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RHEUMATOID SERUM FACTOR IN POPULATIONS IN THE U.K.

I. LUNG DISEASE AND RHEUMATOID SERUM FACTOR

J. S. LAWRENCE, G. B. LOCKE AND J. BALL

Department of Radiology, Manchester Royal Infirmary, the MRC Epidemiological Research Unit (South Wales), the Rheumatism Research Centre and the Arthritis and Rheumatism Council Field Unit, Manchester

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SUMMARY

In population samples in England and Wales a greater frequency of positive sheep cell agglutination tests has been found in Leigh and the Rhondda than in Wensleydale, the Vale of Glamorgan or Watford.

The urban population of Leigh had more X-ray evidence of lung pathology than the rural population of Wensleydale. Seropositive persons in both the urban populations of Leigh and the Rhondda and the rural populations of Wensleydale and Glamorgan had more X-ray evidence of lung pathology than seronegative individuals, the difference being significant for healed tuberculosis of the lungs, thickened basal pleura and increased basal vascular markings. The association between the first two and rheumatoid factor was equally present in those with and without arthritis but in the third it was limited to those with arthritis. A history of bronchitis was no more common in persons with a positive sheep cell test than in those with a negative test and the indirect maximum breathing capacity showed no significant relationship to rheumatoid factor titre.

No association was found between cigarette smoking and the sheep cell titre.

It is concluded that parenchymal lung and pleural disease may act as a stimulus to the production of rheumatoid serum factor and that this stimulus is independent of the presence or absence of arthritis.

INTRODUCTION

In a comparison of rheumatoid arthritis in seven populations in Northern Europe in 1961, it was observed that positive tests for rheumatoid factor as determined by the sheep cell agglutination (SCA) test, were more frequent in urban than in rural populations (Ball & Lawrence, 1961). No urban excess of rheumatoid arthritis was observed in these surveys nor was it found in a more detailed study by Kellgren in 1966. It was concluded that the

Correspondence: Dr J. S. Lawrence, Clinical Sciences Building, York Place, Manchester, 13.

excess of rheumatoid factor in the city dwellers must have some cause other than arthritis (de Graaf, Laine & Lawrence, 1963). Since then a population surveyed in Watford, Hertfordshire has shown a low prevalence of positive sheep cell tests, and it is clear that urbanization is not of itself responsible (Ansell & Lawrence, 1966). The two populations in Northern Europe with the largest proportion of positive tests, Leigh and the Rhondda were both coal-mining towns, had a high density of population and a high degree of atmospheric pollution. In 1958 and 1959, the last 2 years of the Leigh survey, the mean annual smoke concentrations in Leigh were 339 and 259 $\mu g/m^3$ whereas in Watford it was only 92 $\mu g/m^3$ in 1962 during the last year of that survey. The SO_2 level in Leigh is not available for the whole of 1958. In 1959 the mean annual value was 301 $\mu g/m^3$. In Watford in 1962 it was 126 $\mu g/m^3$. No data are available for smoke or SO_2 in the years in which other areas were surveyed nor are SO_3 levels in the atmosphere known at the time of the surveys except for Watford.

There has been a reduction of atmospheric pollution in some areas during the past few years. In Leigh the mean annual concentrations have fallen from 339 $\mu g/m^3$ in 1958 to 223 $\mu g/m^3$ in 1962. At the same time new housing developments have resulted in a spreading of the population. It is of interest that in two 5-year follow-up studies of persons seen in earlier surveys in Leigh, one from 1954–9 and the other from 1956–61, there has been a reduction in SSC titre in 22% but an increase in titre in only 10% (Ball & Lawrence, 1963).

In view of this apparent association between rheumatoid factor and atmospheric pollution it was decided to compare the prevalence of bronchial and pulmonary disease in an urban and a rural population and the relationship of such disease to rheumatoid serum factors.

MATERIALS AND METHODS

Persons studied

The following three clinical groups were studied:

1. The first 165 persons in a random sample of the town of Leigh in Lancashire and the last 345 of a rural population sample in Wensleydale were submitted to a routine chest X-ray in 1956–9. The samples were aged 15 years and over but the 55–64 age group in Leigh, which was examined earlier, did not have chest X-rays. The methods of sampling have been described elsewhere (Lawrence & Bennett, 1960; Bremner, 1961).

2. 5 years later, during a follow-up survey, chest radiographs were taken, questions were asked on bronchitis and the forced expiratory volume measured in those persons in the total 1956–9 samples in Leigh and Wensleydale with a positive SCA test at a titre of 32 or more together with controls from the same population samples of persons with titres of 4–16 and <4, matched for age and sex with the seropositive group. The SCA test was repeated during this follow-up and many which were positive had become negative. There were, thus, more seronegative persons in the final sample in these two population samples. Persons with a positive latex fixation test and controls were also included in this follow-up.

3. In 1953 and 1955 surveys were undertaken by the Pneumoconiosis Research Unit of persons aged 15 years and over in the Rhondda and Vale of Glamorgan in Wales. Persons suspected of having arthritis had an SCA test and chest X-rays were done routinely. In 1958 equal samples of miners and non-miners aged 35–64 and of females aged 55–64 from the Rhondda had routine chest X-rays and SCA tests. The methods of sampling have been described by Miall, Ball & Kellgren (1958) and Ball & Lawrence (1961). Persons with a positive SCA test and seronegative controls were included in the present study.

Radiological investigation

X-rays from Groups 1, 2 and 3 were mixed and read blind by one observer (G.B.L.). They were graded on a 0–4 scale for each of the following: tuberculosis, calcified shadows, pleural thickening, increased basal vascular markings (as described by Locke, 1963), fibrosis, pneumoconiosis, Kerley B lines and Caplan's disease. Clinical evidence of rheumatoid arthritis was also graded on a 0–4 scale as described by Lawrence & Wood (1968).

The results of a questionnaire on bronchitis and measurements of the forced expiratory volume by Dr I. T. T. Higgins and radiological assessments of primary and post-primary tuberculosis by Professor A. L. Cochrane on the Rhondda population sample have also been used. The Medical Research Council's definition of bronchitis, persistent sputum and at least one chest illness sufficient to cause incapacity of 1 week's duration in the previous three years, was used. The 0·75 sec forced expiratory volume was measured and expressed as the indirect maximum breathing capacity by multiplying by 40.

RESULTS

Leigh and Wensleydale random samples

In the study of 165 Leigh and 345 Wensleydale random sample chest films (Group 1) a composite score of the lung readings was used (Table 1). In this assessment a score of 1 can be disregarded since it indicates only one doubtful lesion. A score of two could be given by one minimal or two doubtful lesions and had about the same frequency in Leigh and Wensleydale. A score of three or more was twice as common in Leigh as in Wensleydale, the difference being significant after correction for age distribution (by taking an unweighted mean). It showed a steep rise in both populations but the critical age was about a decade earlier in Leigh than in Wensleydale.

A breakdown of the data showed that healed tuberculosis, apical pleural thickening, pulmonary fibrosis, and increased basal vascular markings were more common in the urban population. There were only three persons with pneumoconiosis and these were all in the urban population (Table 2). None of the differences was individually significant and it was only when the composite score was used that the significance of the association between lung affection and urban living became apparent. A grading for emphysema was also made but showed no urban–rural difference.

There was no evidence that rheumatoid disease played an important aetiological role in the lung changes found in these random samples. Only six of the ninety-four persons with a composite score of 2 or more had clinical evidence of rheumatoid arthritis (grade 2–4) compared with 5·5 expected. There was, however, suggestive evidence of an association between rheumatoid factor and the lung changes which were observed. Five of the ninety-four persons with a composite score of 2 or more for lung changes had a positive SCA test compared with 2·3 expected.

Relationship of lung pathology to SCA test

To study this relationship in a larger number of seropositive individuals all persons in four surveys in Leigh, Wensleydale, the Rhondda and the Vale of Glamorgan who had shown a sheep cell titre of 32 or more together with two control series with lower titres have been studied (Groups 2 and 3). The age and geographical distribution of these groups

is shown in Tables 3 and 4. The mean age was slightly higher in the seropositive group but the differences were slight. Those in Leigh and Wensleydale were mainly seronegative whereas in the Rhondda and Glamorgan samples there were equal numbers of seropositive and seronegative.

TABLE 1. Lung pathology in Leigh and Wensleydale random samples (Group 1)

Age (years)	Total read	Composite score of X-ray changes*												
		0	1	2	3	4	5	6	7	8	9	10	11	12+	3+
Leigh															
15–24	35	34	0	1											0%
–34	27	23	0	2	0	1	0	1							7%
–44	34	25	3	4		2									6%
–54	55	34	1	5	8	4	0	1	1	1					27%†
–64	0														
65+	14	9	0	3								2			14%
Total	165	125	4	15	8	7	0	2	1	1		2			13%†
Wensleydale															
15–24	63	58	0	5											0%
–34	37	35	2												0%
–44	75	61	2	7	1	2	0	1	0	0	0	0	0	1	7%
–54	68	57	1	8	2										3%†
–64	38	23	2	5	2	3	2			1					21%
65+	64	43	2	8	5	2	0	1	0	1	2				17%
Total	345	277	9	33	10	7	2	2	0	2	2	0	0	1	
Total without 55–64	307	254	7	28	8	4	0	2	0	1	2	0	0	1 >	6%†

N.B. X-rays of the lungs were not taken in the 55–64 age group in the Leigh random sample. They have therefore been omitted from the Wensleydale sample in assessing urban–rural differences, though included in assessing the relationship to rheumatoid arthritis.

* X-ray changes of tuberculosis, calcified shadows, pleural thickening, fibrosis, pneumoconiosis, Caplan's disease, increased basal vascular markings or Kerley B lines were each graded 0–4. For this table the gradings on the individual X-ray were summated.

† $P<0{\cdot}01$ Sum of χ^2 for 35–44, –54 and 65+ age groups = 15·20.

TABLE 2. Types of lung pathology in Leigh and Wensleydale random samples (Group 1)

Population sample	Total X-rayed	TB		Calcified shadows	Pleuro-thickening		Pneumo-coniosis	Basal vascular markings	Caplan	Emphysema	Fibrosis
		Active	Inactive		Apex	Base					
Leigh	165	0	8 (5%)	12 (7%)	12 (7%)	7 (4%)	3 (2%)	5 (3%)	0%	11 (7%)	6 (4%)
Wensleydale*	307	1	7 (2%)	18 (6%)	14 (5%)	11 (4%)	0%	1 (0·3%)	0%	28 (9%)	7 (2%)

*The 55–64 year age group has been omitted from the Wensleydale sample.

The most striking difference between the seropositive and seronegative groups was in the prevalence of healed tuberculosis which was present in 11% of the 104 persons with a positive SCA test but in only 3% of the seronegative persons (Table 5). Those with titres of 4–16 held an intermediate position. The disease was mainly of the post-primary type (Fig. 1). In only four was it considered primary (one seropositive and three with intermediate titres).

TABLE 3. Age distribution in relation to SCA test (Groups 2 and 3)

Age (years)	SCA titre		
	<4	4–16	32+
Total	251	66	104
15–24	5	4	3
–34	15	5	8
–44	52	21	11
–54	59	7	18
–64	59	15	34
65+	61	14	30
Mean age	53	49	56

TABLE 4. Geographical distribution in relation to SCA test (Groups 2 and 3)

Population	SCA titre		
	<4	4–16	32+
Urban			
Leigh	118	45	40
Rhondda	31	4	33
Rural			
Wensleydale	88	16	18
Glamorgan	14	1	13

The seropositive group also included significantly more persons with thickened basal pleura (Fig. 2) or with increased basal vascular markings. Though pneumoconiosis, Caplan's disease, fibrosis, and emphysema were more common in the seropositive group the numbers were too small to be significant. Calcified shadows were present in much the same proportion in the three groups. Of the five seropositive persons labelled fibrosis, four had healed tuberculosis. The fifth had only minimal fibrosis.

When samples were further subdivided into rheumatoid and non-rheumatoid groups it was found that the association between the SCA titre and X-ray evidence of healed tuberculosis was present in both (Table 6). This also applied to thickening of the basal pleura,

TABLE 5. Type of lung pathology in relation to SCA test (Groups 2 and 3)

Pathology	SCA titre					
	<4		4–16		32+	
Total	251		66		104	
Inactive TB	8	3%*	5	8%	11	11%*
Calcified shadows	28	11%	10	15%	14	13%^{NS}
Thickened pleura; apical	12	5%	1	2%	6	6%
basal	11	4%	5	8%	12	12%*
Pneumoconiosis	10	4%	1	2%	10	10%^{NS}
Caplan's disease	1	0·4%	0	0%	6	6%^{NS}
Fibrosis	8	3%	2	3%	5	5%
Basal vascular markings	11	4%†	2	3%	13	13%†
Emphysema	22	9%	8	12%	15	14%^{NS}
Kerley B lines	2		0		0	

* $0{\cdot}05 > P > 0{\cdot}01$. † $P \simeq 0{\cdot}04$.

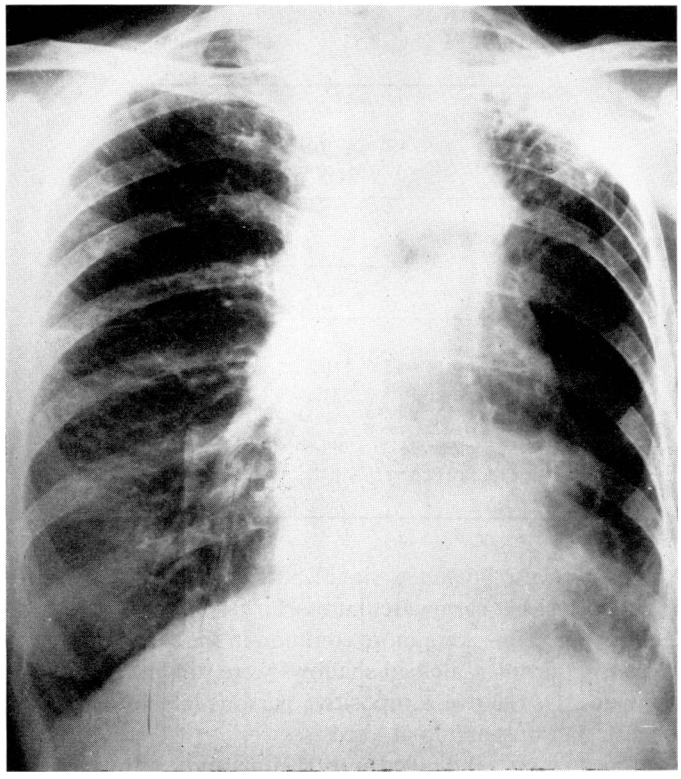

FIG 1. Healed pulmonary tuberculosis in female aged 70 with a SCA titre of 128, LF titre of 5120. No arthritis.

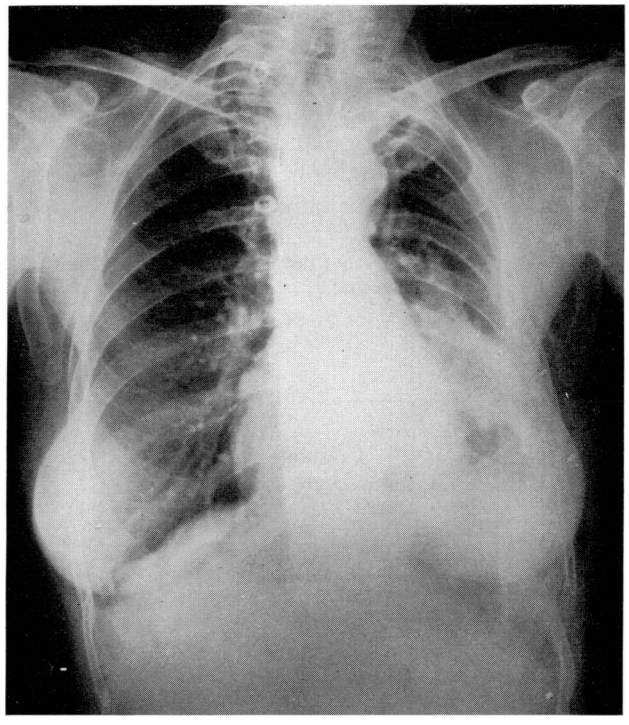

FIG. 2. Basal plural thickening in female aged 70 with SCA titre of 128, LF titre of 12,240. Grade 4 rheumatoid arthritis.

TABLE 6. Type of lung pathology in relation to SCA test (Groups 2 and 3)

	No clinical RA			Clinical RA		
	SCA test					
	<4	4–16	32+	<4	4–16	32+
Healed tuberculosis	3%*	8%	11%*	0%	0%	10%^{NS}
Calcified shadows	10%	15%	12%	17%	20%	16%
Thickened pleura: apical	5%	2%	5%	4%	0%	8%
basal	4%	8%	11%	4%	0%	13%
Pneumoconiosis	3%	2%	8%	9%	0%	13%
Caplan's disease	0·4%	0%	6%	0%	0%	5%
Fibrosis	3%	3%	6%	0%	0%	3%
Basal vascular markings	5%	3%	6%	0%	0%	24%^{NS}
Emphysema	10%	13%	9%	0%	0%	24%^{NS}
Kerley B lines	0·9%	0%	0%	0%	0%	0%
Total X-rayed	228	61	66	23	5	38

* $P \simeq 0{\cdot}05$. NS = not significant.

pneumoconiosis, Caplan's disease and diffuse fibrosis, but increased basal vascular markings and emphysema showed a relationship to the SCA test only in those with arthritis.

When all those with fibrosis or calcification in the lungs or pleura whether tuberculous or pneumoconiotic or of unknown origin were grouped together it was found that 47% of the seropositive individuals had such lung pathology compared with 25% of those with a negative SCA test (Table 7). This was not due to differences in age distribution between the seropositive and seronegative groups since only 28% of the seropositive group would be

TABLE 7. Lung pathology and the SCA test (Groups 2 and 3)

Population sample	Total tested	SCA titre		
		<4	4–16	32+
Urban				
Leigh X-rayed	203	118	45	40
Lung pathology present	61	31	12	18
Rhondda X-rayed	68	31	4	33
Lung pathology present	37	13	2	22
Rural				
Wensleydale X-rayed	122	88	16	18
Lung pathology present	23	14	4	5
Glamorgan X-rayed	28	14	1	13
Lung pathology present	8	4	0	4
Total X-rayed and tested	421	251	66	104
Per cent with lung pathology				
Urban	36%	29%*	27%	55%*
Rural	21%	18%	24%	29%
Urban and rural observed		25%	27%	47%*
expected		27%	25%	28%*
Urban				
Total	271	149	49	73
Miners No. X-rayed	74	37	8	29
Lung pathology present	46	20	3	23
		54%*	38%	79%*
Male non-miners No. X-rayed	62	36	11	15
Lung pathology present	21	11	3	7
		31%	27%	47%
Females No. X-rayed	135	76	30	29
Lung pathology present	31	13	8	10
		17%^{NS}	27%	34%^{NS}

Expected rate based on Leigh and Wensleydale random samples corrected for age.

* $P<0{\cdot}01$. NS = not significant.

expected to have lung pathology on the basis of age. Those with titres of 4–16 had little more pathology than the seronegative group. The urban population showed the most significant relationship between the SCA test and lung pathology. Within the urban group the coalminers had more lung changes than non-mining males and the latter had more than the females, but in each category there was the same relationship to the SCA test, and, though this was significant only in the miners it was of the same order in all categories.

When each group was divided into those with and without rheumatoid arthritis there was a relationship between SCA titre and lung pathology in both groups, but it was significant only in those without arthritis (Table 8). It was, however, of the same order in those with arthritis, the lack of significance being due to the small numbers available. The relationship between SCA titre and lung pathology in non-rheumatoid subjects, though highly significant in the urban populations, was not found in the rural areas.

TABLE 8. Lung pathology and the SCA test (Groups 2 and 3)

		No clinical RA				Clinical RA			
		SCA titre							
		Total	<4	4–16	32+	Total	<4	4–16	32+
Urban	No. X-rayed	229	136	44	49	42	13	5	24
	Lung pathology	82	42*	12	28*	16	2	2	12
Rural	No. X-rayed	126	92	17	17	24	10	0	14
	Lung pathology	20	15	4	1	11	3	0	8
Urban+rural									
	No. X-rayed	355	228	61	66	66	23	5	38
	Lung pathology	29%^{NS}	25%*	26%	44%*	41%^{NS}	22%	40%	53%

* $P \simeq 0{\cdot}01$.

TABLE 9. Relationship of bronchitis to the SCA test (Groups 2 and 3)

	Initial SCA positive titre (32+)		Initial SCA negative titre (<32)	
	Total questioned	Bronchitis	Total questioned	Bronchitis
Leigh follow up	58	2 } (3%)	118	10 } (7%)
Wensleydale follow up	16	0 }	85	5 }
Rhondda stratified sample	24	3 (13%)	681	112 (16%)
	LFT only positive		LFT negative	
Leigh follow up	12	1	90	12
Wensleydale follow up	27	3	60	2
Total	39	4 (10%)	150	14 (9%)

Data from Rhondda based on 1958 survey (Higgins & Cochrane, 1961).

Bronchitis

Bronchitis was slightly less common in individuals with a positive SCA test in Leigh, Wensleydale and the Rhondda (Groups 2 and 3) but the differences are not significant and are small compared with that between the Rhondda and the other two areas (Table 9). The sample in the Rhondda from which these figures were taken was equally divided between miners and non-miners. This and the nature of the coal mined in the area accounts

for the high prevalence of bronchitis in the Rhondda group. Rheumatoid factor reacting with human γ-globulin showed no association with bronchitis.

On follow up there were thirty-six persons in Leigh and Wensleydale with a positive SCA test and none of these had bronchitis, whereas 229 had a negative SCA test (titre <32) and seventeen had bronchitis. This difference is also not significant but it is clear that bronchitis as defined here does not stimulate rheumatoid factor production. Whether rheumatoid factor protects against bronchitis is less certain.

The indirect maximum breathing capacity (IMBC) was also measured in the Rhondda

TABLE 10. Relationship of SCA titre to indirect maximum breathing capacity (IMBC) in Rhondda, Leigh, Wensleydale and the vale of Glamorgan (Groups 2 and 3)

Age	Reciprocal of sheep cell agglutination titre				
	<4	4	8–16	32–64	128+
All ages					
No. of individuals tested	715	42	43	30	21
Mean IMBC	86	86	77	68	66
Age 55–64					
No. of individuals tested	309	16	18	22	
Mean IMBC	72	66	60	62	

TABLE 11. Relationship of SCA test to cigarette smoking (Group 3)

Total smoked in g per day	Total tested	Positive SSC No.	%
0	186	6	3
1–14	256	11	4
15+	181	5	3
Ex smokers	84	3	4
Total	707	25	

and Glamorgan populations and in a proportion of the Leigh and Wensleydale samples (Groups 2 and 3). It was compared with the SCA titre (Table 10). The mean IMBC was 86 in those with an SCA titre of <4, dropping to 66 in those with a titre of 128–1024. The scatter in each titre range was considerable and such differences as there are cannot be considered significant. As both the IMBC and the SCA test are age related the 55–64 year age group has been analysed separately. The mean IMBC in those with a positive SCA test was again not significantly less than in the seronegative group.

Cigarette smoking and rheumatoid factor

In view of the known association between the IMBC and cigarette smoking (Higgins & Cochrane, 1961) a comparison has been made between cigarette smoking and the SCA titre

in Group 3 (Table 11). Smoking habits were recorded in six categories as advocated by Doll & Hill (1950), but have been reduced to four in the table because of small numbers. There was no relationship between the amount smoked and the SCA test, 3–4% in each smoking category having a positive test. Thus, if there is a substance in the atmosphere which directly or indirectly stimulates the production of rheumatoid factor it would not appear to be present in tobacco smoke.

DISCUSSION

An association between lung disease and rheumatoid arthritis, first described by Ellman in 1947 has attracted considerable attention. Ellman regarded a chronic diffuse fibrosing bronchopneumonia as characteristic. This was confirmed by Dixon & Ball (1957), and has since been described on a morbid anatomical basis as fibrosing alveolitis (Turner-Warwick, 1967; Scadding, 1969). It has been found in association with rheumatoid factor in the absence of arthritis and more commonly without evidence of either. It occurs only rarely in patients with rheumatoid arthritis, and Scadding considers that at most the two diseases may share a factor in multifactorial causation.

Intrapulmonary nodules of the Caplan type or having a histological structure similar to rheumatoid subcutaneous nodules show a closer association with rheumatoid arthritis and pleural effusions may be associated with pleural 'rheumatoid' nodules. Rheumatoid pleural effusions, which often have an unusually low glucose content, are significantly more frequent in rheumatoid patients than in controls (Christie, 1954; Horler & Thompson, 1959; Walker & Wright, 1967; Scadding, 1969; Turner-Warwick, 1969). References in the literature to the association of lung disease and rheumatoid serum factors have been concerned mainly with diffuse pulmonary fibrosis (Tomasi, Fudenberg & Finby, 1961; Spiera, 1963) or those forms encountered in coalminers such as Caplan's (1953) syndrome and progressive massive fibrosis (Wagner & McCormick, 1967; Lindars & Davies, 1967). These have been fully discussed by Scadding (1969).

In about 35% of Caplan's cases lung changes and rheumatoid factor are present in the absence of arthritis (Miall *et al.*, 1953; Davies & Lindars, 1968) suggesting that the antiglobulin is being produced in the diseased lung, and this is confirmed by the relationship between the severity of the Caplan lesion and the SCA titre (Gorringe, 1962). This apparently applies also in progressive massive fibrosis since in miners with rheumatoid arthritis the titres of rheumatoid factor are higher in subjects with progressive massive fibrosis than in those with normal chest X-rays, though the severity of the arthritis is not increased in such cases (Ball, 1955). Increased titres have also been found in progressive massive fibrosis without arthritis (Wagner & McCormick, 1967), and Bonomo and his colleagues (Bonomo, Gillardi & Tursi, 1965) have reported a positive test using human FII globulin as substrate in 40% of patients with chronic bronchitis but only in those associated with hypergammaglobulinaemia, and the titre was markedly reduced by antibiotic treatment. The SCA test was positive in 18% of cases.

Little mention has been made of tuberculosis in the literature though Rheims and his colleagues (1957) found the LF test positive in 22% of cases, Dresner & Trombly (1959) in 13% and Singer and his colleagues (1962) in 13% of active cases though not related to disease activity. Gundel (1969) mentions the high prevalence of a number of rheumatoid factors in the serum of miners and the early appearance of tuberculin allergy in these workers.

The present study indicates that there is a significant association between lung pathology and rheumatoid factor production in populations in England and Wales and that lung disease may be responsible for some 19% of the rheumatoid factor production. This is not surprising when one considers the immunological potential of the lung, an organ rich in immunologically competent cells (Askonas & Humphrey, 1958). Evidence of rheumatoid factor production in the lungs has been demonstrated in Caplan's disease and silicosis, but not so far in other lung disease. Lung disease plays a more important role in urban than in rural populations and in miners than in non-miners, and could account for the greater frequency of positive tests in urban populations.

Rheumatoid lung disease appears to play a relatively minor role in this association since the relationship between lung pathology and rheumatoid factor is much the same in those with and without arthritis. This is to be expected since the diffuse pulmonary infiltration and fibrosis which accompanies rheumatoid arthritis is a rare disorder and would be unlikely to turn up in so small a sample (Ellman, 1947; Patterson, Harville & Pierce, 1965; Stack & Grant, 1965; Walker & Wright, 1969). The most significant changes found in the seropositive individuals in these populations were fibrosis in the upper zones, characteristic of healed tuberculosis, and thickened basal pleura which may also have been tuberculous.

TABLE 12. Severity of rheumatoid arthritis (mean grade of clinical RA) in relation to SCA and lung pathology (Groups 2 and 3)

	SCA positive	SCA negative
Lung pathology	3·0	2·3
No lung pathology	2·9	2·2

Some of those with thickened pleura gave a history of one or more attacks of pneumonia, but in most there was only a vague history of chest troubles. Though Miall (1955) and Cobb & Hall (1965) found some association between tuberculosis and rheumatoid arthritis it would seem unlikely that tuberculosis or other lung pathology is aetiologically related to arthritis since this was no more common in those with lung changes in our series than expected in random samples, the prevalence of tuberculosis being 6% in those with and also in those without arthritis. The relationship between the SCA test and healed pulmonary tuberculosis or thickened basal pleura, moreover, is similar in those with and without arthritis, confirming the opinion of Stack & Grant (1965) who found no association between apical tuberculosis and arthritis. It is interesting to consider whether tuberculosis or other lung disease plays a part in determining whether rheumatoid arthritis is seropositive and contributes, possibly by acting as a Freund's adjuvant to the more serious prognosis usually associated with seropositive arthritis. If this were the case it would be expected that the arthritis would be more severe in populations with a high rate of seropositivity such as our urban populations or, for example, the Pima Indians in Arizona, but this has not been found to be the case (Kellgren, 1966; Lawrence *et al.*, 1966; Bunim, Burch & O'Brien, 1964). In the present study (Groups 2 and 3) the mean severity of the arthritis was somewhat greater in the seropositive than in the seronegative individuals as would be expected, but was quite unaffected by the presence of lung pathology in either group (Table 12). It would

thus appear that lung disease simply adds another source of rheumatoid factor. In this connection it is of interest that Bonomo (1965) found the concentration of rheumatoid factor-containing cells to be in the affected tissues, e.g. the liver in hepatitis, the synovium in rheumatoid arthritis, and the bone marrow in macroglobulinaemia. He concluded that rheumatoid factor production was the result of local antigenic stimulation.

In the present study healed pulmonary tuberculosis shows the most significant association

TABLE 13. SCA in persons with healed tuberculosis in Rhondda stratified sample (Group 3)

Age (years)	Healed primary tuberculosis				Healed post primary tuberculosis			
	SCA titre				SCA titre			
	Total	4–16	32+		Total	4–16	32+	
			Obs	Exp			Obs	Exp
Males								
35–44	20	5	1		12	2	1	
–54	17	2	1		11	0	0	
–64	35	1	3		26	3	0	
Females								
55–64	4	1	1		12	2	0	
Both sexes	76	9	6	2·9[NS]	61	7	1	2·5

	Grade of clinical RA													
							Expected							
	Total	0	1	2	3	4	2–4	3–4	Total	0	1	2	3	4
Males														
35–44	20	15	4	1					12	12				
–54	16	16							11	8	3			
–64	35	33		1	1				26	24	2			
Females														
55–64	4	4							12	10	2			
Both sexes	75	68	4	2	1		3·3	1·1	61	54	7			

NS = not significant.

with rheumatoid factor and this was mainly of the post primary type. A similar conclusion of an association between tuberculosis and the SCA test was reached by Cochrane (personal communication) in a study of lung X-rays from the entire Rhondda population sample but the association was with primary tuberculosis (Table 13). Individuals with primary tuberculosis had more than twice the expected number of positive SCA tests. As, however, there were only seventy-six of them the numbers were not significant. The cases of post primary tuberculosis had rather less than the expected amount. Clinical evidence of

rheumatoid arthritis occurred with exactly the expected frequency in persons with primary tuberculosis and was not found in those with post primary tuberculosis.

Tuberculosis might stimulate rheumatoid factor production in one of two ways. It might act as a Freund's adjuvant and so stimulate the formation of auto-antibodies such as rheumatoid factors or the rheumatoid factor might be formed in response to the presence of altered γ-globulin. A Freund's adjuvant mechanism would seem unlikely since IgM production is not usually stimulated by adjuvant and experimental adjuvant arthritis is not associated with rheumatoid factor production (White, 1968; Pearson, 1964). The second mechanism would be expected to operate when antibodies, combined with antigen, had access to the lymphatic system. Humoral antibodies are produced to certain protein and carbohydrate antigens in the tubercle bacillus and tuberculosis, because of its prolonged course and the persistence of the organism in the healed stage, would seem ideally suited to the production of rheumatoid factor. In earlier studies by one of us (J.B.) few patients with active tuberculous infection had a positive SCA test despite extensive lung disease, and it would seem that rheumatoid factor is inhibited during the active stage, possibly by being bound to γ-globulin as shown experimentally by Hannestad (1968). High serum levels of γ-globulin are found in the active stage (Houston & Lawrence, 1955).

TABLE 14. LFT and lung pathology in Wensleydale and Leigh

		Total	Lung pathology	
			Observed	Expected
I	LFT positive alone	40	22 55%	10·9
II	SCAT+LFT Positive	29	17 59%	7
III	SCAT+alone	9	4 44%	1·

The association of increased basal vascular markings with a positive SCA test in our study appears to be limited to those with rheumatoid arthritis. This confirms an earlier study by Locke (1963) and we would, therefore, regard this as an extra-articular manifestation of the rheumatoid process. Roujeau & Amouroux (1968) found vascular changes in 96% of lungs of rheumatoid patients at autopsy. The lesions affected the precapillary arterioles and less frequently the arteries of medium size. The thickening was due to homogeneous hyaline-like substance.

It must be considered whether the increased evidence of pathology in the lungs in seropositive individuals simply reflects an increased tendency of the tissues in such individuals to react. Klosterkötter (1965) found that rabbits, in which the production of antiglobulin factors had been induced by prolonged immunization with heterologous serum proteins or gram-negative bacteria, when subjected to experimental silicosis showed more extensive processes and the nodules were richer in cells. Verhaeghe & Delcambre (1967) found that 82% of arthritics exposed to silica dust had radiological evidence of silicosis whereas only 52% of non-arthritics matched for age and duration of exposure had such evidence. Caplan's disease is also an example of an excessive tissue response by arthritics to silica dust and this also occurs in seropositive persons without arthritis. Caplan's disease does in

fact occur in persons who are neither arthritic nor seropositive but the nodules are scanty. Those with multiple nodules are nearly always seropositive and more often have arthritis (Davies & Lindars, 1968). We feel, however, that the changes seen on the X-ray could not be altogether explained on this basis.

The possibility that the rheumatoid factor which is present in persons with lung pathology differs from that found in rheumatoid arthritics must be considered. It is a feature of the rheumatoid factor associated with arthritis that it reacts with both rabbit and altered human γ-globulin (Valkenburg *et al.*, 1966; Heimer & Schwartz, 1961; Williams & Kunkel, 1963). In a proportion of the respondents in Leigh and Wensleydale the latex fixation test was performed in addition to the SCA test, and seventy-eight sera had one or other test positive (Table 14). It was thus possible to divide these seventy-eight persons into three groups. Group I had a positive LF test associated with a negative SCA test, Group II had both tests positive and Group III had a positive SCA test with a negative LF test. Each of the three groups had twice the expected amount of lung pathology. It may be concluded that the rheumatoid factor in lung disease is mainly mono-reactive and thus differs from that found in rheumatoid arthritis. A feature of those in Group I was the high prevalence of calcified shadows (30%) and also of emphysema (35%).

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ABBREVIATIONS

LFT	latex fixation test for rheumatoid factor.
IMBC	indirect maximum breathing capacity.
SCA	sheep cell agglutination.