smokers with degenerative joint disease. The prevalence of low MMEFR was considerable in non-smokers with rheumatoid disease and mean MMEFR was significantly lower in the rheumatoid patients. Tests repeated at 6 months showed no correlation between changes in lung function and changes in rheumatoid status. They also performed perfusion and inhalation lung scans, but these did not detect additional abnormalities.

Whorwell, Wojtulewski and Lacey⁴⁶ compared 85 rheumatoid patients with matched controls. Excluding patients with anaemia or heart disease and patients with abnormal chest radiographs or history of dust exposure, they found T_L significantly different from predicted values in the rheumatoid group, but not in the controls. The reduction correlated with smoking and with log Rose Waaler titre, but there was no relation to treatment with gold, steroids or penicillamine.

Two groups of workers reported their findings both in 1975 and 1976.

Laitinen et al⁴⁷ (1975) studied 129 patients, excluding smokers with cough or signs of acute bronchitis and patients with anaemia, heart failure or other chest disease. T_L levels were corrected to Hb of 13.5G % for females, 14.5G % for males. In patients with disease of less than 6 years duration, FEV_1 and VC were decreased more than T_L . In patients with arthritis over 10 years duration T_L was significantly lower than in those with arthritis of less than 2 years duration. In 5% of patients with normal chest radiographs VC and T_L were low while 8 patients with mild or moderately abnormal chest radiographs had normal VC and T_L . T_L was lower in a group of patients found to have marked radiograph abnormalities. They were unable to find any correlation with Rose Waaler titre or the number of joints involved. On the other hand, Schernthaner et al⁴⁸ in a group of 62 patients (55 female), by dividing patients into those with KCO above or below 4.5 mls/min/mm Hg/L and ranking them according to increasing Rose Waaler titre, found a linear relation between titre and the prevalence of pathological KCO. Their study also excluded patients with heart disease or

with Hb < 9G %. The prevalence of increased airways resistance was similar in sero-positive and sero-negative patients, the total prevalence being 17.7% compared with 41.8% found by Morere et al³⁸. Perhaps this was related to the larger proportion of female patients studied. The percentage of patients with low specific compliance was significantly greater ($p < .025$) in the sero-positive group.

In another study designed to look for evidence of small airways disease Geddes et al⁴⁹ found that measurement of MMEFR increased the prevalence of abnormal findings from 24% with low FEV/VC%, or 28% with low FEV₁, to 38%, smokers being more affected.

These published studies provide evidence that patients with rheumatoid disease have abnormal airways function, impaired gas transfer and from some reports, reduced lung compliance.

TABLE 1

<u>INVESTIGATORS</u>	<u>NO. OF PATIENTS</u>	<u>CONTROLS/COMPARISON</u>	<u>EXCLUSIONS</u>	<u>TESTS PERFORMED</u>	<u>FOLLOW-UP</u>
Newcomer, Miller, Hepper, Carter	13	SLE		VC, RV, MMEFR	16 years Tested response to cortisone
Huang and Lyons	11	SLE Scleroderma	Pleurisy or pneumonia within 1 year	FEV ₁ , VC, MVV, RV, TLC, TL _{SB} , SaO ₂	
Gray and Gray	14	3 ankylosing spondylitis	Clinical evidence of lung disease	VC, MVV, RV (N ₂ washout), TLC, TL _{SS} , SO ₂ , pO ₂ , pCO ₂	
Walker & Wright	9	-	Selected because of lung disease	Min Vol, FEV ₁ , VC, pCO ₂ , TL _{SB}	
Loddenkemper, Bach and Carton	9	SLE		FEV ₁ , VC, MVV, RV, TLC, TL _{SB}	
Moreère, Stain, Nonvet, Lefrancois, Pasquis, Pietrini-Lenail, Deshayes, Maisse, Degraeve	74 (91)	-	Those presenting with lung disease, TB, carcinoma, heart failure	FEV ₁ , VC, Raw, C _{dyn} , TL _{SS} , Blood gases	
Popper, Bogdonoff and Hughes	32	Degenerative joint disease	(Not criteria for exclusion but no anaemia. No compromised cardiac function)	FEV ₁ , MVV, VC, RV, TLC, TL _{SB}	

TABLE 1 (contd)

<u>INVESTIGATORS</u>	<u>NO. OF PATIENTS</u>	<u>CONTROLS/COMPARISON</u>	<u>EXCLUSIONS</u>	<u>TESTS PERFORMED</u>	<u>FOLLOW-UP</u>
Davidson, Brooks, and Bacon	42	-	Arthritis <3 years duration. Age >65 Clinical or X-ray evidence of lung disease. Clinical or ECG evidence of heart disease. Hb 11.0G% ♀ 12.0G% ♂ Corticosteroids	FEV ₁ , VC, PEFR, RV, TLC, TL _{SB}	
Frank, Weg, Harkleroad, Fitch	41	Normal		FEV ₁ , VC, RV, TLC, TL _{SB} , (Dm & Vc) If abnormal blood gases, minute ventilation and $\dot{V}O_2$ rest and exercise	2 years
Collins, Turner, Johnson, Whitley and McLean Collins, Turner, Leyrer, McLean	43	Degenerative joint disease	Drug treatment of arthritis other than aspirin during past 6 months	FEV ₁ , VC, MMEFR, arterial blood gases. Ventilation and perfusion lung scans	6 months
Whorwell, Wojtulewski and Lacey	85	Normal	Anaemia. Heart disease. Dust exposure	FEV ₁ , VC, TL _{SB}	

TABLE 1 (contd)

<u>INVESTIGATORS</u>	<u>NO. OF PATIENTS</u>	<u>CONTROLS/COMPARISON</u>	<u>EXCLUSIONS</u>	<u>TESTS PERFORMED</u>	<u>FOLLOW-UP</u>
Laitinen, Nissila, Salorinne, Aalto, Salorinne	129	-	Hb < 10G % cardiac decompensation other chest disease including acute bronchitis	VC, T _L , (TLC from VA obtained T _L test)	
Schernthaner, Scherak, Kolarz, Kummer Kolarz, Schernthaner, Scherak, Kummer	62	-	Hb < 90% Heart disease	FEV ₁ , VC, MBC, RV, TLC, Raw, C (quasi static expressed as C _{st} /FRC) T _L /FRC, SS, pO ₂ , pCO ₂	
Geddes, Webley and Emerson	100	Normal	Significant abnormality of chest radiograph	FEV ₁ , VC, MMEFR	

Transfer factor depends on normal distribution of ventilation, normal alveoli and normal blood supply. It is therefore likely to be diminished by inflammatory change affecting bronchioles, alveoli or pulmonary blood vessels, all of which have been shown to be involved in rheumatoid disease.

The present study which started in 1971 before many of these reports were published, was designed both to compare the frequency of abnormal findings with that in a matched control population and to repeat lung function tests over a 5 year period to see if abnormal findings were persistent.

Bagg and Hughes⁵⁰ performed serial lung function tests in patients with systemic sclerosis, the longest period of follow-up being 16 years. They found that reduction in T_L was the first abnormality seen in 4 patients who later developed lung volume abnormalities, but that progressive fall in T_L was only seen in patients with T_L less than 50% predicted normal at the first visit. Colp et al⁵¹ concluded that the progress of patients with systemic sclerosis, followed for periods of up to 8 years, was more indolent than that of patients with fibrosing alveolitis.

In both studies there was considerable variability in individuals' progress, and the response to treatment was also unpredictable.

In rheumatoid disease previous workers (Bloom and Rubin⁷ 1950, Harris¹⁰ 1954, Christie¹¹ 1954) have described transient radiological changes, exacerbation of the lung lesion at the time of the exacerbation of arthritis (Brannan et al²³) and changes in lung function related to corticosteroid treatment (Gray and Gray³⁶, Doctor and Snider³²). Only 3 previous studies have reported any follow-up. Gray and Gray³⁶ had studied 2 patients over a 16 year

period. Collins et al⁴⁵ repeated tests after 6 months, Frank et al⁴⁴ after 2 years.

Tests were also included to look for evidence of disease affecting the bronchioles or pulmonary blood vessels and therefore contributing to the impairment of gas transfer.

To look for disease of small airways dynamic compliance (C_{dyn}) was measured at increasing rates of respiration. Otis et al⁵² (1955) showed that alteration of time constants due to narrowing of small airways causing increased resistance would lead to changes in the distribution of ventilation. It would tend to go to areas of lower resistance and at increased rates of respiration the total measured compliance would be expected to fall. Mead⁵³ (1969) published curves predicting changes in compliance and resistance and therefore in time constants which would be expected in patients with emphysema.

The technique has given results which support the theory. Woodcock et al⁵⁴ and Grimby⁵⁵ demonstrated frequency dependence in patients with chronic bronchitis whose FEV_1/VC was normal at the time and in asymptomatic asthmatics. Hill et al⁵⁶ also found frequency dependence of compliance to be common in adolescent asthmatics whose routine lung function tests were normal.

The use of the test in asthmatics might be debated. Asthmatic patients show increased airways resistance over a series of normal expirations (Gayrard et al⁵⁷) and during hyperventilation (Chan Yeung et al⁵⁸). Therefore successive respirations at slow rates might show a fall in compliance and it is likely that more rapid respiration will increase airways resistance in general and thus lead to a fall in compliance.

The concept was questioned by Ingram and Schilder⁵⁹ (1967) who failed to show a significant difference between normal subjects and those with chronic bronchitis or emphysema. Defares and Donleben⁶⁰ found frequency dependence in normal subjects who had normal nitrogen washout curves. Guyatt et al⁶¹ (1975) found poor reproducibility of the test in normal subjects. The criteria for claiming frequency dependence as indicating small airways disease and the requirement for recording equipment with good frequency response were reviewed by Gayrard⁶² in 1975.

Following these early studies in patients with known airways disease, Seaton, Lapp and Morgan⁶³ demonstrated frequency dependence in coal workers with normal FEV₁/VC and concluded that it was indicative of dust deposits causing disease at bronchiolar level.

A study by Fulmer et al⁶⁴ studied patients with biopsy evidence of fibrosing alveolitis, 1 of whom had rheumatoid disease. The narrowing of small airways was assessed microscopically in all patients. Patients with biopsy evidence of narrowed bronchioles showed frequency dependence of dynamic compliance. No patient with bronchioles of normal diameter showed frequency dependence. This striking finding was in no way influenced by the smoking habits of the patients and the clear cut difference between the groups was not obscured by including patients whose static pressure volume curves were abnormal. The inflammation was peribronchiolar and it was stated that no patient had 'end stage' lung disease, but the related severity of the alveolar change is not tabulated. The possibility cannot be excluded that frequency dependence arose from altered time constants in the lung rather than the airways, but the relation to bronchiolar disease appeared clear.

The vascular component of transfer factor was to be assessed by measuring transfer factor at 2 levels of inspired oxygen.

Roughton and Forster⁶⁵ showed that the membrane component (D_m) and vascular component (V_c) of transfer factor may be considered as 2 resistances in series

$$\frac{1}{T_L} = \frac{1}{D_m} + \frac{1}{\theta V_c}$$

θ is the rate of uptake of carbon monoxide by the red blood cell and it changes with different concentrations of oxygen. If T_L is measured at different levels of oxygen tension D_m and V_c may be derived graphically or calculated.

The calculation of θ depends on assumptions made about the ratio of oxygen uptake by the red cell membrane to uptake by the red cell interior (λ). Roughton and Forster⁶⁵ published figures for λ of 1.5, 2.5 or ∞ . They found that $\lambda = 1.5$ fitted well with the observed measurements at low oxygen tensions and $\lambda = 2.5$ to measurements at higher oxygen tensions. Cotes recommends using $\lambda = \infty$ ⁶⁶. The predicted normal values used in this study assume $\lambda = \infty$, therefore this value was used in calculation of $\frac{1}{\theta}$, although in several reported studies λ was taken as 2.5 (McNeill⁶⁷, Johnson⁶⁸, and Krumholz⁶⁹). There are also different formulae for calculating $\frac{1}{\theta}$ and different methods of correcting the haemoglobin concentration and these differences may make it difficult to compare the results found by different sets of workers. As values from one laboratory to another are likely to vary from many causes, the rheumatoid patients in this study in whom D_m and V_c were measured, were compared with a matched normal population.

D_m and V_c were measured in sarcoidosis by Hamer⁷⁰ who found that V_c tended to be low in patients with fibrosis known to be of long

duration, whereas Dm was found to be low in patients with normal chest radiographs. It is probable that Vc is also associated with more severe lung disease in systemic sclerosis. Georges et al⁷¹ found Vc normal in patients with systemic sclerosis and normal chest radiographs, but reduced in those with abnormal chest radiographs and in patients with diffuse interstitial pulmonary fibrosis. T_L was low in all groups of patients.

Gold and Jennings⁷² studied 20 patients with systemic lupus erythematosus. They found Dm reduced in 5 of 12 patients with restrictive ventilation, but did not report Dm/alveolar volume values, and Vc was reduced in 3 of these patients. Five other patients with low Vc were considered to belong to a group with predominant vascular disease.

Thus in all forms of interstitial pulmonary fibrosis so far studied the presence of vascular involvement has been indicated by low Vc and reduction seems to have been related to more advanced disease. Measurement of Dm and Vc has not up to now been reported in rheumatoid disease and the present study provides new information about this.

SUBJECTS STUDIED:

Patients with classic or definite rheumatoid arthritis were asked to take part in the study. It was known that patients newly referred to the out-patient clinic might have disease of long duration or of recent onset and that patients with mild disease as well as those with severe arthritis were likely to be referred for specialist advice. It was therefore hoped that a random sample would be obtained by approaching patients at their second visit to the clinic.

The ward was also visited weekly. Patients were admitted to hospital for periods of rest, for surgery and sometimes for assessment of problems other than arthritis. Patients found in the ward were also asked to participate, but tests were not performed within 7 days after receiving a general anaesthetic.

The nature of the test to be carried out was explained to the patient. No attempt was made to persuade the many patients who were reluctant to swallow an oesophageal balloon to take part in the study.

Patients were not excluded from the study by the presence of respiratory symptoms which could have been related to rheumatoid lung disease, but patients known to have other respiratory disease were excluded. Tests were not performed on patients when suffering from respiratory infections. As follow-up tests would be required, patients were not recruited if they lived more than 20 miles from the hospital.

Control subjects for the initial study were recruited from hospital staff, from spouses of patients and from patients admitted to hospital for other conditions, usually surgical. They were matched with the rheumatoid patients in 4 age groups according to sex and smoking

habits. Only 2 rheumatoid men were non-smokers, therefore no control male non-smokers were studied.

The original intention was to recruit an equal number of normal volunteers, but as recruitment was slow it was decided to continue the intake until each control group included at least half the number of comparable rheumatoid subjects.

Further normal volunteers were recruited for Dm and Vc studies as these measurements had not been made in the first controls studied. These normal subjects were free of respiratory symptoms, had normal chest radiographs and normal FEV₁ and VC. As before they were recruited in age groups to match the rheumatoid subjects for sex and smoking habits.

METHODS:

After the first visit the patients were asked to attend at intervals over a 5 year period so that the total number of visits would be 5. Intervals between visits, therefore, ranged between 12 and 16 months.

A questionnaire was completed at each visit (Fig. 1). See page 24. Details of smoking habits were recorded for ex-smokers as well as current smokers. A detailed occupational history was taken to assess possible exposure to dusts and questions were asked about exposure to organic dust which might cause allergic alveolitis.

Patients were examined to assess the number of joints actively involved: a set of metacarpal, metatarsal or interphalangeal joints were counted as 1 joint. The presence of nodules and of clubbing was noted and the heart and lungs examined.

A chest radiograph was obtained in the routine department. There were no special precautions to ensure that films were of comparable quality. A record was kept of radiological findings coded as 1) normal, 2) pleural shadowing, 3) abnormal shadowing in the lung fields, either minimal or marked and 4) other abnormality with a note of its nature. I classified each x-ray without reference to the previous films and their coding.

An electrocardiograph was taken and the findings recorded as showing evidence of 1) normality, 2) right ventricular abnormality, left ventricular abnormality and 3) other abnormality with a note as to its nature.

Blood was taken for estimation of haemoglobin, ESR, Rose Waaler titre and latex test. In those patients in whom some abnormality of lung function had been found and the patients kept a bird, blood was sent for examination for avian precipitens.

FIG. 1

INVESTIGATION OF LUNG FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

1. Name: Mr/Mrs/Miss	Address:					
Hospital No.	Date of Birth					
2. Smoking history: None Cigarettes...Cigars...Pipe...per day						
No. of years:						
If ex-smoker date of stopping:						
3. Occupational history:						
Other: exposure to dust, birds, hay, etc.						
4. Family history of allergic disease:		Present		Absent		
5. Personal history of allergic disease:						
None						
Hayfever						
Rash - type precipitating agent						
6. Arthritis		Initial D.A.T.				
Duration in years						
Presenting symptoms:						
Evidence of Sicca syndrome		Arteritis		Nodules		
7. Present state						
Date						
No. joints involved						
Work: nil=0 part=1 full=2						
Dyspnoea: rest, walking, stairs, nil						
Cough						
Clubbing						
Creps						
D.A.T.						
Latex test						
E.S.R.						
Chest x-ray						
E.C.G.						

Please tick if patient on: Gold Penicillamine Steroids

Respiratory Function Tests

Lung volumes and transfer factor were measured at every visit, dynamic compliance at the first visit, and usually at one follow-up visit. Where there was some abnormality at the first visit, the examination was repeated earlier than the fifth visit. Dm and Vc were measured after the second visit if transfer factor had been low, or at the fourth or fifth visit.

Forced expiratory volume in 1 second (FEV_1) and vital capacity (VC) were measured first with a McDermott dry spirometer with the patients standing if possible. After 2 or more practice attempts the mean of 3 measurements was recorded. Where the FEV_1/VC ratio was less than 70%, 160 mcgs isoprenaline were inhaled and the test repeated after 5 minutes. Mean values of 3 measurements of FEV_1 and VC were also recorded with the patient seated using a P.K. Morgan Resparameter. In patients who had not received isoprenaline the best mean values for FEV_1 and VC were used in analysis. Residual volume was measured by helium dilution and TLC calculated.

Transfer factor was measured twice at rest and twice on exercise using the steady state (end-tidal) method (Bates, Boucot and Dormer⁷³ 1955). The mean of duplicate measurements was used in analysis. The steady state method was chosen chiefly because of the exercise tests. Although trained subjects are able to exercise and perform single breath manoeuvres, it was thought that this would be troublesome for patients, especially those with arthritis, who might be finding the exercise difficult.

Exercise was carried out for 3 minutes and patients were encouraged to accept a load they felt they could continue with for that period.

Arms or legs were used to peddle a bicycle ergometer. Oxygen uptake was recorded by a Servomex oxygen analyser, but was not available for some of the earlier visits.

At the start of the study reproducibility of TL_{SS} results was found to be within 2 mls/min/mm Hg. for 20 estimations in each of 2 laboratory technicians. Over the period of follow-up the accuracy of the method was checked by repeated measurements in laboratory staff.

At the fourth and fifth year of follow-up transfer factor was measured by the single breath method using a P.K. Morgan Resparameter or Transfertest. This provided results which could be more easily compared with recent reported studies of lung function in rheumatoid disease^{42, 43, 44, 46, 47} and also allowed measurement of D_m and V_c . To continue the longitudinal study in the patients, transfer factor was measured as before by the steady state method at the fourth or fifth year. For a short period no steady state measurements were made as control readings on the laboratory staff were producing high results, but the fourth and fifth year SB measurements combined with SS at fourth or fifth year allowed continuous follow-up.

Dynamic compliance was measured with the patients seated. A balloon 10 cm long, 1 cm diameter containing 0.5 mls of air was placed at approximately 40 cm from the nostril and was used to record intra-thoracic pressure (Mead and Whittenberger⁷⁴ 1953). Mouth pressure was recorded from the proximal side of the Lilley pneumotachygraph and differential pressure was recorded using a Hewlett Packard 267B transducer. Flow was recorded from the pneumotachygraph connected to a Hewlett Packard 270 transducer. Volume was recorded

from a McDermott spirometer fitted with a potentiometer. The 3 recordings of pressure flow and volume were recorded on a four channel thermal recorder at paper speeds of 25 to 50 mm/sec. Dynamic compliance was calculated from the volume/pressure changes between points of no flow over 5 complete cycles at each speed.

The accuracy of the zero flow record and absence of phase difference was checked as recommended by Macklem⁷⁵ and care was taken during the tests that tubing did not become kinked as this would have produced phase shifts. The frequency response of the spirometer and pneumotachygraph and 270 transducer were tested by a square wave. Fifteen hundred gramme weights were attached to the hook at the base of the spirometer bellows which was supported and then suddenly released. The response was measured at paper speeds of 100 and 500 mm/sec. For the 2 McDermott spirometers used the 90% response time for 500 mls was 0.05 to 0.072 sec., giving a frequency response of 4.63 to 6.67 Hz. For the pneumotachygraph and transducer at a flow rate of 100 L/min., 90% response time was 0.015 secs., the frequency response 22.2 Hz. These were considered satisfactory.

The patient was instructed to inspire to total lung capacity, then to expire into the spirometer as far as possible. This vital capacity was noted and the patient breathed into his mid-vital capacity range which was marked on the dial of the spirometer. He breathed in time with a metronome over a tidal range of about 500 mls and the range was noted. Runs of 10 or more respirations were recorded, 2 runs at each of 4 speeds with metronome settings of 40, 72, 120 and 176. This gave respiratory rates of about 20, 36, 60 and 80 per minute. Runs were not accepted when patients

did not achieve their vital capacity or return to within 200 mls of the set tidal volume range. Mills, Cumming and Harris⁷⁶ showed that change in compliance with increased respiratory rate was accentuated at low lung volume, and least at mid-inflation level as measured by a strain gauge encircling the upper chest.

Static recoil pressures were obtained where possible. Patients were asked to take 3 maximal breaths then to inspire to total lung capacity and hold their breath. Static expiratory pressure volume curves were obtained for some patients who were able to expire in short steps to allow pressure and volume to be recorded. The chief limit to the amount of information which could be obtained from the patients was often time available because many patients were dependant on hospital transport.

D_m and V_c were obtained by making 2 measurements of transfer factor_{SB} at high concentrations of oxygen and 2 with the patient breathing air. The 2 measurements of high oxygen concentration were made first, each immediately after the patient had breathed 100% oxygen for 5 minutes. The inspired carbon monoxide 0.28% and helium 14% was contained in oxygen. Twenty minutes or more elapsed between these 2 measurements and those made using an inspired mixture of carbon monoxide and helium in air.

D_m increases with increasing alveolar volume and V_c decreases (Hamer⁷⁷). Every effort was made to see that patients expired fully and took a full inspiration for the T_I measurements.

Back tension of carbon monoxide was measured by a re-breathing method before the first test and either before the second test or after the last test.

From Cotes⁶⁶

$$BT = \frac{\text{Re-breathing CO concentration} \times \text{expired O}_2}{\text{re-breathing O}_2 \text{ concentration}}$$

From these 2 measurements back tension for each test was estimated and the measured inspired and expired carbon monoxide levels corrected.

The necessity for measurement of back tension was confirmed by 24 calculations of Dm and Vc with and without back tension correction. The effect on results was unpredictable and sometimes very large. It was also noted that back tension in non-smokers could be very high so that it would not be wise to neglect measurement of back tension in them.

Dm and Vc may be calculated from the formulae:

$$Dm = \frac{T_1 \times T_2 \times (P_2 - P_1) - 0.827 \dot{v}O_2 \times (T_1 - T_2)}{T_2 \times P_2 - T_1 \times P_1 - 57.9 (T_1 - T_2)}$$

$\dot{v}O_2$ = oxygen uptake mls/min

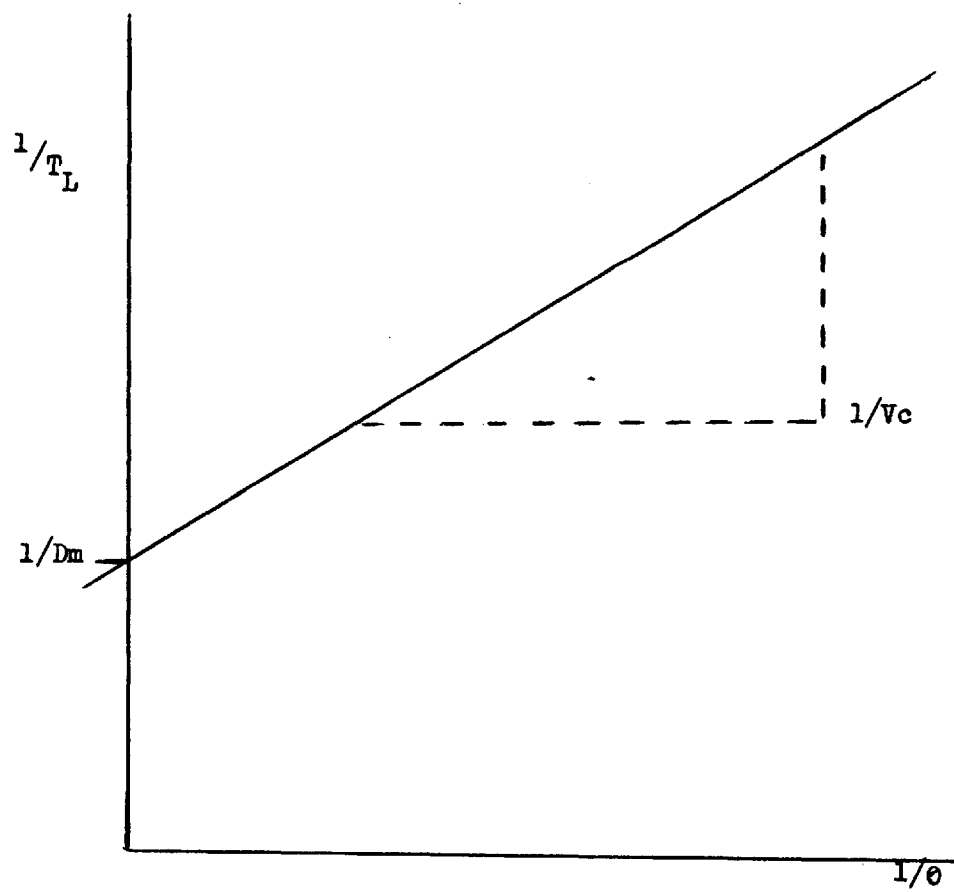
$$Vc = \frac{0.744 (P_2 - P_1) \times T_1 \times T_2}{Hb \times (T_1 - T_2)} \quad (\text{Cotes}^{66})$$

T_1 and T_2 are the measured values of T_L at the 2 oxygen tensions P_1 and P_2 .

The values may also be obtained graphically since:

$$1/T_L = 1/Dm + 1/\theta Vc \quad (\text{Roughton and Forster}^{65})$$

See Fig. 2 overleaf.

FIG. 2GRAPHICAL DERIVATION OF D_m AND V_c 

$\dot{V}_O$ = rate of carbon monoxide uptake/ml blood/mm Hg.

After using both methods for a time, the graphical method was found easier and was used for this study.

Where the first 2 estimations of T_L were found to have been made at similar oxygen concentrations the mean of the 2 tests was plotted. Occasionally 1 oxygen concentration was much higher than the other; in these circumstances a line was drawn through all points. Where the oxygen concentrations were different and the points did not fall on a straight line, the results were discarded.

$$\dot{V}_O = \frac{.0057 \times pO_2 + .33}{Hb\%} \quad (\text{Frans}^{78})$$

Hb% = per cent of 14.8 G Hb per 100 mls blood.

This formula assumes that λ (the rate of oxygen uptake by the red cell membrane/ratio of uptake by the red cell interior = ∞).

Statistical Methods

Mean values and differences between visits for lung volumes, T_L , D_m and V_c were compared by Student's t test.

For comparison of rheumatoid and control groups for dynamic compliance, and for longitudinal changes in compliance or transfer factor in relation to symptoms and signs, the Mann Whitney U test was used.

Correlation coefficients were calculated to study trends in transfer factor for the group as a whole over the 5 year period and for individual patients to relate measured transfer factor to the number of joints involved, Rose Waaler titre or the exercise performed by the patient.

The prevalence of various patterns of abnormality in relation to

clinical features was tested for significance by χ^2 with Yates correction.

To compare visits where symptoms or signs were present (SP) with those where they were absent (SA) the mean value for a measurement was calculated for each individual for SP and SA visits. The mean of the difference SP - SA was then calculated for all the patients showing variability in the symptoms or signs.

RESULTS:

1. Comparison of the Rheumatoid and Control Populations

One hundred and one patients with rheumatoid disease were recruited and 61 control subjects. Two rheumatoid patients who attended were rejected because they had very severe airways obstruction; 1 had bronchial asthma, the other smoker's chronic bronchitis and emphysema. One female subject was rejected as a normal volunteer because her Rose Waaler titre was found to be 1/256; she had never had any arthritis.

The distribution of the 2 populations in terms of age, sex and smoking habits is shown in Table 2, as shown overleaf. There was a slightly higher proportion of female non-smoking controls.

This was because several of the subjects failed to produce satisfactory dynamic compliance tracings and 3 additional volunteers were recruited to balance the numbers for comparison of compliance.

TABLE 2

<u>DISTRIBUTION OF AGE, SEX AND SMOKING HABITS FOR RHEUMATOID PATIENTS AND CONTROL SUBJECTS</u>								
99 Rheumatoid Patients					60 Control Subjects			
Age	Male		Female		Male		Female	
	S	NS	S	NS	S	NS	S	NS
25 years	1	0	0	1	1	0	0	0
26-40 years	3	1	7	8	3	0	4	5
41-55 years	18	0	8	13	10	0	6	8
56-70 years	13	1	13	12	7	0	8	8
Totals by sex	35	2	28	34	21	0	18	21
	37		62		21		39	
S = smoker								
NS = non-smoker								

TABLE 3 shows the distribution of smoking habits; there was a slight excess of heavy smokers (> 20 cigarettes per day) in the control group.

	Rheumatoid		Control	
	Male	Female	Male	Female
No.	37	62	21	39
Non-smokers	2	32	0	18
Up to 10 cigarettes/day	9	12	2	2
11 to 20 cigarettes/day	3	6	5	7
More than 20 cigarettes/day	10	4	9	8
Pipe/cigars	5	0	2	0
Ex-smokers	8	8	3	4

TABLE 4 shows possible exposure to agents which affect lung function; obtained from the occupational history and questions about exposure to birds and other organic dusts.

		Rheumatoid		Control	
		Male	Female	Male	Female
Occupational fumes - Past		2	2	0	2
Present		5	0	2	0
Occupational inorganic dusts	- Past	9	0	2	2
	Present	6	0	4	0
Organic dusts	- Past	12	27	4	16
	Present	11	13	5	8

Exposure was similar in the rheumatoid and control groups.

The frequency of symptoms and signs in the rheumatoid patients and controls is shown in Table 5 overleaf. There was no significant difference between the groups in terms of breathlessness or cough, although the latter was more common in smokers. Abnormal lung fields on the chest radiograph were significantly more common in the rheumatoid group. $\chi^2 = 9.4$, $p = < 0.001$. The slightly higher incidence in smokers was not significant. Crepitations were heard equally frequently in rheumatoid and control subjects.

TABLE 5

THE PREVALENCE OF SYMPTOMS & SIGNS IN RHEUMATOID PATIENTS AND CONTROL SUBJECTS

	Male Smokers		Male non-smokers		Female smokers		Female non-smokers	
	R	C	R		R	C	R	C
TOTAL	35	21	2		28	18	34	21
Breathlessness	12 (34%)	10 (48%)	1		*8 (29%)	7 (39%)	11 (32%)	6 (29%)
Grade 1	1	6	1		2	4	2	1
2A	8	3	0		5	3	6	5
2B	3	1	0		0	0	3	0
Cough	12 (34%)	11 (52%)			12 (43%)	3 (17%)	8 (24%)	3 (14%)
Crepitations	3 (9%)	4 (19%)	1 (50%)		4 (14%)	2 (11%)	7 (21%)	3 (14%)
Clubbing	5 (14%)	0	0		0	0	1 (3%)	1 (5%)
X-ray shadowing in lung fields	16 (46%)	3 (14%)	1 (50%)		11 (39%)	4 (22%)	9 (26%)	1 (5%)

Grade 1 = breathlessness on extreme exertion

2A = breathlessness when climbing stairs or walking up hills

SB = breathlessness walking on the flat

* Grade not recorded for 1 patient

Lung Function Measurements

Mean values for lung volume measurements, transfer factor and dynamic compliance are shown in Tables 6A and 6B, overleaf.

Predicted values for lung volumes were taken from Cotes⁷⁹, for TL_{SS} resting, from Bates, Macklem and Christie⁸⁰ and for C_{dyn} from Pasquis et al⁸¹.

Vital capacity was significantly lower in the rheumatoid patients and exercise T_L lower. In terms of % predicted normal values the significant difference in exercise T_L was only found for males. As the males were nearly all smokers, female smokers and non-smokers were then considered separately. No significant difference was found between rheumatoid and control female smokers or between rheumatoid female smokers and non-smokers.

Types of Abnormality

An obstructive pattern of ventilation (Obs) was said to be present when FEV_1 or FEV_1/VC % was $< PN - 2SD$, or when both FEV_1 and FEV_1/VC % were $< \text{mean} - 1SD$. This was seen in 7 male smokers (RMS), 10 female smokers (RFS) and 6 female non-smokers (FRNS) amongst the rheumatoid population (total 23%) and in 4 non-rheumatoid MS, 6 non-rheumatoid FS and 1 non-rheumatoid FNS in the control group (total 18.3%). When tested with inhaled isoprenaline, 3 MRS, 1 FRS, and 1 FRNS and 1 non-rheumatoid MS showed an increase $> 10\%$ in FEV_1 . The larger number of non-smoking females in the rheumatoid Obs group and the higher proportion of patients responding to isoprenaline did not differ significantly from the number in the control group.

Sixteen of the rheumatoid patients (70%) and 4 (36%) of the non-rheumatoid subjects with Obs had a personal or family history of allergy. These proportions were not significantly different ($\chi^2 = 0.06$).

TABLE 6A

COMPARISON OF THE RHEUMATOID POPULATION AT THE FIRST VISIT WITH THE CONTROL POPULATION

<u>Males</u>				
	Rheumatoid	% PN	Control	% PN
No.	37		21	
Smokers	35 (95%)		21	
Mean age years	51.6 $\pm$ 10.0		50.7 $\pm$ 12.3	
Mean height m	1.73 $\pm$ 0.07		1.76 $\pm$ 0.05	
FEV ₁	3.09 $\pm$ 0.69	95.9 $\pm$ 14.4	3.28 $\pm$ 0.74	96.5 $\pm$ 14.7
VC	4.32 $\pm$ 0.86	97.5 $\pm$ 13.5	4.76 $\pm$ 0.89	106.5 $\pm$ 14.0 *
RV	2.20 $\pm$ 0.61	105.9 $\pm$ 35.9	2.28 $\pm$ 0.72	105.9 $\pm$ 35.2
TLC	6.54 $\pm$ 1.20	101.2 $\pm$ 13.7	7.08 $\pm$ 1.13	105.3 $\pm$ 15.5
TL _{SS} rest	18.8 $\pm$ 5.9	120.1 $\pm$ 30.6	17.9 $\pm$ 6.3	109.1 $\pm$ 35.3
TL _{SS} exercise	29.5 $\pm$ 8.9	184.9 $\pm$ 42.7	36.5 $\pm$ 9.3	222.7 $\pm$ 51.4 **
No. for C _{dyn}		35 (33S)		17
C _{dyn} 20/min	.204 $\pm$.078	108.7 $\pm$ 45.3	.232 $\pm$.116	116.7 $\pm$ 56.8

** p $\leq$.02* p $\leq$.05

(S) Number of smokers

TABLE 6B

COMPARISON OF THE RHEUMATOID POPULATION AT THE FIRST VISIT WITH THE CONTROL POPULATION

<u>Females</u>				
	Rheumatoid	% PN	Control	% PN
No.	62		39	
Smokers	29 (47%)		21 (54%)	
Mean age years	51.0 $\pm$ 11.8		50.0 $\pm$ 11.4	
Mean height m	1.61 $\pm$ 0.06		1.62 $\pm$ 0.06	
FEV ₁	2.37 $\pm$ 0.56	102.3 $\pm$ 17.4	2.55 $\pm$ 0.63	109.1 $\pm$ 17.6
VC	3.18 $\pm$ 0.62	106.9 $\pm$ 16.2	3.48 $\pm$ 0.68*	121.9 $\pm$ 15.8 ***
RV	1.82 $\pm$ 0.54	107.4 $\pm$ 31.1	1.75 $\pm$ 0.56	99.7 $\pm$ 27.4
TLC	5.04 $\pm$ 0.79	107.8 $\pm$ 14.4	5.21 $\pm$ 0.71	110.1 $\pm$ 11.4
TL _{SS} rest	14.6 $\pm$ 4.0	117.8 $\pm$ 39.1	13.7 $\pm$ 4.8	99.6 $\pm$ 24.3
TL _{SS} exercise	22.8 $\pm$ 6.3	179.3 $\pm$ 32.5	26.3 $\pm$ 6.4	191.0 $\pm$ 44.7
No. for C _{dyn}		51 (24S)		34 (18S)
C _{dyn} 20/min	.176 $\pm$.078	125.3 $\pm$ 52.1	.168 $\pm$.074	121.8 $\pm$ 54.5

* p = <.05 *** p = <.001 (S) Number of smokers

In 10 rheumatoid patients (43%) and 2 controls (18%) there was hypertension or clinical or electrocardiographic evidence of left ventricular dominance which might predispose to left ventricular failure.

Low Transfer Factor

The prediction formula of Bates⁸² and the tables of normal values published in Bates, Christie and Macklem⁸⁰ do not give SD. A level of 80% PN has therefore been used to define normality as this allows comparison with the findings of other workers. After the correction for anaemia (Dinakara et al⁸³) in 7 rheumatoid patients and in 8 control subjects T_L was low. If the limits of normality had been taken as mean % PN - 2SD for the control series, no patient or control would have been considered to have low resting T_L .

Exercise T_L was considered as 'low' and possibly abnormal when < mean control value - 1SD. This level for males was 223 - 51 (172% PN), for females 191 - 45 (146% PN).

Fifteen male and 17 female rheumatoid patients were identified as having 'low' values so that their future progress could be studied, 5 of the 7 with low resting T_L being included. Seven non-rheumatoid subjects also had exercise T_L values in this range, 3 of whom had low resting T_L .

Only 1 male patient had abnormal exercise T_L at the first visit below mean control - 2SD.

The mean values for rest and exercise T_L % PN did not differ significantly between patients receiving or not receiving treatment with corticosteroids.

2. Measurement of Dynamic Compliance and Frequency Dependence of Compliance

Some patients and normal volunteers were unable to produce satisfactory compliance tracings because they could not breath at a set rate or could not maintain a steady tidal volume in the set range. Other tracings were impossible to analyse because of frequent oesophageal contractions. The number remaining in each group with mean values for C_{dyn} at a rate of about 20 per minute is shown in Tables 6A and 6B.

In 2 male patients C_{dyn} was $< PN - 2SD$ and in 2 female non-smokers was $< 50\% PN$; these 4 patients all had low T_L . In 3 male patients and 4 females C_{dyn} was greater than $PN + SD$. Six of the 7 patients had nodules. In 2 T_L was low and 2 had Obs.

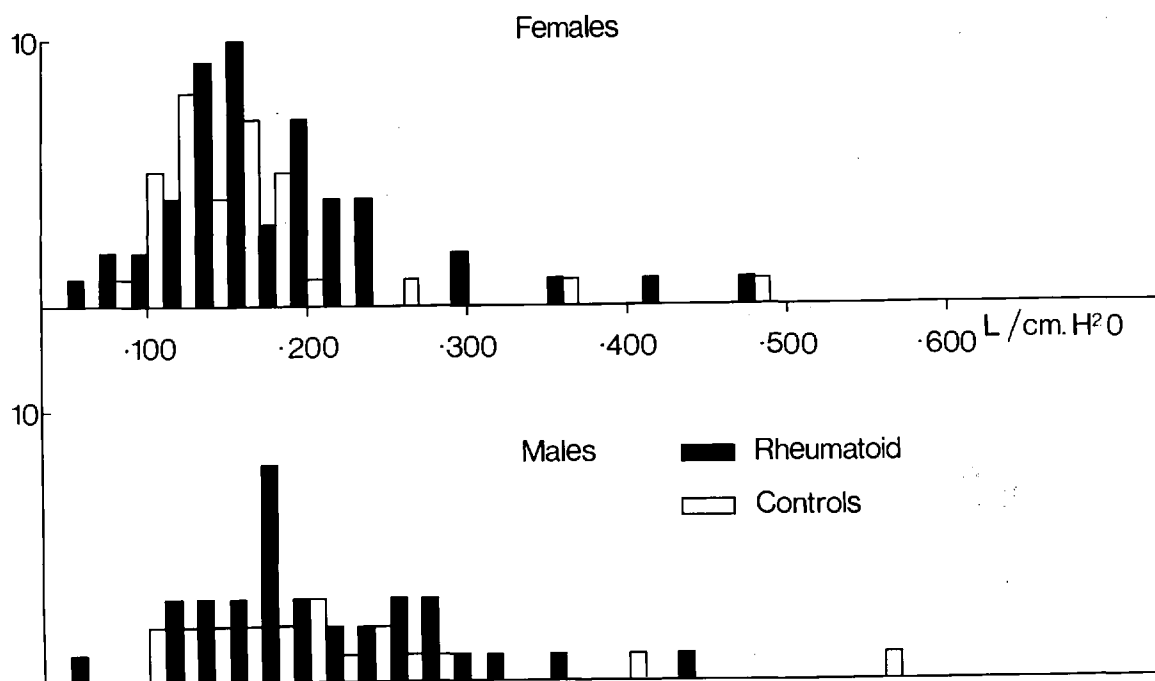
Fig. 3, overleaf, shows the distribution of dynamic compliance at a rate of about 20/min in the rheumatoid and control population.

Because the distribution of C_{dyn} appeared somewhat skew, rheumatoid and control groups were compared by the Mann Whitney U Test. There was no significant difference between them.

Mean values had suggested that C_{dyn} tended to be a little lower in rheumatoid males compared with male volunteers.

FIG. 3

DISTRIBUTION OF COMPLIANCE IN RHEUMATOID AND CONTROL POPULATIONS



For all patients C_{dyn} was not significantly different in patients with low resting or exercise T_L and was not different in patients with abnormal chest radiographs. In male patients with nodules C_{dyn} was significantly higher ($p < .001$) than in those without, but was not significantly different in females with nodules, nor in patients with the sicca syndrome.

If patients with technically unsatisfactory tracings at the first visit were able to produce a good tracing at a follow-up visit this was included in the analysis for frequency dependence, but patients and non-rheumatoid volunteers with abnormal compliance values were excluded. Patients with abnormal compliance due to disease of the lung parenchyma would be expected to have altered time constants which would give rise to frequency dependence^{52,54}. As gross frequency dependence is also caused by disease affecting the bronchi and this study was designed to look for evidence of disease at bronchiolar level, patients with $FEV_1 < 80\%$ PN were also excluded, this being an arbitrary limit often chosen by other workers to limit normality.

These exclusions being made, Table 7, overleaf, shows mean values for C_{dyn} at increasing rates of respiration in litres/cm H₂O.

TABLE 7

MEAN VALUES $\dot{V}_{DYN}$ AT INCREASING RATES OF RESPIRATION IN L/cm H₂O

GROUP	N	15-25/min		30-40/min		55-65/min		78-90/min	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male Rheumatoid Smokers	22	0.181	0.058	0.179	0.067	0.174	0.062	0.178	0.083
All Male Rheumatoid	24	0.185	0.058	0.181	0.065	0.175	0.060	0.176	0.086
Male non-rheumatoid smokers	12	0.208	0.059	0.216	0.068	0.218	0.069	0.245	0.093
Female rheumatoid smokers	22	0.163	0.041	0.159	0.059	0.154	0.056	0.126	0.040
Female non-rheumatoid smokers	16	0.150	0.033	0.137	0.032	0.150	0.044	0.140	0.044
Female rheumatoid non-smokers	19	0.150	0.037	0.152	0.035	0.145	0.034	0.139	0.036
Female non-rheumatoid non-smokers	12	0.149	0.033	0.133	0.025	0.125	0.026	0.131	0.026

SD = Standard deviation

Conversion to SI units - 1 L/KPa = 0.098 L/cm H₂O

N = Number suitable for analysis

There was no difference between rheumatoid and control groups at any rate of respiration and within each group C_{dyn} was not significantly different at higher rates of respiration.

Frequency dependence of compliance (FDC) was said to be present within individual patients when C_{dyn} at a rate of 60/min was 20% lower than at a rate of 20/min. (Hill et al⁵⁶). Table 8, overleaf, shows the number of patients showing FDC in each group.

Frequency dependence was significantly more common in the rheumatoid patients, $p < .025$.

It was noted that amongst the female smokers showing frequency dependence there were subjects with normal or high FEV_1 , but also with high VC, so that $FEV_1/VC\%$ fell 2SD below predicted normal.

Table 9, on page 49, shows the influence of differing criteria for airways obstruction excluding patients from the analysis for frequency dependence.

Using the strictest criteria for abnormality, including patients with both FEV_1 and $FEV_1/VC\% < PN - 1SD$, in addition to those with FEV_1 or $FEV_1/VC\% PN - 2SD$, the significant difference in FDC for the group as a whole disappears, but a significant difference remains between rheumatoid and control subjects over the age of 50, $p < .05$.

Amongst the 10 patients and 1 normal volunteer with FDC and no evidence of airways obstruction by any criteria, the 1 non-rheumatoid female subject with FDC had contact dermatitis and also worked in the printing industry. Two rheumatoid patients had first degree relatives with asthma. Four male patients had been exposed to industrial dust or fumes and 2 also kept birds.

TABLE 8

PREVALENCE OF FREQUENCY DEPENDENCE

	Rheumatoid	%	Non-rheumatoid	%
Male Smokers	5/22	23	0/13	0
Male non-smokers	1/2	50	0	0
All male	6/24	25	0/13 $\chi^2 = 2.3$ $p > .05$	0
Female smokers	5/22	23	0/15	0
Female non-smokers	3/20	15	1/12	8
All female	8/24	19	1/27 $\chi^2 = 2.19$ $p > .05$	4
Total	14/66	21	1/40 $\chi^2 = 5.85$ $p < .025$	3
All over the age of 50 years	10/35	28	0/24 $\chi^2 = 5.25$ $p < .025$	0

TABLE 9

Definition of airways obstruction and exclusion from analysis	FEV ₁ < 80% PN		FEV ₁ normal but FEV ₁ /VC < PN-2SD		FEV ₁ < PN-2SD or FEV ₁ /VC < PN-2SD or FEV ₁ < PN-1SD and FEV ₁ /VC < PN-1SD	
	R	C	R	C	R	C
Male Smokers	5/22	0/13	5/21	0/12	5/19	0/12
Male non-smokers	1/2	0	1/2	0	1/2	0
All male	6/24	0/13	6/22	0/12	6/21	0/12
Female smokers	3/22	0/15	2/17	0/13	1/15	0/13
Female non-smokers	3/20	1/12	4/20	1/13	3/19	1/12
All female	8/42	1/27	6/37	1/26	4/34	1/25
Male and female	14/66	1/40	12/59	1/38	10/55	1/37
		$\chi^2 = 5.58$		$\chi^2 = 2.25$		$\chi^2 = 1.45$
Over the age of 50	10/35	0/24			7/31	0/24
		$\chi^2 = 5.25$				$\chi^2 = 4.34$

Table 9 shows the influence of differing criteria for airways obstruction excluding patients from the analysis for frequency dependence.

Static Recoil Pressures

Static recoil pressures were measured in 37 patients and in 12 normal subjects. Expressed in terms of per cent predicted normal values (Knudson⁸⁴), the mean value for normal subjects was $117 \pm 83\%$ PN and for rheumatoid patients $91 \pm 38.7\%$ PN; this difference is not significant. Two patients with low C_{dyn} had recoil pressures $> PN + 2SD$. Recoil pressures were measured in 4 patients with high C_{dyn} ; in 2 cases the level was below $PN - 2SD$; in the other 2 the pressure was in the lower part of the normal range.

The mean value for patients with airways obstruction, $97.8 \pm 54.3\%$ PN did not differ significantly from the mean value for the other patients $87.0 \pm 29.1\%$ PN, nor did the mean value for patients with low T_L , $93.6 \pm 44.3\%$ differ from that for patients with normal T_L , $83.8 \pm 25.4\%$.

3. The Five Year Follow-up Period

Over the 5 year period 11 patients died; 4 developed new illnesses; in 3 the rheumatoid arthritis became more severe so that they were unable to attend; 6 moved from the area. Fifteen patients decided that they did not wish to come again.

The causes of death in 11 patients were:-

Myocardial infarction - 3 males aged 49, 58 and 63

1 female aged 66

Carcinoma of the bronchus - male aged 62 * (See Appendix 5)

Pneumonia - male aged 68

Ruptured oesophagus - male aged 64

Goodpastures' syndrome - male aged 63 treated with penicillamine

Severe abdominal pain with death the same day - female aged 46

Heart failure following gastro-intestinal haemorrhage complicated by jaundice - female aged 66

Cause unknown, gradual deterioration - female aged 62

In terms of clinical characteristics and lung function the patients who died did not differ significantly from the others, but 2 of the 4 patients with low lung compliance died.

The total numbers of patients seen at the second to fifth visits were 76, 65, 51 and 60.

The duration of follow-up at the fifth visit ranged from 4 years 5 months to 6 years. Mean follow-up period was 5 years 2 months + 4 months. Fifty-two patients attended between 4 years 8 months and 5 years 8 months after the original visit.

The comparison of the fifth year population with the original population and with patients lost to follow-up is shown in

Table 10 overleaf.

TABLE 10

COMPARISON OF THE ORIGINAL POPULATION, THE FIFTH YEAR POPULATION
AND THOSE LOST TO FOLLOW-UP

	FIRST YEAR	FIFTH YEAR	PER CENT	LOST TO FOLLOW-UP	
				No.	%
Number	99	60		39	
Male	37	26	43	12	31
A. Mean age: Male	51	54		58	
Female	52	53		54	
Smokers	63	40	67	23	59
Steroid treatment	52	39(10)	65	22	56
Penicillamine	4	4(2)	7	3(2)	8
DAT 1/256	65	42	70	22	56
DAT 1/512	34	18	30	17	44
More than 8 joints involved	32	23	38	16	41
Duration 5 years	42	1	2	12	31
5 - 10 years	32	38	63	14*	36
Duration 15 years	25	21	35	12	31
Respiratory symptoms	46	29	48	16	41
Crepitations &/or finger clubbing	20	19	32	15	38
CXR shadowing	36	16	27	17	44
B. Sicca syndrome	18	13	22	5	13
Nodules	37	25	42	12	31
Arteritis	8	5	9	3	8

There were no significant differences, but it would have been expected that at 5 years the mean age might have been higher. Seven of the 11 deaths occurred in patients over the age of 60.

Section A: Figures relate to findings at the last visit.

Section B: Figures relate to presence of non-articular syndromes during the entire 5 year period.

() Started treatment during study

* Information missing for 1 patient

Table 1, overleaf, shows mean changes in lung function measurements between the first and fifth years for the 60 patients attending at the fifth year.

Table 11 shows mean changes in lung function measurements between the first and fifth years for the 60 patients attending at the fifth year.

TABLE 11

MEAN CHANGES FROM ADMISSION TO 5TH YEAR (60 patients)

	Litres	p	% PN	p
FEV ₁	- 0.31 $\pm$ 0.38	< 0.001	- 6.1 $\pm$ 14.1	< 0.01
VC	- 0.33 $\pm$ 0.45	< 0.001	- 4.4 $\pm$ 14.2	< 0.05
RV	+ 0.13 $\pm$ 0.47	< 0.05	+ 1.2 $\pm$ 27.4	NS
TLC	- 0.16 $\pm$ 0.56	< 0.05	- 1.3 $\pm$ 11.6	NS
TL _{SS} rest	- 2.1 $\pm$ 7.6 mls/min/mm Hg	NS	- 1.0 $\pm$ 42.8	NS
TL _{SS} exercise	+ 2.8 $\pm$ 9.8 mls/min/mm Hg	NS	+ 34.0 $\pm$ 56.7	< 0.001
C _{dyn} 20/m	-0.009 $\pm$ 0.104 L/cm H ₂ O	NS	- 3.5 $\pm$ 57.0	NS

Lung Volumes

There were significant falls in FEV_1 and VC, both in absolute terms and as per cent predicted normal. One male and 1 female patient showed falls of greater than 1 litre in both FEV_1 and VC over the 5 year period. The fall in FEV_1 was significantly greater ($p < .05$) than the predicted fall over a 5 year period. The female started with low exercise T_L ; the male developed bronchiolitis between the fourth and fifth visits (Appendix In 1 other male, VC fell by more than 1 litre, but his initial VC was 142% PN, and at the fifth year it was 108% PN.

There were small but significant changes in absolute measurements of RV and TLC, but changes as % PN were not significant.

There was no significant association between changes in FEV_1 or VC over the total 5 year period and respiratory symptoms or the sicca syndrome. There was a significantly greater fall in FEV_1 , $p < .02$, but not in VC, in patients with nodules.

Mean changes for individual patients between visits where respiratory symptoms or signs were present or were absent are shown in Table 12 overleaf.

TABLE 12

	FEV ₁ litres		VC litres	
Respiratory symptoms/signs present-absent	0.06 ± 0.27	NS	0.04 ± 0.41	NS
Crepitations present-absent	0.08 ± 0.18	p .05	0.06 ± 0.24	NS
Clubbing present-absent	0.05 ± 0.21	NS	0.10 ± 0.29	NS
Chest x-ray abnormal-normal	0.01 ± 0.18	NS	-0.01 ± 0.23	NS

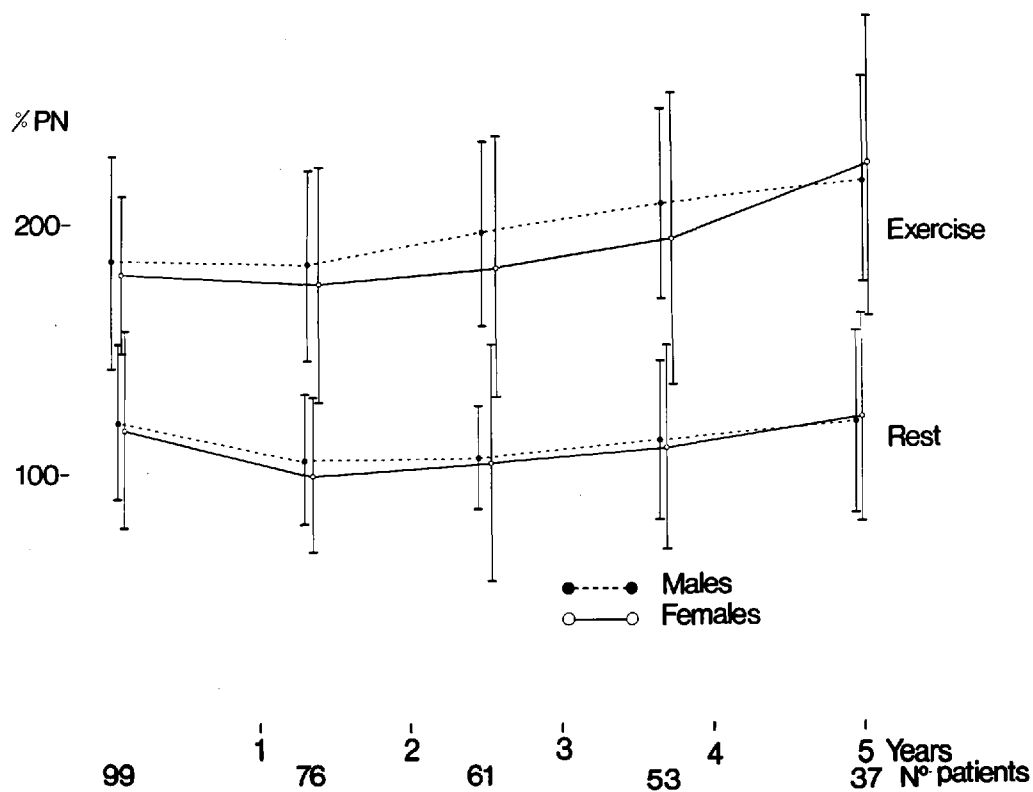
Transfer Factor

Mean values for rest and exercise T_L in terms of % PN for all patients at each visit are shown in Fig. 4.

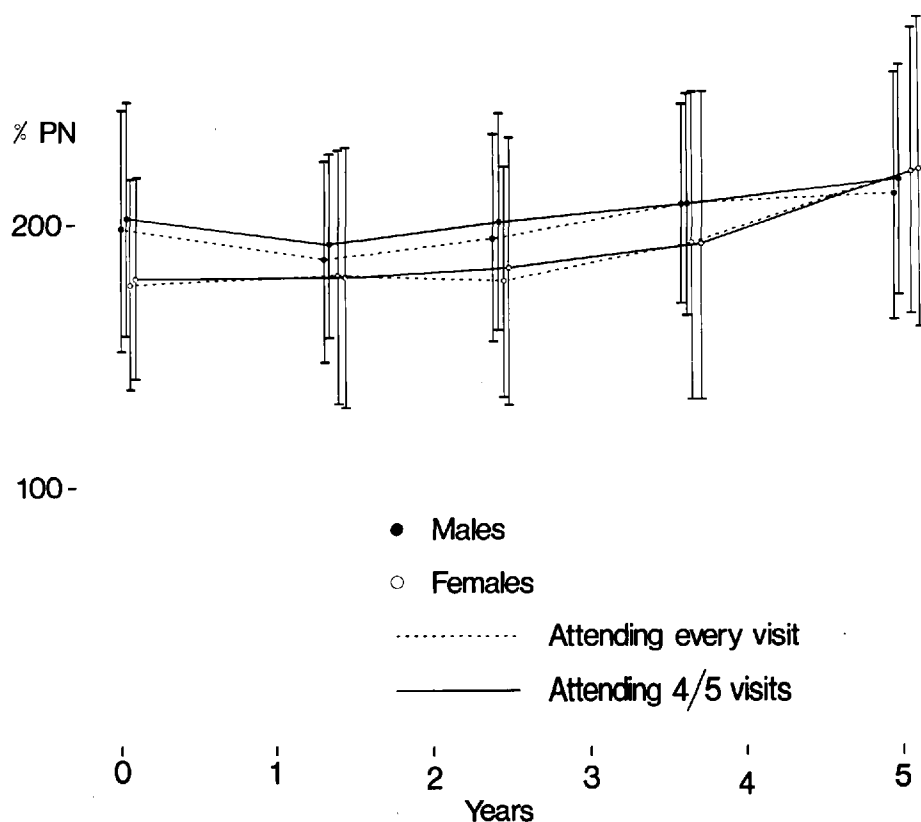
At the fifth visit when all 60 patients were tested by the SB method, in 8 (13%), T_L was less than $PN - 2SD$, in 19 (32%), T_L was less than 80% PN. On this occasion TL_{SS} was $< 80\%$ PN in 6 of 39 patients (15%) tested by that method.

FIG. 4

MEAN VALUES FOR : ———— TRANSFER FACTOR FOR ALL PATIENTS AT ALL VISITS



As there was an upward trend and the possibility existed that patients with lower T_L might have dropped out, mean values for exercise T_L in the patients attending up to the fifth year are shown in Fig. 5. Some patients had missed 1 of the 5 visits; values when they were included were similar.



The upward trend in exercise T_L was confirmed by calculating the correlation coefficient between mean value for T_L as % PN and the time of follow-up. For the 60 patients attending up to the fifth year, in males $r = 0.725$, for females $r = 0.831$; when all patients, including those with shorter follow-up were included, for males $r = 0.945$, for females $r = 0.831$. In terms of % PN exercise T_L showed a significant increase at the fifth year compared with the first but in absolute terms the difference was not significant.

To consider the possibility that patients might have exercised harder at follow-up visits, correlation coefficients were calculated for individual patients between time of follow-up and workload. These varied between -0.999 and 0.944 , the mean of all coefficients being -0.174 , so that there was no evidence that patients worked harder.

Correlation coefficients for individuals between exercise T_L in mls/min/mm Hg. and number of actively inflamed joints ranged from -0.873 to 0.991 (mean 0.087 ± 0.557), between resting T_L and Rose Waaler titre from -0.941 to 0.993 (mean 0.036 ± 0.566), between exercise T_L and Rose Waaler titre from -0.887 to 0.992 (mean 0.066 ± 0.502).

There was no significant association between changes in resting or exercise T_L over the total 5 year period and the presence of respiratory symptoms or signs, nodules or the sicca syndrome or treatment with corticosteroids (see Appendix 1).

Ten patients started treatment with corticosteroids during the course of the study. Mean change in resting T_L to the next visit after starting treatment was 3.3% PN SD ± 38 ; exercise T_L increased significantly by 32.3% PN SD ± 34.3 ($p < .05$).

Over the 5 year period exercise T_L increased by 46.8% $PN \pm 61.8$ in 10 patients starting corticosteroid treatment compared with 24.1 % $PN \pm 56.8$ in the other 50 patients. There was no significant difference between the 2 groups.

The mean differences for T_L between visits where symptoms and signs were present compared with those when they were absent are shown in Table 13 overleaf.

Resting T_L was significantly lower when symptoms and signs were present and exercise T_L when clubbing was present.

TABLE 13

	<u>RESTING T_L</u>		<u>EXERCISE T_L</u>	
	Mean difference mls/min/mm Hg		Mean difference mls/min/mm Hg	
Symptoms and signs present-absent	2.0 ± 4.1	p < .02	0.26 ± 6.85	NS
Crepitations present-absent	- 0.22 ± 3.9	NS	- 0.63 ± 6.0	NS
Chest x-ray abnormal-normal	- 0.38 ± 3.2	NS	0.33 ± 4.2	NS
Clubbing present-absent	0.64 ± 2.7	NS	2.9 ± 4.4	p < .05

Changes in the Prevalence of Functional Abnormality

The progress of patients with initial abnormalities of lung function and the development of the 3 types of abnormality, Obs, low T_L or abnormal C_{dyn} in other patients is summarised in Tables, 14, 15 and 16 overleaf.

TABLE 14

CHANGES IN FUNCTIONAL ABNORMALITY OVER THE 5 YEAR PERIOD

	<u>1st visit</u>	<u>2nd visit</u>	<u>3rd visit</u>	<u>4th visit</u>	<u>5th year</u>
Number attending	99	75	65	56	60
<u>Changes in the Incidence of the Obstructive Pattern over the 5 year period</u>					
Abnormality first shown	23	4	1	1	1
No. abnormal re-tested		18	19	14	19
Persistent abnormality		14 (78)	11(58)	7(50)	10(53)
Returned to normal*		4 (12)	3(16)	1(7)	1(5)

* First normal value since abnormal recorded: those returned to normal at previous visit and remaining normal not included.

TABLE 15
CHANGES IN FUNCTIONAL ABNORMALITY OVER THE 5 YEAR PERIOD

	<u>1st visit</u>	<u>2nd visit</u>	<u>3rd visit</u>	<u>4th visit</u>	<u>5th year</u>
Number attending	99	75	65	56	60
<u>Changes in Transfer Factor abnormality over the 5 year period</u>					
<u>Low resting T_L first seen</u>	7	13	6	1	2
No. abnormal re-tested		5	13	15	9
Persistent abnormality		2(40)	6(46)	6(40)	3(33)
Returned to normal		3(60)	5(38)	6(40)	1(11)
<u>Low exercise T_L first seen</u>	31	13	3	3	0
No. abnormal re-tested		21	27	21	14
Persistent abnormality		12(57)	15(56)	6(29)	3(21)
Developed low resting T _L		7(33)	3(11)	0(0)	1(7)
Returned to normal		9(43)	9(33)	5(24)	3(21)
<u>No. abnormal resting SS tested</u> _{SB}		9	4	9	20
No. found abnormal		4(44)	4(100)	5(56)	9(45)
<u>No. abnormal exercise SS tested</u> _{SB}		12	6	14	30
No. found abnormal		4(33)	5(83)	7(50)	11(37)
No. tested SB	4	13	11	38	60
Abnormal SB isolated abnormality	0		1(9)	0	0

TABLE 16
CHANGES IN FUNCTIONAL ABNORMALITY OVER THE 5 YEAR PERIOD

	<u>1st visit</u>	<u>2nd visit</u>	<u>3rd visit</u>	<u>4th visit</u>	<u>5th year</u>
Number attending	99	75	65	56	60
<u>Changes in Abnormality of Compliance during the 5 year period</u>					
Low compliance first found	4				3
No. low re-tested		2			1
Persistent abnormality		1			
Returned to normal		1			1
High compliance first seen	7	2		1	1
No. high re-tested		2	1		4
Persistent abnormality		0			1(25)
Returned to normal		2	1		3(75)
Frequency dependence	10	2	0	0	6
No. re-tested		3	2		6
Persistent abnormality		2(67)	1(50)		1(17%)
Developed low compliance					1(17)
Returned to normal		1(33)	1(50)		4

Patterns of Functional Abnormality

At the first visit, of 61 rheumatoid patients with some abnormality of lung function, 44 showed only 1 abnormal feature. Over the period of follow-up multiple abnormalities became evident and repeated testing increased the total incidence of abnormal findings. For the 60 patients the total incidence of some abnormal finding over the 5 year period was 90%.

The association of different types of functional abnormality, both initially and for all tests in the 60 patients over the 5 year period is shown in Table 17, overleaf.

TABLE 17

INCIDENCE OF PATTERNS OF ASSOCIATED FUNCTIONAL ABNORMALITIESAT THE FIRST VISIT AND OVER THE 5 YEAR PERIOD IN THOSE ATTENDING AT THE 5TH YEAR

		Number of patients	No associated abnormality		Obs		T _L		C _{dyn}	
			%		%		%		%	
Obs	1st visit	99	14	61	23	* 23	8(+1)	35	3	13
	All visits	60	7	33	21	* 34	10	48	6	29
T _L	1st visit	99	21	62	8(+1)	24	34(+6)	*34	8(+2)	24
	All visits	60	14	39	10	28	36	*60	17	47
C _{dyn}	1st visit	99	9	45	3	14	8(+2)	38	20	* 20
	All visits	60	3	14	6	25	17	71	24	* 40

+ () patients who developed abnormalities after the first visit but who did not attend for 5 years

* percentage of total patients

Horizontal figures = percentage of patients with associated abnormality described by vertical heading.

Over the 5 year period only 1 of the 60 patients showed low T_L as an isolated finding on 1 occasion and 1 patient Obs on an isolated occasion. Because C_{dyn} was not measured at every visit the possible frequency of isolated abnormal findings cannot be assessed. Of 5 patients in whom C_{dyn} was measured at 4 visits, 4 showed abnormality on a single occasion.

The Distribution of Functional Abnormality in Relation
to Clinical Findings

As the patients who were lost to follow-up did not differ significantly in terms of any characteristics studied, all findings of abnormal lung function in the 99 patients, whether at the initial or follow-up visits, were included. Table 18, overleaf, shows the patients in each of the 3 categories of abnormality, Obs, low T_L and abnormal C_{dyn} and the number of patients in each group according to sex, smoking habits, the rheumatoid arthritis and its treatment.

TABLE 18

FACTORS ASSOCIATED WITH TOTAL INCIDENCE OF ABNORMAL FUNCTION OVER THE FIVE YEAR PERIOD (99 patients)

	Obstructive	Low T_L rest	Low T_L exercise	Compliance
Total abnormal	30	31	51	30
Males	10(33)	5(16)	21(41)	15(50)
Smokers	22(73)	16(52)	35(69)	20(67)
Duration arthritis < 5 years (at entry)	14(47)	11(35)	17(33)	11(37)
5 - 15 years	9(35)	10(32)	14(27)	12(40)
> 15 years	7(23)	10(32)	20(39)	7(23)
Less than 5 joints involved (at entry)	7(23)	7(23)	9(18)	6(20)
5 - 10 joints involved	16(53)	18(58)	29(57)	18(60)
More than 10 joints involved	7(23)	6(19)	13(25)	6(20)
Initial DAT $\leq 1/8$	9(30)	11(35)	18(35)	12(40)
1/16 - 1/256	12(40)	11(35)	16(31)	9(30)
DAT $\geq 1/512$	9(30)	9(29)	17(33)	* 8(27)
Steroid treatment	16(53)	16(52)	27(53)	19(63)
Penicillamine	5(17)	4(13)	2(4)	1(3)

(per cent)

* 1 DAT result missing

Table 19,overleaf, shows the number of patients with or without non-articular syndromes associated with rheumatoid disease and the incidence of abnormal lung function in each group.

The proportion of patients with abnormal resting T_L was significantly higher in patients with nodules ($p = <.05$) and with arteritis ($p <.02$) and combining rest and exercise T_L abnormality,in patients with the sicca syndrome ($p <.02$). (Appendix 3).

TABLE 19

TOTAL INCIDENCE OF ABNORMAL FUNCTION IN ASSOCIATION WITH CLINICAL FEATURES

	Number	Male	Smokers	Obstructive	T _L		Compliance
					Rest	Exercise	
Nodules	37	13(35)	25(68)	11(30)	17(46)	21(57)	15(41)
No nodules	62	24(39)	40(65)	19(31)	14(23)	30(48)	15(24)
Sicca syndrome	18	5(28)	12(67)	7(39)	8(44)	11(61)	6(33)
No sicca syndrome	81	32(40)	51(63)	23(28)	23(28)	40(49)	24(30)
Arteritis	8	3(38)	6(75)	2(25)	6(75)	5(63)	1(13)
No nodules, sicca, arteritis	47	17(36)	30(64)	15(32)	10(21)	19(40)	11(23)

(per cent)

There were 24 patients who had high blood pressure or clinical, radiographic or ECG evidence of left ventricular dominance or ischaemic heart disease. The incidence of Obs, low T_L and abnormal C_{dyn} was not significantly different from that in the other patients. Six of the 24 patients were amongst those with the greatest falls in VC over the 5 year period, but when the change in VC was directly compared with that of the other patients there was no significant difference.

Diffuse abnormality of the chest radiograph was significantly associated with the total incidence of airways obstruction $p < .05$, but not with abnormal T_L . There was no significant association between respiratory symptoms or signs and total incidence of any functional abnormality.

Table 20, shows the number of patients with respiratory symptoms or signs or diffuse abnormality of the chest radiograph and the incidence of abnormal lung function in each group.

TABLE 20

ASSOCIATION OF ABNORMAL FUNCTION WITH SYMPTOMS AND SIGNS

	Number	Male	Smokers	Obstructive	Rest ^{T_L} Exercise	Compliance
2/3 of symptoms, signs and CXR abnormal on more than 1 occasion	18	9(50)	13(72)	7(39)	9(50) 12(67)	7(39)
No symptoms or CXR shadowing	53	18(34)	32(60)	14(26)	20(38) 29(55)	14(26)
Finger clubbing	9	5(56)	5(56)	5(56)	3(33) 6(67)	3(33)
Crepitations at more than 50% of visits	19	8(42)	13(68)	7(37)	7(37) 14(74)	7(37)
No clubbing or crepitations	27	10(37)	17(63)	7(26)	11(41) 18(67)	10(37)
No clubbing, crepitations, symptoms or abnormal CXR at any visit	24	9(38)	15(63)	6(25)	8(33) 17(71)	10(42)
CXR abnormal at more than 50% of visits	24	16(67)	19(79)	6(25)	8(33) 12(50)	9(38)
CXR never abnormal	24	6(25)	11(46)	7(29)	10(42) 14(58)	7(29)

(per cent)

4. Dm and Vc Measurements

Satisfactory measurements of Dm and Vc were obtained in 50 rheumatoid subjects. In 3 subjects the 2 values for T_L breathing oxygen were widely disparate; 6 patients attended during a period when back tension was not measured. The 2 male non-smokers were not included in the comparison with non-rheumatoid subjects. In the younger of the 2 non-smokers Vc was below predicted normal limits. This patient was not receiving corticosteroids or penicillamine. The comparison of the rheumatoid and matched control population in terms of age, height and T_L is shown in Table 21, overleaf, with mean values for Dm and Vc.

There was no significant difference between rheumatoid and control groups for age, height, T_L or Dm. Vc was significantly lower $p < .05$ in the male rheumatoid patients compared with controls, and in RFS compared with RFNS $p < .01$. There was no significant difference between CFS and CFNS.

TABLE 21

MEAN T_L AIR, Dm and Vc IN RHEUMATOID AND CONTROL PATIENTS

Group	No.	Mean age in yrs	SD Mean	Mean Ht in metres	SD	Mean T_L air	SD	Dm	SD	Vc mls	SD
Rheumatoid Male Smokers RMS	18	51.5	10.6	1.73	0.08	23.8	4.6	42.3	14.0	64.0*	16.5
Control Male Smokers CMS	18	49.4	13.0	1.77	0.07	27.0	4.9	47.3	13.3	76.3*	18.0
Rheumatoid Female Smokers RFS	15	51.0	11.3	1.63	0.07	17.9	2.4	37.7	11.7	43.4**	13.3
Control Female Smokers CFS	15	53.3	11.1	1.65	0.07	18.6	3.8	34.1	11.0	55.3	22.1
Rheumatoid Female non-smokers RFNS	15	55.1	12.6	1.60	0.07	19.5	3.0	31.3	8.8	58.4**	15.4
Control Female non-smokers CFNS	15	52.6	14.6	1.65	0.07	21.2	2.8	36.0	8.9	60.7	14.2

T_L and Dm in mls/min/mm Hg. $\div 2.98 = \text{m mol/k Pa}$

* $p = < .05$

** $p = < .01$

Dm and Vc were expressed as % PN (Dm: Cotes and Hall⁸⁵, VC: Frans⁸⁶) to allow comparison between groups of patients. Mean values are shown in Table 22 overleaf.

Vc was significantly lower, ($p < .02$), in patients not being treated with corticosteroids compared with those being treated and in patients with nodules, ($p < .05$), compared with those without, but difference in relation to respiratory symptoms or the presence of the sicca syndrome were not significant.

In patients in whom T_L had been persistently low at most visits compared with those in whom T_L had been normal on most occasions, Vc was significantly lower, ($p < .02$), but there was no significant difference for Dm.

TABLE 22

Dm & Vc IN TERMS OF PER CENT PREDICTED NORMAL IN VARIOUS SUB-GROUPS

Group	No.	Smokers	Mean Dm	SD	Mean Vc	SD
Corticosteroid treatment	25	17	84.1	30.0	81.8**	22.4
No corticosteroid or penicillamine	16	11	90.7	26.6	65.1**	22.7
Corticosteroids + penicillamine	7	5	79.4	27.7	70.9	24.3
Patients with nodules	19	13	87.4	34.01	62.5*	22.2
No nodules or sicca syndrome	27	21	83.7	23.1	80.9*	25.3
Definite or possible sicca syndrome	7	5	84.1	24.6	66.9	17.9
DSCAT $\leq 1/256$	14	13	87.4	31.1	65.7	26.3
DSCAT $> 1/256$	34	23	84.9	26.7	77.1	24.2
Duration of arthritis < 10 years	21	14	84.6	32.4	66.5	19.6
Duration of arthritis ≥ 10 years	27	19	82.6	28.7	79.4	27.7
< 10 joints involved	32	22	87.1	27.6	75.9	28.3
≥ 10 joints involved	16	11	87.1	27.4	67.8	15.6
Airways obstruction	15	12	81.5	19.9	79.1	29.2
No airways obstruction	33	21	87.5	30.7	73.1	21.3
Persistent symptoms and abnormal chest radiograph	13	9	82.3	23.2	78.7	24.7
No persistence of symptoms and abnormal chest radiograph	35	24	96.9	29.5	72.0	25.3
Persistently low T_L	17	12	81.4	25.3	62.2**	20.2
T_L not persistently low	30	20	89.2	28.7	81.2**	24.8

* $p = < .05$ ** $p = < .02$

Five of 15 patients in whom Dm was less than 70% PN, and 10 of 26 patients with Vc less than 70% PN had shown persistently low T_L . In 7 patients both Dm and Vc were less than 70 % PN; in 4 T_L had been persistently low and 2 had persistent symptoms and abnormal chest radiographs.

There was no significant correlation between Dm or Vc and Rose Waaler titre, nor between Dm and duration of arthritis, but the correlation coefficient for Vc and duration of arthritis, $r = -0.337$, was significant ($p = <.01$).

Correlation coefficients between Dm and Vc and mechanical measurements are shown in Table 23 below.

TABLE 23

		Correlation Coefficients	
		Dm	Vc
With C_{dyn}			
Male Smokers	17	- 0.392	0.200
Female Smokers	11	0.435	-0.711
Female non-smokers	11	0.572	-0.329
Dm and Vc as % PN Static recoil pressure % PN	28	0.407	-0.159

DISCUSSION

The Rheumatoid Population Studied

Although it had been hoped that random selection would provide a representative population, the study group contained a high proportion of males and 52% of the patients were receiving corticosteroid treatment. This suggests that they had severe disease, but their disease was not necessarily of longer duration. Forty-two patients had suffered from arthritis for less than 5 years.

It is likely the males were slightly more reluctant to refuse to participate in the study even if they were apprehensive about swallowing an oesophageal balloon. Patients receiving corticosteroids may have been attending hospital more frequently, but it seems probable that the large number of patients in the community with mild disease were not being seen at hospital. Alternatively patients with milder disease may not have been motivated to help with the research project. I did not keep a record of the considerable number of patients who were approached and refused to participate; this would have been valuable in considering the atypical features of the population recruited.

The male preponderance contrasts with Schernthaner's⁴⁸ population which contained 89% females and the number of patients receiving corticosteroids provided a population very different from those studied by Collins et al⁴⁵ or Davidson et al⁴³. The latter group also excluded patients with disease of short duration, whereas nearly half the present population were in this category.

The proportion of sero-negative patients was similar to that included

by Schernthaner et al⁴⁸, who were particularly interested in the relation of transfer factor to Rose Waaler titre.

Five of the previous studies have excluded patients with heart disease, but in 2 cases only 'heart failure' was mentioned. The criteria for diagnosing heart disease are not given in detail. In the present study 24 patients at some stage were found to have a high blood pressure or the ECG showed left axis deviation or left ventricular hypertrophy or evidence of ischaemia; occasionally the chest radiograph also provided evidence of left ventricular hypertrophy. These patients were considered separately, but the incidence of abnormality was not different to that in the other patients and therefore their inclusion does not seem to invalidate comparison of this population with the others studied. No patient was in heart failure when tests were performed, although they had to be deferred in one hypertensive patient who had an episode of left ventricular failure.

Previous workers have set varying limits for exclusion of patients with anaemia. In the present study T_L in patients with haemoglobin levels lower than 13.0 G % were corrected to that level using a formula derived by Dinakara et al⁸³. Laitinen et al⁴⁷ corrected T_L values using a formula investigated in more detail by Salorinne⁸⁷. They suspected that their correction might have been too high as in 16 patients T_L was high. Inspection of the haemoglobin and corrected T_L values over the 5 year period of the present study shows no consistent trend for T_L values to be higher at visits where haemoglobin was low and therefore no evidence that T_L values were over-corrected.

One male and 2 females would have been excluded from the present study by a lower limit of 10.0 G %⁴⁷, 2 males and 7 females by a lower

limit of 11.0G %⁴³. As a long term study was proposed it did not seem appropriate to exclude patients who were anaemic at their first visit as it was likely that the levels would vary over the 5 year period. Six of the 9 patients with low haemoglobin did not come again.

The control group contained a slightly higher proportion of heavy smokers. This might have accounted for the higher proportion of non-rheumatoid males with cough, but amongst female smokers, a higher proportion of rheumatoid patients admitted to cough. The slight tendency to heavier smoking habits in the control group might produce some small bias towards underestimation of differences between rheumatoid and control populations. The rheumatoid and control populations were well matched in terms of dust exposure.

Abnormalities of lung function in the original population were similar to those reported by previous workers. The earliest noted abnormality was restriction of ventilation⁸ and mean VC was significantly reduced in the rheumatoid population compared with the controls. The difference in terms of per cent predicted normal was significant for both sexes; in terms of measured volume only for females.

In this study airways obstruction was detected by low FEV_1 or FEV_1/VC %. The proportion of patients with airways obstruction (23%) is similar to the 26% found by Schernthaner et al⁴⁸ or the 24% with low FEV_1/VC % found by Geddes et al.⁴⁹ They noted that smokers and non-smokers were equally affected and in this study the slightly greater number of female smokers in the obstructive group was not statistically significant.

The proportion of patients with airways obstruction has been found higher when other investigations were performed^{34, 38, 45, 49}.

Gray and Gray³⁶ found values for TL_{SS} ranging from 8.3 to 18.3 mls/min/mm Hg. with a mean value of 13.5 mls/min/mm Hg. which is lower than the mean resting value found in the present study. They comment on the difficulty of calculating predicted normal values for rheumatoid patients whose height cannot be accurately measured. In the present study height was marginally lower in the rheumatoid groups and T_L % PN higher, but measured resting T_L was also slightly higher than in the control group. Schernthaner et al⁴⁸ found TL_{SS} low in 47% and Morere et al³⁸ in 55% of patients. The total figure in the present study combining rest and exercise T_L was 38%.

The present higher mean values and lower proportion of abnormal values is probably explained by the correction used for low haemoglobin. Mean values for T_L in the rheumatoid population were a little higher than in the control group before any correction was made for haemoglobin level. It was thought that this was probably due to nervousness and hyperventilation as lower figures were seen at the second visit. Gray and Gray³⁶ had to exclude 2 patients in their study because of hyperventilation. A record was only kept of treatment with gold, corticosteroids and penicillamine and one cannot say if patients were taking very large doses of salicylate.

Other workers measured T_L by the single breath method. Huang and Lyons³⁵ found a mean value for TL_{SB} of 79% PN. The prevalence at the fifth year of low TL_{SB} , 13% < PN - 2SD, 32% < 80% PN, was also a little lower than previously reported. Popper et al⁴² found T_L low in 19% of their rheumatoid patients and in no control, Frank et al⁴⁴ in 41% of patients and no control. Whorwell⁴⁶ found T_L PN - 2SD in 18.4% of the rheumatoid patients (44.7% taking < 80% PN as abnormal) and no abnormality in the controls. In the present study low resting T_L was found as frequently in the control

population and it is surprising that other workers never randomly selected any volunteer with abnormal findings.

The series studied by Whorwell et al⁴⁶ excluded patients with abnormal chest radiographs like the very selective series of patients studied by Davidson et al⁴³, while 7 of the 9 patients studied by Loddenkemper et al³⁷ had abnormal chest radiographs and all 9 patients had low T_L . In this study mean T_L was not significantly different in patients with abnormal chest radiographs. Davidson et al⁴³ and Whorwell et al⁴⁶ both found reduction in T_L correlated with smoking, while Popper et al⁴² found no correlation. In this study mean values for T_L did not differ between female smokers and non-smokers.

Compliance has been measured by Morère et al³⁸ and Schernthaner et al⁴⁸. Both groups were more interested in low compliance and using arbitrary limits found high rates of abnormality, 38.4% and 40.5%. This is a much higher rate than the 4% found in the present study, but predicted values were calculated. Two prediction formulae (Pasquis et al⁸¹, Frank et al⁸⁸) give very large standard deviations and both are based on height. Thus many patients with values lower than the 0.150 L/cm H₂O quoted by Morère³⁸ would be normal. If Morère's figure of 0.150 L/cm H₂O had been taken as the lower limit of normal, 34% of patients in this study would have fallen into that category. This figure is almost identical with theirs and it seems likely that only a small number of patients were studied in the supine position so that results were little affected.

They noted that reduction in lung compliance was associated with airways obstruction in 12 patients and 2 of the 4 patients in this study with low compliance also had airways obstruction. The triad of low compliance, low transfer factor and low PO_2 was significantly related to sero-positivity. One of the present 4 patients with low

compliance and low transfer factor, also with airways obstruction, was sero-negative.

Schernthaner et al⁴⁸ took a figure of 0.060 L/cm H₂O/L as the lower limit of normal for specific compliance. This value was calculated for patients in this study and 39% fell below that lower limit of normal which agrees very well with their finding, but 50% of the normal control population also fell below that level suggesting that it is too high. Other workers have quoted lower figures for normal specific compliance (Krumholz et al⁸⁹, Kamel et al⁹⁰).

Calculation of specific compliance for comparative purposes used the FRC in this study measured by helium dilution. Results for compliance are ideally related to TLC which can vary by at least 0.5 litre depending on the subject's relaxation and it is easy to check this level in relation to the measurement of compliance when the subject is seated in a body plethysmograph as was done by Schernthaner et al⁴⁸. The population in the present study included a considerable number of patients who attended the laboratory during a period of rehabilitation after surgery and they came with legs elevated to a horizontal level so that they could not be fitted into a body plethysmograph even though it was designed to accommodate patients seated in wheelchairs. The measurements for C_{dyn} looking for frequency dependence were carried out with very careful attention to the volume history and being preceded by a vital capacity the possibility of error due to altered lung volume (Mills, Cumming and Harris⁷⁶) was avoided.

This method was found less satisfactory for static compliance measurements as it was necessary to have the patient breathing into the spirometer while assessing the baseline for FRC and when this

was not rapidly achieved the consumption of oxygen in a limited volume caused shift in the baseline and it was sometimes difficult to assess the percentage of TLC reached by the patient. Because of these difficulties, the study has not placed any great emphasis on static recoil pressures as they are open to this criticism and no conclusions can be drawn about pressures which appear to be high for volumes apparently less than TLC. Because of the shape of the pressure volume curve of the lung, small differences in volume, particularly at the upper limit of total lung capacity range, are related to large changes in expected recoil pressure.

The finding of high compliance was more common than that of low compliance. The proportion of patients 7% was like that of 8% found by Morère et al³⁸ to have compliance 'at the upper limit of normal or high', but was not dissimilar to the proportion of the control population with similar levels. In the patients of Morère et al³⁸ high compliance was associated with airways obstruction, but this was not true of all the patients in the present study.

It was notable that high compliance seemed to be associated with nodules, but it is difficult to interpret the significance of this. The likely explanation of high compliance would be the presence of emphysema, but it was found in female non-smokers, both rheumatoid and control. There was a suggestion in the rheumatoid population that recoil pressures fell towards the lower end of the normal range, but as explained previously it was not possible to exclude errors in the percentage measurement of related lung volume. In 8 patients the chest radiograph was suggestive of emphysema, in 2 of these patients compliance was high.

Cox and Huber⁹¹ studied α_1 antitrypsin phenotypes in patients with classic rheumatoid arthritis. There was a slight excess of heterozygotes for MZ and SZ Pi types. If heterozygosity were associated with an increased risk of emphysema this could be a possible explanation for the present findings, but there is still considerable debate as to whether the heterozygous state is associated with impaired lung function. The other likely reason for low recoil pressures would be muscular weakness, either due to rheumatoid disease or to corticosteroid treatment. Gibson et al⁹² found low recoil pressures in patients with muscle weakness, but compliance was also low.

Frequency Dependence of Compliance

The new aspect of the present study which has not been previously considered was the finding of an increased prevalence of frequency dependence of compliance in the rheumatoid population. This is expected when there is obstruction of larger airways and it was interesting to see how patients within the frequency dependant group could be re-classified as having large airways obstruction by using stricter criteria than $FEV_1 < 80\%$ PN which is sometimes used as indicative of airways obstruction. The use of mean PN - 2SD produces very wide limits in elderly patients who have lower predicted normal values. Berglund et al⁹³ commented on this difficulty when they published the prediction formulae used in this study, but their normal population included subjects up to the age of 70 years. In this study 3 patients who did not fall into the obstructive group at the time that they were shown to have FDC showed low FEV_1 or low $FEV_1/VC\%$ at subsequent visits confirming the strong association of FDC with airways obstruction.

In 3 patients with FDC, FEV_1 was normal, but because VC was large, $FEV_1/VC\%$ fell below PN - 2SD. The presence of FDC would seem to provide confirmation that the low FEV_1/VC ratio is pathological in the presence of a high vital capacity.

If all these patients with evidence of large airways obstruction were excluded there remained a significantly higher proportion of rheumatoid subjects with FDC over the age of 50.

Begin et al⁹⁴ found that C_{dyn} fell significantly between rates of 15/min and 60/min in non-smokers over the age of 50 and Frank et al⁹⁵ found a fall in C_{dyn} at increased respiratory rates in patients over the age of 50 if flow resistance was increased, although this tendency

was much smaller than the changes seen in the presence of emphysema. On the other hand Knudson et al⁸⁴ concluded that there was no evidence that change in C_{dyn} at rapid respiratory rates was more common in older patients. The inclusion of a control group in this study avoids the question of attributing the FDC to age alone as the proportion of rheumatoid patients showing this phenomenon was significantly greater.

Patients with abnormal compliance and generalised airways obstruction having been excluded, this would be compatible with some pathological process at bronchiolar level. Alternatively, alteration of time constants may be caused by patchy fibrosis affecting such small areas of lung tissue that total lung compliance is normal and then the finding of FDC would be indicative of early disease of alveolar or interstitial tissue.

Eight of the patients with FDC had abnormal T_L at the same visit or later and 1 patient who showed FDC on 2 successive visits subsequently developed low compliance which suggests that FDC may be present at a stage of the lung disease before total compliance is affected. The uneven ventilation implied by FDC would contribute to reduction in T_L .

The finding that FDC was significantly greater in rheumatoid subjects only after the age of 50 would be consistent with the previously reported incidence of rheumatoid lung disease which has tended to occur in older patients. The proportion of males has also been greater in the population with lung involvement compared with other rheumatoid patients and in this study FDC was seen in 29% of rheumatoid men and 9% of women. The frequency dependent population contained a higher proportion of patients with nodules (50%) or the sicca syndrome (30%)

than the rheumatoid population as a whole. The higher proportion of patients with nodules has also been a feature of descriptions of rheumatoid lung disease.

There was no evidence that patients with FDC had a larger number of joints involved which might have indicated more severe generalised disease and which might also have suggested that immobility of the chest wall had contributed to the fall in compliance at increased respiratory rates.

Previous studies of small airway function in idiopathic fibrosing alveolitis have produced conflicting results. The report by Fulmer et al⁶⁴ showed a very convincing association of FDC with histologically proven bronchiolar disease. These patients, one of whom had normal T_L and one normal TLC, probably had less advanced disease than the 9 patients reported by Schofield et al⁹⁶ who looked at closing volume. Although closing volume was high in relation to VC or TLC the absolute volume at which airway closure occurred was found to be normal and they therefore concluded that there was no evidence for narrowing of functional small airways in ventilated parts of the lung. Gibson and Pride⁹⁷ found FDC in only 1 of 4 patients with fibrosing alveolitis; he was a heavy smoker, but compliance in the 8 patients they studied was low and again the disease was possibly more advanced than in the patients studied by Fulmer et al⁶⁴. Uchiyama et al⁹⁸ found no FDC in 41 patients with 'pulmonary fibrosis' (English abstract of Japanese article).

These reports suggest that once disease has progressed sufficiently to reduce total lung compliance, the fall in compliance at increased rates of respiration, whether due to differing areas of compliance in diseased lung or to uneven narrowing of small airways, disappears.

The number of patients with low compliance in this study was too small to draw any conclusions about this. Two of the patients and the 'normal' female with low compliance had low FEV_1 . In all 3 compliance fell with increasing rates of respiration, but this could have been due to upper airway disease. There was no fall with increasing rate in the other 2 rheumatoid patients and, as mentioned before, in one patient FDC disappeared when compliance was low at a follow-up visit.

The presence of FDC was not significantly related to smoking in this study. The only normal volunteer showing FDC was a female non-smoker and it was found in one of the two non-smoking rheumatoid males. Previous workers, including Hüttemann et al⁹⁹ and Martin et al¹⁰⁰, have found an increased incidence of FDC in smokers compared with non-smokers; the latter workers found that FDC returned to normal in 5 of 8 smokers who stopped smoking. In this study 2 males and 1 female with FDC were ex-smokers.

Amongst the rheumatoid patients with FDC 3 had a personal or family history of allergy. The one control female non-smoker with FDC had contact dermatitis and worked in the printing industry where there are many allergens. Four subjects who had suffered from asthma in childhood did not show FDC. In the previous studies relating FDC to asymptomatic asthma^{54,56}, the asthmatic symptoms were less remote and from the small number studied here it would seem that FDC eventually disappears.

Bobbaers et al¹⁰¹ found that in 6 patients with chronic bronchitis and normal FEV_1 , C_{dyn} fell at increased rates rates of respiration. Of 40 smokers in this study with cough, in 34 FEV_1 was within normal limits; 5 showed FDC.

Seaton et al⁶³ found an increased incidence of FDC in coal workers with simple pneumoconiosis and thought that this probably was due to dust deposits affecting the bronchioles. Of the rheumatoid patients with FDC, 5 had been exposed to inorganic dust and 1 was a welder. Thus 25% of rheumatoid subjects exposed to dust and fumes developed FDC, compared with 8% of the control population. The numbers are too small for this to be significant, but there is a suggestion that rheumatoid patients react more vigorously to irritants at bronchiolar level in the way that coal workers with rheumatoid arthritis develop modified pneumoconiosis with nodules and an increased incidence of massive fibrosis¹⁵.

The Membrane and Vascular Components of Transfer Factor

Although there were no significant differences between the rheumatoid and control populations for T_L , Vc was significantly lower in rheumatoid males. The probability that the reduction in Vc was related to the rheumatoid disease was strengthened by the other significant differences found: (a) the lower value found in patients with nodules (b) the lower value in patients not being treated with corticosteroids. Vc was significantly lower in rheumatoid female smokers compared with rheumatoid female non-smokers whereas the difference did not exist for control females. In our laboratory it has also been found that there is no difference between non-rheumatoid male smokers and non-smokers. Other workers found Vc significantly lower in smokers than in non-smokers. Frans et al¹⁰² attributed this difference to back tension of carbon monoxide, although it had been measured in their subjects and correction made. Van Gance et al¹⁰³, who found reduced Vc in smokers, assumed that back tension was negligible. Correction for back tension often makes a considerable difference to the value found for Vc. This was confirmed in the present study.

The precise role of smoking in vascular disease has not yet been clearly defined. Cigarette smokers have a higher incidence of coronary artery disease and limb artery disease, both of these conditions being primarily atheromatous, while Buerger's disease, which seems to be an inflammatory condition, occurs in younger men and is very strongly related to cigarette smoking. It seems probable that smoking has a potentiating effect on other causes of vascular disease and therefore might well exacerbate the vascular changes known to be present in rheumatoid arthritis, both in systemic muscular

arteries (Cruickshank¹⁰⁴, Sokoloff et al¹⁰⁵) and within pulmonary vessels (Ellman and Ball³, Cruickshank²¹ and Edge and Rickards¹⁷).

Vc was significantly lower in the patients in whom T_L had been persistently low. The significant reduction in Vc in patients with nodules fits with pattern of rheumatoid lung involvement, although no correlation was found with Rose Waaler titre. The patients receiving penicillamine nearly all became sero-negative, but if they were excluded from analysis there was still no correlation with Rose Waaler titre.

In sarcoidosis Hamer⁷⁷ found that reduction in Vc tended to be associated with recognised pulmonary fibrosis of longer duration. Within the group of rheumatoid patients who had not received corticosteroids there were 8 patients in whom Vc was less than 60% PN; only 2 of these had suffered from arthritis for 10 years or more. As the Dm and Vc measurements were mostly made during the second part of a 5 year study, few patients with disease of less than 5 years duration were included. Rheumatoid lung disease may precede arthritis so that there might well be no correlation between Dm or Vc and duration of joint symptoms.

It was interesting to find that reduction in Vc appeared to be prevented by corticosteroid treatment. This beneficial effect was probably the reason for the significant correlation found between Vc and duration of disease. Twenty-one of the 27 patients whose arthritis had been present for more than 10 years were in the steroid treated group with significantly higher Vc.

It seems probable that corticosteroids suppress inflammatory changes in pulmonary blood vessels. De Horatius and Williams¹⁰⁶ injected

rheumatoid factor into rabbits with diffuse granulomata induced by Freund's adjuvant and subsequently antigammaglobulin deposits were found in alveolar walls and arterioles. In studies on lung tissue from 5 patients with rheumatoid lung disease (De horatius et al¹⁰⁷) IgM was demonstrated in pulmonary arteries as well as alveolar walls, rheumatoid factor showing the same distribution. There was moderate staining for IgG and IgA.

Tomasi et al¹⁰⁸ compared rheumatoid patients with or without lung disease with patients with idiopathic interstitial pulmonary fibrosis. They found 9 - 15S rheumatoid factors in patients with rheumatoid lung disease, not in other patients, and suggested that rheumatoid factor might be produced in lymph nodes, joints or subcutaneous nodules and aggregates deposited in the lungs.

Immune complexes have been demonstrated more frequently in serum from patients with nodules (Hay et al¹⁰⁹), and nodules have figured prominently in descriptions of rheumatoid lung disease, particularly in male patients. The finding that Vc was significantly lower in patients with nodules confirmed the significance of the lower Vc in rheumatoid patients, and supported the hypothesis that the reduction in Vc might be related to immune complex deposition.

Systemic lupus erythematosus is a related condition characterised by anti DNA antibodies and the presence of immune complexes leading to arteritis affecting the lungs as well as the kidneys, the central nervous system and many organs. Gold and Jennings⁷² describing a characteristic picture suggestive of vascular lung disease in SLE included reduced Vc as one of the criteria for inclusion.

Corticosteroids are used to treat the important manifestations of SLE and would be expected to suppress similar reactions in the pulmonary blood vessels of patients with rheumatoid disease. Kolarz et al¹¹⁰

and Schernthaner et al⁴⁸ suggested that the correlation between KCO and Rose Waaler titre would be consistent with immune complex deposits in pulmonary blood vessels.

The reported response of rheumatoid lung disease to corticosteroid treatment has been variable. Gray and Gray³⁶ found that lung function improved while patients were receiving cortisone treatment and declined when it was withdrawn. Stack and Grant² reported that none of their 8 patients improved on treatment. Failure to improve might be due to the advanced stage of the disease as corticosteroids would have little effect on established fibrosis, but would be expected to reduce inflammatory response.

The patients in this study who started treatment with prednisolone showed significant mean increase in exercise T_L at the next visit. Both components of T_L increase on exercise (Johnson et al⁶⁸ and Lewis et al¹¹¹) but percentage rise in Vc is slightly greater suggesting that capillaries expand. Reduction in inflammatory changes in capillaries might then improve this response. However, the most probable explanation of improved exercise T_L at the next visit in the present study was the increased capacity for exercise and the tendency seen to accept a slightly larger workload.

The other factor which might lead to a difference in Vc in patients receiving corticosteroids would be the presence of hypertension or left ventricular failure which might increase Vc due to increased back pressure from the left atrium as was found by Pande et al¹¹² in patients with mitral valve disease or McNeill et al⁶⁷ in patients with pulmonary congestion. There was no clinical evidence that this was the explanation for the findings.

In this study Dm seemed to have no relation to any features of the rheumatoid disease. $1/Dm$ must include all other resistances to gas

transfer other than the vascular component and this includes the ventilation of the alveoli as well as integrity of the alveolar membrane. Marshall¹¹³ concluded that SB measurement of T_L was not affected by unevenness of ventilation and therefore reduction in D_m would be due to alveolar disease. In this study, although airways obstruction ($FEV_1 < \text{mean FN} - 2SD$) was fairly common, there was no evidence that it was associated with abnormal D_m or V_c and the patients with FDC showed no particular pattern of D_m or V_c abnormality.

Previous workers have studied the relation between D_m and V_c and the mechanical properties of the lung. Georges et al⁷¹ found a significant correlation between effective compliance and V_c , the similarity of their results for patients with DIPF and systemic sclerosis being very striking. It is possible that the majority of their patients were female.

In the female rheumatoid patients the correlation of V_c with C_{dyn} was negative, while correlation of D_m with C_{dyn} was positive. This might suggest that increased compliance allowed patients to achieve higher alveolar volumes. Hamer¹¹⁴ showed that in normal subjects D_m increased and V_c decreased with increasing alveolar volume. However, in these rheumatoid patients no significant correlation existed between D_m or V_c and alveolar volume achieved as per cent of measured TLC, (for D_m $r = 0.277$ for V_c $r = 0.065$).

D_m showed better correlation with static recoil pressure. Staub et al¹¹⁵, in normal subjects, found that increased recoil pressure leads to increased T_L and increased V_c . This might not be possible if there were pathological narrowing of the arteries. Macklem and Becklake¹¹⁶ were unable to find any correlation between TL_{SS} and recoil pressure in patients with pulmonary fibrosis. Perhaps it is not surprising

if there are scattered small areas of disease in the lungs, that gas transfer may be very disturbed by defects in perfusion before the disease is severe enough to produce generalised stiffening of the lungs.

The findings of this study suggest that the vascular abnormality is the most important cause for the transfer defect seen in rheumatoid disease.

The Five Year Follow-up

The interesting findings over the 5 year period were of different rates of change for different groups of rheumatoid patients, and for differences between groups in total incidence of the three types of functional abnormality. Without the inclusion of a control group it is impossible to draw conclusions about the changes for the group as a whole.

Gray and Gray³⁶ in their 2 patients with rheumatoid disease found that MVV and VC fell more than would have been predicted. The difficulty of predicting longitudinal change in lung function from the predicted normal values obtained by cross-sectional surveys has been noted previously.

Corbin et al¹¹⁷, in a study of smokers over a 4 year period, and Astrand et al¹¹⁸ re-examining physical education teachers after 20 years, both noted lung volume changes greater than expected from prediction formulae. Dehn and Bruce¹¹⁹ over a relatively short period of 3 years, found a greater than expected decline in exercise oxygen uptake in 86 healthy subjects.

In the present study there was a significant fall in FEV₁ and VC over the 5 year period which is similar to the fall seen by Gray and Gray³⁶ over a longer period and there were also small increases in RV and TLC which are similar to the changes seen in normal subjects by Corbin et al¹¹⁷ and Astrand et al¹¹⁸.

There was, however, a significant increase in T_L over the 5 year period in terms of per cent predicted normal, although in absolute terms this was not significant. This unexpected finding may be partly due to the inappropriateness of prediction formulae in relation to longitudinal change. Ten of the 60 patients in the study started

treatment with corticosteroids during the course of it; this will have partly contributed to the mean increase in transfer factor, although the increase in T_L in these patients did not differ significantly from the increase in the other 50 patients. Some patients tolerated greater workloads and some showed increased oxygen uptake at later visits, but for the group as a whole there did not appear to be any correlation between these factors and duration of follow-up. It is possible that in patients with arthritis T_L may not be directly related to workload, as oxygen uptake on exercise is reduced by effective treatment of joint disease (Pugh¹²⁰). One might therefore see increased workload and possibly reduced oxygen uptake and T_L when the number of involved joints is smaller.

The use of repeated testing in the rheumatoid subjects augmented the total incidence of abnormality found so that by the end of the 5 year period 90% of 60 patients had shown some abnormality. There was a greater tendency for abnormality of lung volumes or gas transfer, once detected, to persist than for recognised abnormality to disappear, but lung function was seen to improve in some patients.

In 16 of 18 patients airways obstruction persisted; 2 patients with increased RV and TLC and a further patient with increased TLC showed persistent abnormality at all visits. New abnormalities of RV or TLC did not develop in any other patients during the 5 year period.

In 3 patients T_L was low at every visit before the fifth when it was normal. One of these patients had clinical and radiological findings suggestive of pneumonitis and at the time her transfer factor had risen to the lower end of the normal range, the number of actively involved joints was greater and the Rose Waaler titre was higher. This patient had started treatment with prednisolone after her first visit. Frank et al⁴⁴

reported that follow-up measurements in some of their patients with abnormal lung function showed a slow decline over a 2 year period.

Whatever doubts there might be about the quality of exercise performed by the rheumatoid patients, a high proportion of patients who first showed 'low' exercise T_L subsequently developed low resting T_L , and exercise T_L was found to correlate well with the result of single breath measurement. The prevalence of $TL_{SB} < 80\%$ PN in the 60 patients at the fifth visit was the same as that of 'low' exercise T_L (32%) in 99 patients at the first visit. As this prevalence is rather high, and the limit of PN - 2SD more acceptable, the arbitrary limit of control mean - 1SD to define a group of patients for follow-up included some who should have been considered normal. Some of these patients will have shown higher values at follow-up visits. The likelihood that persistent abnormalities of T_L were associated with pathology in the lung was confirmed by the later finding that Vc was significantly lower in these patients. In only 1 patient of the 60 was there an isolated finding of low T_L on one occasion. In all other cases the abnormality of T_L was found at more than 1 visit or associated with other abnormality in lung volumes or compliance.

Change in compliance could not be so easily assessed because fewer measurements were made. Low compliance might seem to be a poor prognostic feature as 2 of the 4 patients with low compliance died; 1 from bronchial carcinoma complicating rheumatoid pneumonitis. In 1 patient a subsequent compliance measurement was in the normal range, although recoil pressures were very high. This particular patient was the only one of the 99 patients to be treated with azothiaprime. This might be expected to have a beneficial effect on rheumatoid lung disease.

Follow-up of patients with compliance abnormality showed that some other abnormality of lung function was likely to develop and change in compliance over the follow-up period was significantly related to the presence of symptoms and signs. A test which involves the swallowing of an oesophageal balloon is not an ideal screening test, but exercise testing of T_L is also uncomfortable for patients with joint disease and it appeared that these 2 tests revealed abnormalities before the more routine tests gave abnormal results. This would only be of benefit if some effective and harmless treatment were available to modify the future progress of the disease.

The statistically significant findings relating changes in lung function to change in clinical findings seemed to be randomly distributed. Thus, FEV_1 was significantly lower at visits where crepitations were heard, resting T_L was significantly lower when patients had breathlessness or cough, this difference being the most significant and exercise T_L was found lower when clubbing was noted. There were no significant changes between visits in relation to radiographic change which has been the commonly accepted marker of fluctuation in rheumatoid involvement^{10, 11, 7.}

Improvement in symptoms when patients are treated with corticosteroids may be ascribed to the general improvement in well-being of the patient if there are no respiratory function tests to support the clinical impression. Doctor and Snider³² and Newcomer³⁴ both reported improvement in symptoms without any radiographic change in their patients. Therefore, it is interesting to note from this study that cough and breathlessness seemed to be clearly associated with reduction in T_L at visits when they were present. There is no doubt that improved lung function in response to treatment may be associated with

radiographic improvement^{12, 32} in many cases.

Brannan et al²³ accepted respiratory symptoms as evidence of pulmonary involvement and commented on the association of exacerbations of respiratory symptoms at times of increased activity of the joints disease. Although T_L was lower in this study when respiratory symptoms were present, no correlation was found between T_L and the number of joints involved or Rose Waaler titre. The total change in T_L over the 5 year period did not differ significantly in patients in whom symptoms had been present at most visits. As different patients had experienced symptoms at different visits, individual fluctuations within the 5 year period were masked by considering the progress of the group as a whole over a long period and between-visits comparison proved to be more revealing.

In this study nodules were the feature of rheumatoid disease most frequently significantly correlated with lung function. Over the 5 year follow-up period their presence was associated with increased total incidence of abnormal resting T_L , a greater fall in FEV_1 over the 5 years in addition to higher compliance in male patients and reduction in V_0 . The findings of increased fall in FEV_1 and higher compliance again emphasized the importance of considering airway function, as well as gas transfer, in studying rheumatoid patients. Both these aspects of lung function may be modified by smoking, but the proportion of smokers in the group with nodules was no different to that in the other patients.

The total 5 year incidence of abnormal resting T_L was significantly higher in patients with recognised arteritis in the systemic circulation and associated abnormality in the pulmonary circulation causing reduction of T_L would not be unexpected. The sicca syndrome is one of the syndromes shared by rheumatoid disease and systemic lupus erythematosus.

Anti-nuclear factors may be present and vascular lesions in the lung have been described (Bucher and Reid¹²¹). The total incidence of abnormal resting T_L was not higher in the patients in this study with the sicca syndrome, but the total incidence of abnormality combining rest and exercise T_L was significantly increased. Schirmer's test was not performed in the patients to confirm the diagnosis or to detect cases of the sicca syndrome not suspected from the history. It is possible that some patients were included in this category who would not have been found to have a positive test, but asymptomatic patients with reduced lacrimal secretion may have been excluded. Airways obstruction was the dominant problem described by Newball and Brahim¹²² in such patients, but the incidence of Obs in the present study did not differ from that in the patients without the sicca syndrome. Apart from this study of rheumatoid disease, over the same period 2 female patients with Sjögren's syndrome have been seen, both disabled by extremely severe airways obstruction. The patient in the 5 year study who developed bronchiolitis was one of the patients with the sicca syndrome, but those symptoms had improved at the time that the bronchiolitis developed.

Although it was expected that the total incidence of abnormal T_L over the 5 year period would show some association with radiographic appearances suggestive of pneumonitis, the only significant association with persistent radiographic changes was the finding of airways obstruction. In this study by Collins et al⁴⁵ where 71% of the patients showed evidence of airways obstruction, 19 of the 35 patients had abnormal chest radiographs. The chest radiographs were only a small part of the present study and no special arrangements were made to obtain films of comparable quality at every visit. It has been noted

in the past that changes in T_L may not be clearly related to abnormal radiographic appearances³⁵. Again outside this study 1 female rheumatoid patient with a much more abnormal chest radiograph than most of those seen in the study had only slight reduction of transfer factor.

A combination of clinical history and examination, chest radiograph and respiratory function tests will increase the proportion of patients found to have some abnormality of their lungs in association with rheumatoid disease. Repeated examination will increase the proportion so that about 90% of patients will fall into this category. It would seem that the established fibrosing alveolitis which is often called 'rheumatoid lung disease' is an extreme manifestation of changes which may be found in some degree in most patients with rheumatoid disease.

CONCLUSIONS

1. The prevalence of airways obstruction, low vital capacity and reduced transfer factor was similar to that found by previous workers. Some normal volunteers were found to show similar abnormalities.
2. Fewer patients were considered to have reduced lung compliance than has been previously reported, but this was chiefly because wider limits of normality were accepted. This was thought to be correct as the compliance measurements in the rheumatoid population did not differ significantly from those in the controls.
3. Frequency dependence of compliance implying disease of small airways was more common in the rheumatoid population and over the age of 50 was significantly more frequent ($p < .05$) than in the controls.
4. There was a suggestion that frequency dependence occurred more commonly in rheumatoid patients exposed to industrial dust or fumes than in controls with similar exposure.
5. The vascular component of transfer factor (V_c) was significantly reduced in male rheumatoid patients compared with controls and in female rheumatoid smokers compared with female rheumatoid non-smokers. Reduced V_c was related to the presence of nodules, was significantly more common in patients known to have previously low T_L and the reduction appeared to be prevented by treatment with corticosteroids. These findings provide evidence that pulmonary blood vessels are involved by the inflammatory changes of rheumatoid disease, the vasculitis contributing to reduction of transfer factor. This abnormality was potentiated by smoking.

6. The presence of respiratory symptoms and signs could be more frequently related to alteration in lung function than could changes in the chest radiograph.

7. Impairment of lung function was more frequently related to the presence of nodules than to any other feature. Changes in transfer factor were associated with peripheral evidence of vasculitis and with the sicca syndrome.

These three features (nodules, vasculitis and sicca syndrome) have been found to be associated with immune complexes in rheumatoid disease and immune complex deposition in the lung is probably an important cause of altered lung function.

8. Since over a 5 year follow-up period 90% of 60 patients showed some abnormality of lung function, lung involvement should be considered a usual manifestation of rheumatoid disease.

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N.B. Reference numbers 78 and 79 have been inadvertently repeated as numbers 85 and 86.

APPENDIX 1* VALUES & SIGNIFICANCE LEVELS FOR MANN WHITNEY U TEST

	FEV ₁		VC		T _L rest		C _{dyn}	
	z	p value	z	p value	z	p value	z	p value
Change related to male/female							1.39	.08
Change related to symptoms or signs/no symptoms or signs	1.06	.14	.98	.16	.81	.21	2.62	.008*
Initial compliance males nodules/no nodules							21.5	.001*
Change related to nodules/no nodules	2.14	.016*	1.09	.14	.90	.18	1.1	.13
Change related to sicca syndrome/no sicca syndrome	.63	.26	.35	.36	.40	.34	1.38	.08
Change related to treatment/no treatment with corticosteroids					.8 exercise T _L 1.6	.21 .055		
Change related to hypertension, IHD, LV/no LV problem			.67	.25				

* Significant difference

APPENDIX 2 χ^2 VALUES FOR TESTING CLINICAL ASSOCIATIONS AT THE INITIAL VISIT

	χ^2
Female Smokers with cough Rheumatoid v. Control	2.33
Abnormal Chest x-ray Male + Female Rheumatoid v. Control	9.44 **
Abnormal chest x-ray in males Rheumatoid v. Control	4.63 *
Abnormal chest x-ray in Rheumatoid Patients Males v. Females	1.32
Abnormal chest x-ray in Rheumatoid Patients Smokers v. Non-smokers Male and Female	1.63
Crepitations in Males Rheumatoid v. Control	0.23

* $p = < .05$ ** $p = < .001$

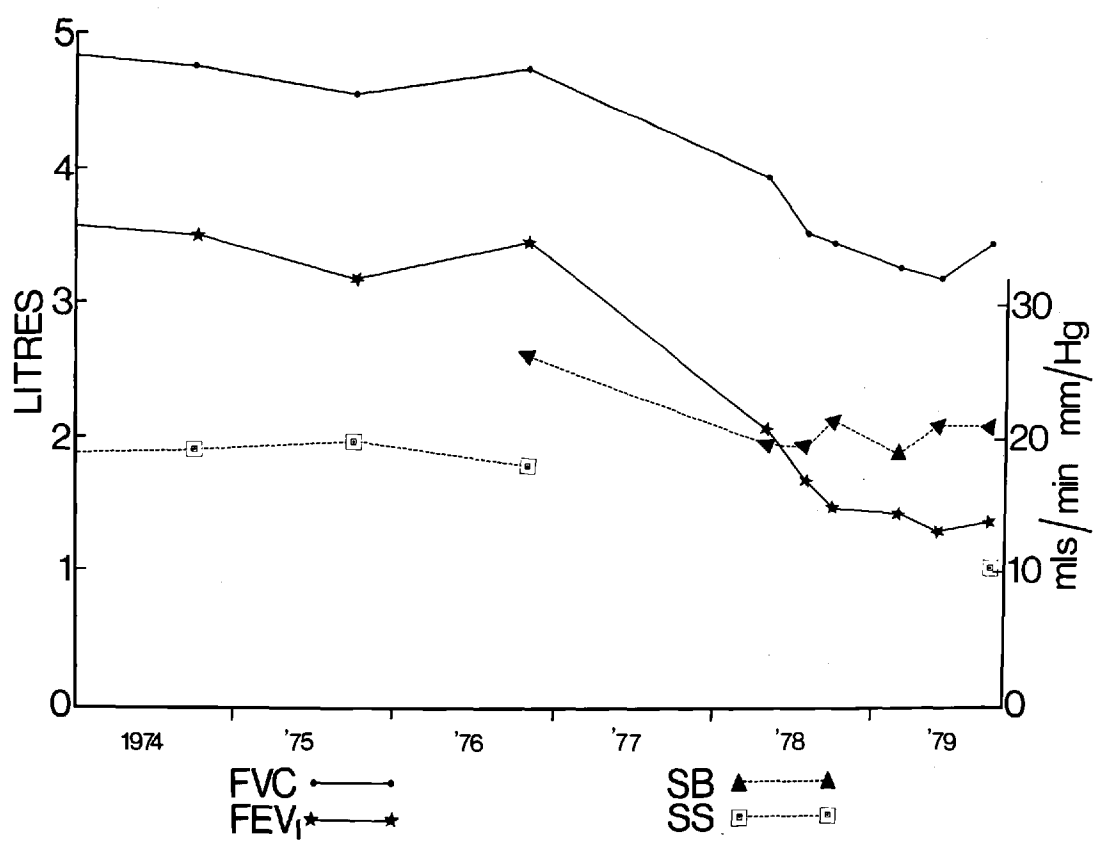
APPENDIX 3

VALUES FOR χ^2 TESTING ASSOCIATION OF ABNORMAL LUNG FUNCTION OVER
THE 5 YEAR PERIOD WITH VARIOUS CLINICAL FEATURES

		Obs	Rest T_L	Exercise T_L	All abnormal T_L	C_{dyn}
Respiratory symptoms v. none		.99	.41	-	-	1.17
Crepitations v. absence		.13	-	-	1.3	3.30
Abnormal chest x-ray >50 per cent visits v. never abnormal		4.45*	-	-	-	.02
DAT < 1/512 v. > 1/512		.14	-	-	.23	.84
Nodules v. none		.004	4.85*	.31	-	.78
Nodules and high v. normal compliance		-	-	-	-	3.38
Arteritis v. absence		-	5.67	.33	-	-
Sicca syndrome v. absence		.05	2.59	.03	5.5**	.76
Low compliance death v. survival		-	-	-	-	2.94
All abnormalities death v. survival	.54	-.1	-	-	-	-

* p = .05

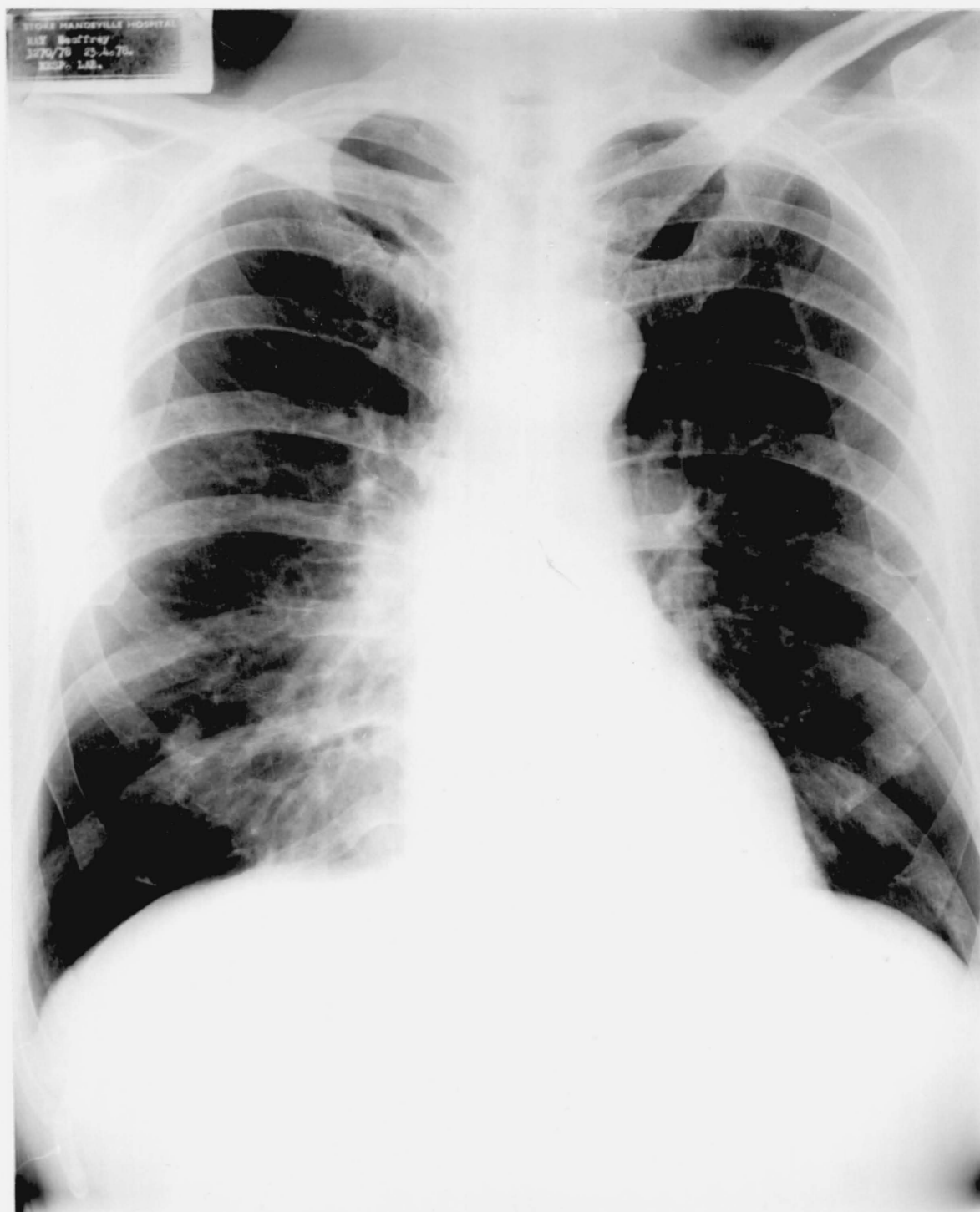
** p = .02

APPENDIX 4PROGRESS OF PATIENT G.M. WHO DEVELOPED BRONCHIOLITIS

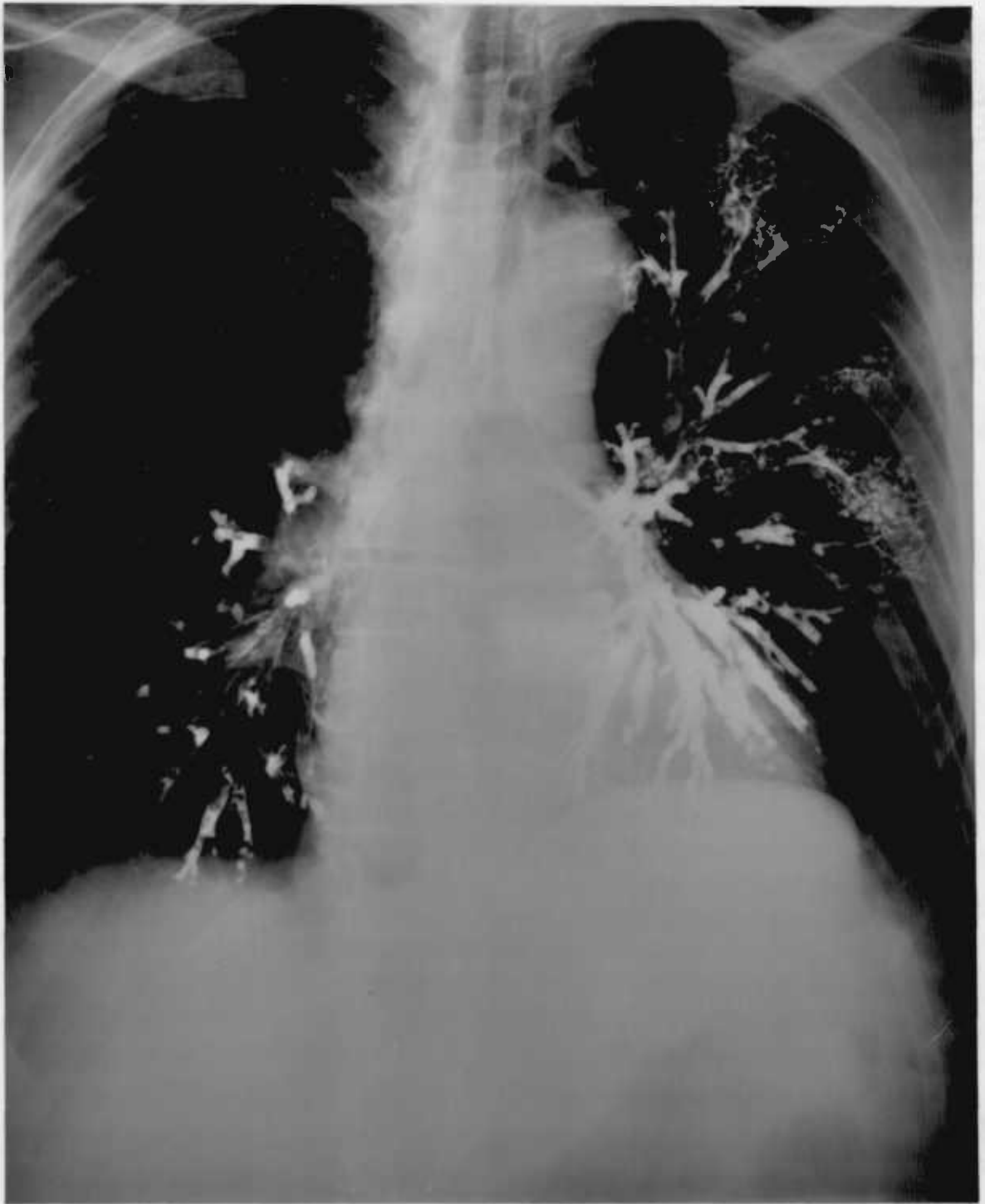
G.M. PA CHEST RADIOGRAPH AT ENTRY OF STUDY.



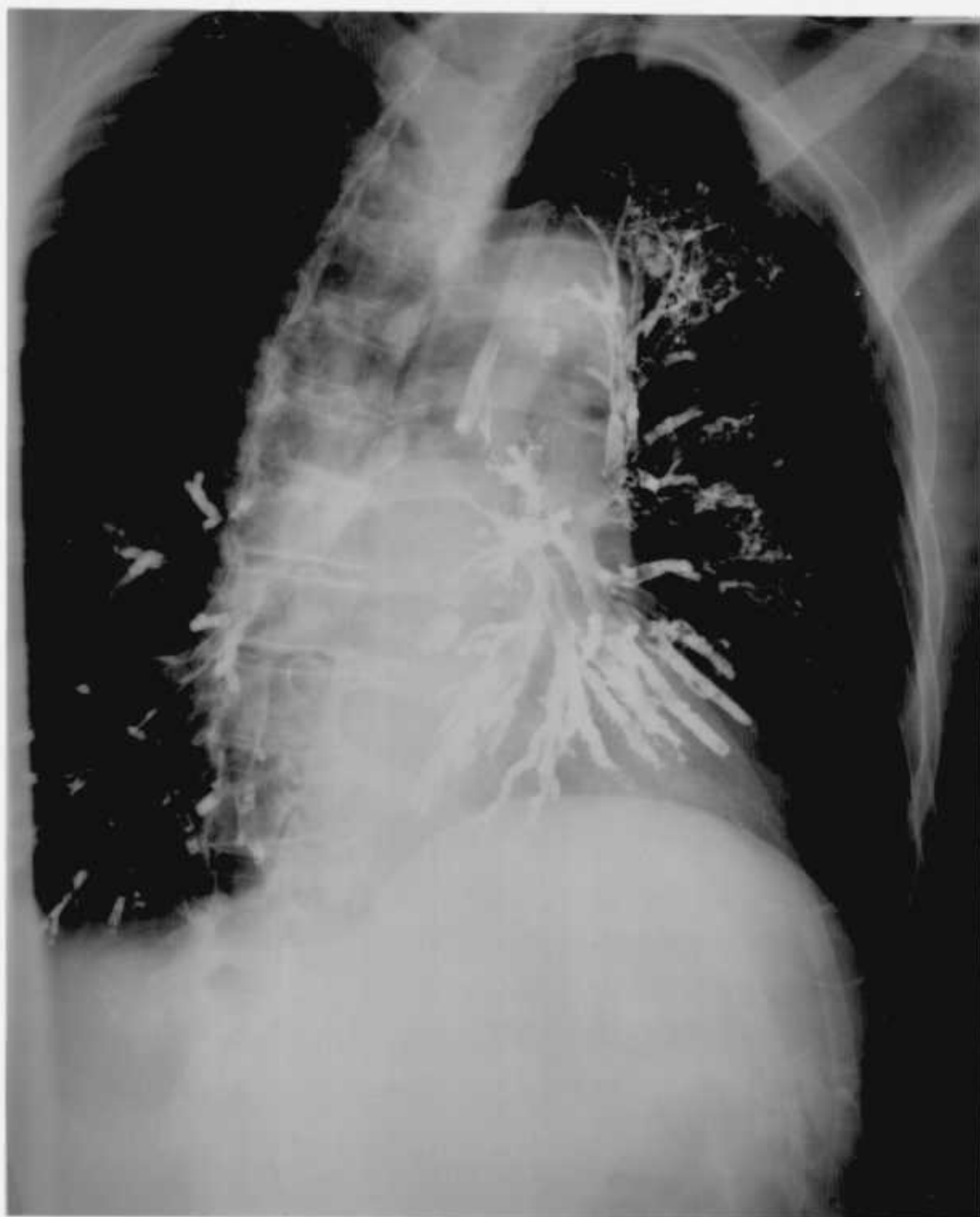
G.M. PA CHEST RADIOGRAPH AT TIME OF DETERIORATION IN LUNG FUNCTION



G.M. AP BRONCHOGRAM SHOWING OBLITERATIVE BRONCHIOLITIS.



G.M. LEFT OBLIQUE BRONCHOGRAM.



APPENDIX 5LUNG FUNCTION RESULTS - A.R.

	Before Isoprenaline	After	Predicted
FEV ₁ L.	2.31	2.58	3.43
FVC L.	4.09	4.26	4.81
FEV ₁ /VC%	56.5	60.6	69.4
RV L.	2.8		2.56
TLC L.	6.89		7.55
RV/TLC%	40.3		37.3
TL _{SS} mls/min/mmHg	Rest 11.9		14.8
	Exercise 24.6		
C _{dyn} L/cm HCo 20/mins	0.126		0.232

A.R. aged 60 AT ENTRY TO STUDY.

X-RAY - PA CHEST RADIOGRAPH 1972, SHOWING BILATERAL
DIFFUSE ABNORMAL SHADOWING.



X-RAY - A.R. 1974 PA CHEST RADIOGRAPH, SHOWING
DEVELOPMENT OF [REDACTED] CARCINOMA IN
THE LEFT LOWER LOBE.



**FREQUENCY DEPENDENCE OF DYNAMIC
COMPLIANCE IN PATIENTS WITH
RHEUMATOID ARTHRITIS**

BY

**ELIZABETH A HILLS, SYLVIA DAVIES, and
MARION GEARY**

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**BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, LONDON
WC1H 9JR**

Frequency dependence of dynamic compliance in patients with rheumatoid arthritis

ELIZABETH A HILLS, SYLVIA DAVIES, AND MARION GEARY

Stoke Mandeville Hospital, Aylesbury, Bucks HP21 8AL, UK

ABSTRACT An investigation of lung function was carried out in 99 randomly selected patients with classic or definite rheumatoid arthritis and in 60 control subjects matched for age, sex, and smoking habits. Mean FEV₁ and mean VC were both significantly lower in the rheumatoid patients due to significant differences for women but mean FEV₁/VC ratio was 73.0% in the rheumatoid group and 72.1% in the control.

Steady-state transfer factor was significantly greater in the normal men than in the comparable rheumatoid group, but there was no difference for women. After excluding patients with FEV₁ less than 80% predicted normal and patients with low compliance, 72 rheumatoid patients and 45 controls provided series of tracings that could be assessed for a fall in C_{dyn} of 20% between 20 cycles and 60 cycles a minute. Dynamic compliance was not significantly different in any group at any rate of respiration. Fourteen of 72 rheumatoid patients and three of 45 controls showed frequency dependence (FDC). After the age of 50 the prevalence in the rheumatoid group was 11/38 and in the control group 2/27. This difference was significant ($P < 0.05$). FDC was not consistently related to other abnormalities of lung function or to the duration, severity, or treatment of the rheumatoid arthritis. In various categories of smoking habits, dust exposure, or allergic tendency, the prevalence was always greater in the rheumatoid group. This provides evidence of patchy involvement of small airways, or alveoli and connective tissue, by the rheumatoid process.

Pleural and pulmonary involvement occur in rheumatoid arthritis and may be the presenting feature (Ellman and Ball, 1948; Cruickshank, 1959; Horler and Thompson, 1959). Early reports were chiefly concerned with radiological and histological abnormalities but during recent years studies of lung function have also been reported. The histological abnormalities affect bronchioles, alveoli, interstitial tissue, and blood vessels, and it is not clear that any particular pattern of involvement is most common. Studies of lung function have shown that there may be a restrictive pattern of ventilation, low lung compliance, low transfer factor and changes in blood gases (Morère *et al*, 1972; Frank *et al*, 1973; Whorwell *et al*, 1975). The low transfer factor might be consequent to abnormal alveolar structure, to loss of capillary volume, or to distortion of respiratory bronchioles leading to uneven alveolar ventilation. Newcomer *et al* (1964) showed that some patients with rheumatoid arthritis had a reduced maximal mid-expiratory flow rate

(MMEFR), and this finding was confirmed by Collins *et al* (1974) who studied 38 patients. The physiological demonstration of possible bronchiolar disease was followed by description of the clinical picture of bronchiolitis by Geddes *et al* (1977) in six patients. Uneven ventilation may be shown by a fall in dynamic compliance (C_{dyn}) when measured at increasing respiratory rates. This frequency dependence of compliance has been studied in smokers in an attempt to show early disease of small airways before an obstructive pattern of ventilation becomes evident on spirometry (Woolcock *et al*, 1969). In coalworkers' pneumoconiosis where histological abnormalities may be seen at the bronchiolar level, frequency dependence has been shown (Seaton *et al*, 1972) and it might be expected that this abnormality would also be seen in patients whose bronchioles are affected by the inflammatory changes of rheumatoid disease.

This study was designed to investigate C_{dyn} at various respiratory rates in patients with rheu-

matoid arthritis and in matched normal volunteers.

Methods

Patients with classic or definite rheumatoid arthritis between the ages of 16 and 70 were asked to volunteer for the study after the investigations had been explained to them. The selection was random including both outpatients and inpatients, but patients admitted for surgery were not studied during the week after operation. Patients were excluded if there was a history of some other pulmonary disease but were not excluded by symptoms of cough or breathlessness that could have been related to rheumatoid disease. Control (normal) volunteers were recruited from other medical and surgical patients, from the spouses of rheumatoid patients and patients with respiratory disease, and from hospital staff. It had been intended to study 100 control subjects who would be matched with rheumatoid patients for age, sex, and smoking habits. It was subsequently decided that 50 controls would be sufficient, and recruitment was continued until each control group contained at least half the number of patients in the matching rheumatoid group.

A completed questionnaire for all patients gave the following information: details of smoking habits and the number of years the subject had smoked; exposure to birds, farm dust, or other agents likely to provoke an extrinsic allergic alveolitis; family history or personal history of allergy; the presence of cough, breathlessness, finger clubbing, or crackles; radiological evidence of changes in the lung areas; the number of joints affected and duration of arthritis, and treatment with corticosteroids, gold, or penicillamine.

Lung volumes were measured with patients standing and compliance with the patients seated. FEV₁ and VC were measured with the McDermott dry spirometer and Resparameter. MMEFR was measured by the Resparameter, and the residual volume by helium dilution. Transfer factor (TL) was measured at rest and on exercise by the steady state method using an end-tidal sampler. Exercise was performed using legs or arms and a bicycle ergometer with a work load adjusted to give an oxygen uptake on exercise of about 1 litre a minute. C_{dyn} was measured at four speeds of about 20, 36, 60, and 85 breaths a minute. Two runs of ten breaths were recorded at each speed. A constant volume history was obtained by asking the patient to inspire to total lung capacity, expire as fully as possible, and then return to the mid-vital capacity range. A volume of 500 ml was marked on the dial of the spirometer so that the patient

would breathe in the same range each time and the range achieved was recorded. If the patient fell short of the vital capacity by more than 200 ml the attempt was repeated after a rest. Runs where the tidal volume fell outside the range by more than 400 ml in either direction were not used in analysis. Volume was recorded using a McDermott spirometer fitted with a potentiometer. An oesophageal balloon 1 cm in diameter 10 cm in length filled with 0.5 ml of air was placed about 40 cm from the mouth. Differential pressure between the balloon and the mouth was recorded using a Hewlett-Packard 268B transducer. Flow was recorded by a Lilley pneumotachograph connected to a Hewlett-Packard 270 transducer. Recordings were made on a thermal recorder at paper speeds of 25 or 50 mm/s. Compliance was measured as the volume/pressure changes between points of no flow over a minimum of 5 cycles at each speed. The frequency response of the McDermott spirometer in series with the Lilley pneumotachograph and 270 transducer were tested by a square wave. This was generated by attaching 1500 g weights to the bottom of the bellows and letting it fall. The response was measured at paper speeds of 100 and 500 mm/s. For the two McDermott spirometers used, the 90% response time for 500 ml was 0.05 to 0.072 s, giving a frequency response between 4.63 and 6.67 Hz. For the pneumotachograph and transducer, at a flow rate of 100 l/min, 90% response time was 0.015 s, giving a frequency response of 22.2 Hz. The accuracy of the zero flow record and the absence of phase difference between oesophageal balloon and pneumotachograph were checked as recommended by Macklem (1974).

Static recoil pressure (P_{st}) was measured where possible. After a period of recorded quiet respiration patients were asked to take three deep breaths then to inhale to total lung capacity and to hold it for three seconds. Some patients also produced expiratory pressure volume curves by exhaling in small steps of 300 to 500 ml, relaxing for one to two seconds at these intervals while pressure and volume were continuously recorded.

Mean values for height, age, lung volume, TL_{SS} and C_{dyn} were compared between groups using Students *t* test. Predicted normal values were taken from Cotes (1975).

Results

CHARACTERISTICS OF PATIENTS AND CONTROLS

One hundred and one patients with rheumatoid arthritis volunteered. Two were excluded from all

investigations because they had severe airways obstruction, in one from bronchial asthma and in the other from emphysema. One woman included in the rheumatoid series had suffered from bronchial asthma during childhood. Sixty control subjects were studied; two men and one woman had suffered from asthma during childhood. Table 1 shows the distribution in terms of age, sex, and smoking habits. Two women who had smoked less than five cigarettes daily 20 years previously were classified as non-smokers, but other ex-smokers were classified as smokers. There was a slight excess of heavy (greater than 20 a day) cigarette smokers in the control population. When divided into groups with past or present exposure to industrial fumes or dust or other organic dust or in terms of social class, inspection showed no apparent difference between the two populations for either sex.

SYMPTOMS

Table 2 shows the prevalence of symptoms. One female and three male patients and one male control had breathlessness walking on the flat. In all other subjects it was of lesser degree.

FEV₁ AND VC

Table 3 shows mean age, height, FEV₁, and VC. There was no difference between rheumatoid and control groups in mean age or height. FEV₁ and VC in terms of percentage predicted normal values

(PN) were both significantly lower in the female rheumatoid patients ($p < 0.05$) but the FEV₁/VC ratio was not significantly reduced. There was no significant difference between rheumatoid and control men for FEV₁, VC, FEV₁/VC, or MMEFR.

TRANSFER FACTOR

Mean values are shown in table 3. The only significant difference between rheumatoid and control groups was the exercise TL in men ($p < 0.05$).

EXCLUSIONS FROM ANALYSIS FOR FREQUENCY DEPENDENCE OF COMPLIANCE

Some traces were very difficult to analyse because of oesophageal contractions; some patients were unable to breathe in time with the metronome or to breathe in the same tidal volume range at different speeds. These have been excluded. Eleven rheumatoid patients and four controls with FEV₁ less than 80% and six rheumatoid patients and one control with low compliance were also excluded. The six rheumatoid patients with a low C_{dyn} (less than 1 l/kPa) at all rates of respiration included one male and two female smokers and three non-smokers. There was no particular age distribution, and duration of arthritis ranged from less than two years to 39 years. Two patients had a low FEV₁, in one case associated with low VC, and in four patients TL was low at rest or on exercise. Three patients had basal crackles but

Table 1 Distribution of age, sex, and smoking habits for rheumatoid patients and control subjects

Age	99 Rheumatoid patients				60 Control subjects			
	Male		Female		Male		Female	
	S	NS	S	NS	S	NS	S	NS
<25 yr	1	0	0	1	1	0	0	0
26-40 yr	3	1	7	8	3	0	4	5
41-55 yr	18	0	8	13	10	0	6	8
56-70 yr	13	1	13	12	7	0	8	8
Totals by sex	35	2	28	34	21	0	18	21
	37		62		21		39	

S=Smoker,
NS=Non-smoker.

Table 2 Symptoms in rheumatoid patients and control subjects. Percentages in parentheses

	Male smokers		Female smokers		Female non-smokers	
	Rheumatoid n=35	Control n=21	Rheumatoid n=28	Control n=18	Rheumatoid n=34	Control n=21
Breathlessness	12 (34)	10 (48)	8 (29)	6 (33)	11 (32)	6 (29)
Cough	12 (34)	11 (52)	12 (43)	3 (17)	8 (24)	3 (14)

chest radiography showed no evidence of fibrosing alveolitis. The volunteer with low compliance also had low TL.

DYNAMIC COMPLIANCE

Table 4 shows the number remaining for analysis in each group with mean values for C_{dyn} at four rates of respiration. There was no difference between rheumatoid and non-rheumatoid groups at any rate of respiration. Within each group there was no significant change in C_{dyn} at higher rates of respiration. There was no significant correlation between exercise TL and C_{dyn}, and table 4 shows that mean values for C_{dyn} for groups of rheumatoid patients with abnormal chest radiograph did not differ from the mean values.

FREQUENCY DEPENDENCE OF COMPLIANCE

Frequency dependence of compliance (FDC) was said to be present if C_{dyn} at a rate of 60/min was 20% and statistically significantly lower than at a rate of 20/min (Hill *et al.*, 1972). Some patients excluded from the mean figures because their rates of respiration did not fall precisely within the stated limits achieved a series of readings at increasing rates of respiration. These were examined to see if they showed a 20% fall over a similar range. Table 5 shows the higher frequency of this phenomenon in the rheumatoid group and

table 6 shows the characteristics of the individuals with this finding. When the frequency of FDC was examined by the χ^2 test using Yates's correction there was no significant difference between the rheumatoid and control groups as a whole. Over the age of 50, using Fisher's exact test, the frequency was significantly higher in the rheumatoid group $0.05 > P > 0.01$.

STATIC RECOIL PRESSURES

Satisfactory recoil pressures were obtained for 32 patients and 12 controls. Abnormally high pressures were found in two patients, both of whom showed a low TL. Six other patients with a low TL included two with low recoil pressures. In the 32 patients there were 10 who had lower than expected recoil pressures using the prediction formulae of Knudson *et al.* (1977).

Discussion

Dynamic compliance was measured using a spirometer because there would be considerable problems in getting some disabled rheumatoid patients inside a body plethysmograph. Some of the patients attending the laboratory had legs in splints. Satisfactory measurements of static recoil pressure are difficult to make without an accurate measurement of lung volumes in relation to TLC,

Table 3 Mean values for age, height, FEV₁ and VC, and TL

	Age	Height		FEV ₁		VC		FEV ₁ /VC%		TLss rest		TLss exercise	
		Mean	SD	Mean	SD	%pred	SD	%pred	SD	Mean	SD	Mean	SD
Female Rheumatoid	62	51.0	11.8	1.61	0.06	102.3	17.4	105.9	16.2	73.9	8.3	116.3	38.8
Female control	39	50.0	11.4	1.62	0.06	109.1	17.6	121.9	15.8	74.2	7.6	100.2	29.0
Male Rheumatoid	37	51.6	10.0	1.73	0.07	95.9	14.4	97.5	13.5	71.6	8.1	120.6	30.7
Male control	21	50.7	12.3	1.76	0.05	96.5	14.7	106.5	14.0	69.9	7.8	117.7	31.8

Table 4 Mean values C_{dyn} at increasing rates of respiration in l/kPa

Group	No	15-25/M		30-40/M		55-65/M		78-90/M	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Male rheumatoid smokers	26	2.05	0.21	2.02	0.21	2.02	0.23	2.03	0.25
All male rheumatoid	28	2.08	0.20	2.04	0.19	2.01	0.21	2.00	0.23
Male non-rheumatoid smokers	15	2.46	0.30	2.48	0.29	2.43	0.23	2.66	0.30
Female rheumatoid smokers	23	1.68	0.09	1.63	0.12	1.56	0.12	1.34	0.15
Female non-rheumatoid smokers	16	1.50	0.08	1.37	0.08	1.50	0.11	1.40	0.11
Female rheumatoid non-smokers	20	1.58	0.13	1.55	0.06	1.55	0.12	1.55	0.15
Female non-rheumatoid non-smokers	15	1.92	0.27	1.79	0.17	1.64	0.22	1.88	0.31

No = Number suitable for analysis.

Conversion: SI to traditional units—1 l/kPa $\approx$ 0.098 l/cmH₂O.

Table 5 Prevalence of frequency dependence

	Rheumatoid	Non-rheumatoid
Male smokers	5/25	1/15
Male non-smokers	1/2	
All males	6/27	1/15
Female smokers	5/23	0/15
Female non-smokers	3/22	2/15
All females	8/45	2/30
Total	14/72	3/45
All aged over 50 years	11/38	2/27

and these can best be obtained using a variable volume plethysmograph. From our tracings it was often difficult to be sure if the patients had achieved TLC, and small errors in measurement of volume are related to very substantial differences in the pressure expected. The results for C_{dyn} were felt to be acceptable and more reliable than measurement of static compliance because on each occasion the patient started with a VC manoeuvre which was measured, and if this fell short by more than 200 ml that particular run was abandoned. Similarly, by watching the values on the dial of the spirometer it was ensured that measurements were recorded in the same tidal volume range for each rate of respiration, as Mills *et al* (1963) have shown that FDC might be produced by changing the levels of inspiration. This study showed no difference between the rheumatoid and the control group for mean C_{dyn} at any rate of respiration. Six patients had a low compliance which is a lower prevalence of abnormality than was found by Morère *et al* in 1972. Some of

their patients, however, were studied in a semi-recumbent position that is likely to affect the findings (Knowles *et al*, 1959).

Smokers were expected to show a fall in compliance at increased respiratory rates (Ingram and O'Cain, 1971; Hüttemann *et al*, 1972), but this finding was not confirmed in the larger number of subjects in this study. There was a slight excess of heavier smokers in the control group and six male volunteers were excluded from analysis for FDC because their FEV_1 was less than 80% of predicted. Only one of the remaining 15 normal men showed FDC while it was present in one of the two randomly enlisted rheumatoid non-smoking men. The prevalence was similar in smoking and non-smoking rheumatoid women. Bobbaers *et al* (1971) found that six patients with mild chronic bronchitis showed FDC. Cough was recorded in 40 smokers in this study. Six were excluded from analysis because of a low FEV_1 , and five others showed FDC. Previous work has shown that adults who have suffered from asthma in childhood showed FDC in later life (Woolcock *et al*, 1969; Hill *et al*, 1972), but four subjects in this series who had previously had asthma did not show this pattern of behaviour.

Most studies of C_{dyn} have involved patients under the age of 50. Frank *et al* (1973) in a study of patients aged between 50 and 85 suggested that C_{dyn} tended to fall with increased rates of breathing if flow resistance was increased, but this tendency was very small compared to changes seen in emphysema. Pierce and Ebert (1958) showed a

Table 6 Features of patients and controls with frequency dependence of compliance

Patient		Age	Treatment	Rose Waaler titre	Duration of RA	Examinations	FEV ₁ /VC % pred	Exercise T _L % pred	Other information
1	FRS	52	—	164/128	20 yr	Crackles X Ray	82/105	185	—
2	FRS	50	—	—	16/12	—	96/122	166	Mother has asthma
3	FRS	57	SP	512/1024	6/12	—	97/127	208	Son has eczema
4	FRS	33	S	<8	3 yr	X Ray	92/100	157	—
5	FRS	58	S	64	26 yr	Crackles	80/96	156	Large hiatus hernia
6	FRNS	64	S	64	18/12	—	105/117	290	—
7	FRNS	68	S	256	22 yr	—	106/130	212	—
8	FRNS	69	S	32	>20 yr	X Ray	89/93	191	Son has asthma
9	RMS	64	?	1024/2048	8 yr	—	93/102	149	—
10	RMS	57	S	256	8 yr	X Ray	102/97.5	160	Welder and brother has asthma
11	RMS	40	—	—ve	2 yr	X Ray	124/117	166	—
12	RMS	58	S	—ve	13 yr	X Ray	105/110	315	Wood dust and birds
13	RMS	69	S	256	24 yr	—	105/104	243	—
14	RMNS	27	—	—ve	3½ yr	—	103/102	177	Engineering dust
15	NRFNS	50	—	—	—	—	135/137	162	Father has asthma
16	NRFNS	31	—	—	—	—	119/125	210	Contact dermatitis
17	NRMS	42	—	—	—	—	96/104	210	Mother ? asthma

S=Corticosteroids; P=Penicillamine; FRS=Female rheumatoid smoker; FRNS=Female rheumatoid non-smoker; RMS=Rheumatoid male smoker; RMNS=Rheumatoid male non-smoker; NRFNS=Non-rheumatoid female non-smoker; NRMS=Non-rheumatoid male smoker; X Ray=Abnormal diffuse shadowing on chest radiograph.

fall in C_{dyn} at increased respiratory rate in 11 male patients over the age of 65. Knudson *et al* (1977) studied patients in three age groups including 18 patients aged 65–75. They found that age had no effect on C_{dyn} at higher respiratory rates. In this study the prevalence of FDC over the age of 50 was significantly higher in rheumatoid patients. The only male control to show FDC was 42. Although these patients were older, their rheumatoid arthritis was not always of longer duration, varying from six months to 24 years. In this way they are similar to patients disabled with rheumatoid lung disease. It was not possible to attribute the fall in compliance at greater speeds to immobility of the chest wall as there was no tendency for patients showing this feature to have a larger number of joints affected by rheumatoid arthritis. Patients with only a few peripheral joints affected would be unlikely to have extensive involvement of the joints and the rib cage. In more than half of the cases it was possible to find some other factor, such as exposure to dust or an allergic tendency, that might have contributed to this finding, but in each of these categories the incidence of FDC in the rheumatoid group was twice that in the control group.

Histologically, changes are seen in respiratory bronchioles in rheumatoid arthritis (Edge and Rickards, 1957; Ognibene, 1960; Stack *et al*, 1965). If inhalation of irritant or antigenic materials led to changes in respiratory bronchioles these changes might be more pronounced in patients with rheumatoid arthritis, where the respiratory bronchioles were already affected by the inflammatory changes associated with rheumatoid disease. Perhaps modification of response to inhaled materials might occur in some way analogous to the modification of coalworkers' pneumoconiosis (Caplan, 1953).

The fall in compliance measured at higher rates of respiration is attributed to differing time constants throughout the lung, thereby being an index of patchy rather than generalised disease. The time constants are a product of resistance and compliance. When used to investigate effects of smoking before clinically evident obstructive airways disease is developed, FDC would be attributed chiefly to change in resistance of small airways. In rheumatoid disease FDC could be due either to bronchiolar involvement causing changes in resistance or to uneven involvement of alveoli and connective tissues by the inflammatory or fibrotic changes of fibrosing alveolitis, leading to scattered areas of altered compliance. Schofield *et al* (1976) found that airways closure occurred at normal

values in nine subjects with established fibrosing alveolitis and concluded that in them there was no airways narrowing. In this study the six patients with a low compliance, including one with a reduced FEV_1/VC , did not show a fall in compliance with increasing rates of respiration (they were excluded from the analysis of incidence of FDC), which could be interpreted as evidence for an evenly distributed disease process, and four of these six patients had abnormal TL at rest or on exercise. The non-rheumatoid young patient with a low compliance showed FDC but the reason for the abnormal result was not evident. If the low compliance figures in the rheumatoid patients indicate generalised lung involvement the fact that the rheumatoid patients with FDC had normal compliance, although six had an abnormal chest radiograph, would support the proposition that they had patchy lung involvement. If FDC occurred in some cases without other abnormal findings it might perhaps detect early lung disease where treatment might be of some benefit. Any biopsy technique might miss scattered lesions. The other possibility is that FDC is not due primarily to rheumatoid inflammation, but that the rheumatoid disease modifies the effect of inhaled fumes or dusts causing small airways disease in a way analogous to the modification of coal workers' disease in rheumatoid arthritis.

The practical approach at present would be careful follow-up of patients showing FDC to discover whether they develop changes in transfer factor, a low compliance, or abnormal clinical or radiological features to suggest the presence of fibrosing alveolitis. The severe bronchiolitis described in rheumatoid disease has been a rapidly progressive or fatal disorder; possibly other patients have a milder form of the disease, and such patients might be detected among the group with frequency dependence. To shed light on these possibilities, a five-year follow-up study is being carried out at Stoke Mandeville Hospital.

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Requests for reprints to: Dr E A Hills, Stoke Mandeville Hospital, Mandeville Road, Aylesbury, Bucks HP21 8AL.

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