THE LUNGS IN RHEUMATOID ARTHRITIS

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I. INTRODUCTION

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The term rheumatoid disease, as opposed to rheumatoid arthritis, draws attention to the systemic complications which may occur in this condition, and it is well known that there may be widespread visceral involvement by specific or non-specific pathological processes. Considerable attention has been devoted to the lesions affecting the pleura and lungs and the resulting clinical manifestations. Those described can be classified under one of the following headings:-

i) Pleural lesions

ii) Intra-pulmonary lesions

Pleural lesions

Both dry pleurisy and pleurisy with effusion are considered to occur as a manifestation of rheumatoid arthritis (Thompson, 1965). Although from pathological studies it might be anticipated that attacks of dry pleurisy would be more frequent in rheumatoid subjects, the evidence for this is scanty. Indeed, in a comprehensive, controlled investigation Short et al. (1957) did not find a significantly higher incidence of pleurisy in their rheumatoid population, although attacks were in fact more frequent than in the control group. Little else in the way of systematic investigation has been undertaken on this point. On the other hand, the evidence, which is reviewed later, is strongly in favour of the concept that pleural effusion may be an integral feature of the rheumatoid process. It is therefore surprising that the large controlled studies which have been undertaken to date have failed to demonstrate a significantly higher incidence of pleural effusion in rheumatoid arthritis. However, no series of sufficient size has yet been compared with an entirely satisfactory control group.

There have been conflicting reports on the incidence of rheumatoid

pleuritis, probably largely due to the method of selection of patients for study. However, it is clear that there has been a striking male predominance in the cases described, for which no satisfactory explanation has yet emerged.

A factor which makes the subject difficult to investigate is the lack of positive criteria for the diagnosis of rheumatoid effusions, which in most of the cases previously described, has been made largely by exclusion. The diagnostic measures which are available require further evaluation. Although some attention has been paid to the accompanying arthritis, there has been no detailed comparative study from this point of view.

It is interesting to observe that Fuller (1860) made reference to pleurisy as an accessory feature of rheumatoid arthritis and one hundred years later the situation is still far from clear.

Intra-pulmonary lesions

These are:-

(a) Caplan's syndrome

(b) non-pneumoconiotic, intra-pulmonary, rheumatoid nodules

(c) interstitial lung disease

(d) an intimal fibrosis of the small pulmonary arteries and arterioles, leading to pulmonary hypertension.

Caplan's syndrome has been widely investigated and has been established as an entity by epidemiological methods. The occurrence of non-pneumoconiotic, intra-pulmonary, rheumatoid nodules has been confirmed by pathological means, but are a rare feature of the disease.

The third intra-pulmonary lesion is usually termed diffuse interstitial pulmonary fibrosis, which throughout this thesis will be referred to as interstitial lung disease. This term has been adapted

from that suggested by Stack et al. (1965) for the idiopathic type and conforms with that employed by Stack and Grant (1965).

Interstitial lung disease has probably aroused more interest in recent years than any of the other pleuro-pulmonary manifestations of rheumatoid arthritis. After initial reluctance to accept that the lung disease was related to the arthritis (Aronoff et al., 1955) most authorities now do so. The evidence supporting the validity of the association is strong and is reviewed later. It is, however, of interest to record at this stage that comparative studies to evaluate the concept have recently been published (Talbott and Calkins, 1964; Stack and Grant, 1965) without a conclusive result, so clearly some dispute persists. There is, therefore, a need for a large controlled investigation of rheumatoid subjects to settle this issue. Such a study should also give an indication of the incidence, which has varied from 1.1 per cent (Patterson et al., 1965) to as high as 28 per cent (Locke, 1963).

According to Cruickshank (1959) the earliest pathological change is an interstitial pneumonia, which in some cases is reversible. Once fibrosis becomes established the prognosis is generally believed to be poor. It would therefore, be interesting to ascertain whether it is possible to detect the earlier stage by means of lung function tests, when radiographic changes are either absent or equivocal. If this were so, the scope of therapy, which in the later stage is limited, might be enlarged.

Although some attention has been paid recently to the details of the arthritis in these cases (Patterson et al., 1965), further investigation is required. Such studies and perhaps evaluation of environmental factors might give an indication of why only selected individuals in

the rheumatoid population develop this complication.

Finally, an intimal fibrosis of the small pulmonary vessels, as an isolated intra-thoracic complication of rheumatoid arthritis and leading to pulmonary hypertension, has been described. This is of great rarity.

A comparatively neglected aspect of the lungs in rheumatoid arthritis has been the relationship, if any, with pulmonary infections. This subject will be reviewed in detail later. Because of the conflicting views about the incidence of pneumonia and the suggestive evidence of an association between bronchiectasis and rheumatoid arthritis, it was decided to investigate other pulmonary conditions in addition to those regarded as being an integral feature of the disease.

Purpose of the investigation

Despite the attention they have received, several aspects of the pleuro-pulmonary manifestations of rheumatoid arthritis require further investigation. The study to be described was designed primarily to answer some of the outstanding questions, and as a second aim to assess in rheumatoid patients the significance of other lung diseases particularly pulmonary infections. It was not anticipated that any contribution would be made to Caplan's syndrome since it has already been well investigated in appropriate communities, and little information concerning intra-pulmonary nodules and pulmonary hypertension as an isolated lesion was expected to emerge because of their extreme rarity. The main emphasis was, therefore, on the pleural lesions, the interstitial lung disease and pulmonary infections.

Outline of the investigation

The pleuro-pulmonary manifestations of rheumatoid arthritis are

either uncommon or rare. It was therefore decided to collect data from cases described in the literature and to analyse them by the same method as will be employed in this investigation. By this means it was hoped to create a more accurate picture of the various lesions than has been possible from the inevitably small series of others. It was felt that not only would this yield information of value, but also the data assembled would form a useful basis for comparison with the cases collected by the present author. The literature was therefore carefully scrutinized and cases with pleural effusion, intra-pulmonary nodules or interstitial lung disease were accepted for analysis if the diagnosis had been proven. If absolute proof was lacking but the diagnosis of rheumatoid involvement of the pleura or lungs seemed the most reasonable one from the facts presented, such cases were included. If it seemed to the author that an alternative pathological process was more likely, these cases were discarded.

It was not always certain from the descriptions given that the criteria for the diagnosis of definite or classical rheumatoid arthritis were fulfilled (Ropes et al., 1959). However, all patients accepted for review had a polyarthritis of rheumatoid type. An attempt was made to determine the extent of the arthritis by the method employed by the author, but this was not always possible because of lack of information. Similar difficulty was encountered in assessing whether subcutaneous nodules and systemic lesions were actually absent, when they were not mentioned in the case reports. The policy here was to accept them as absent if the case was described in sufficient detail for it to be reasonable to expect them to be mentioned if present. The radiographic descriptions of the joints did not always permit grading by the method employed by the author. Despite the obvious limitations of such an analysis the necessary information was in fact available in sufficient

cases for the purpose.

It was clear that several hundred patients with rheumatoid arthritis would be required for study. The essential requirements of the control group were that they should be collected in the same way as the study group, and should consist of subjects in whom there was no known association with respiratory disease. The best available population for this purpose was one with degenerative joint disease. The ideal method would have been to collect consecutive rheumatoid patients and a control group, and to observe them over many years. This, however, is a counsel of perfection not readily achieved in a busy rheumatic unit. It was therefore decided to study a population of rheumatoid subjects selected only by their attendance at hospital because of arthritis, and to include both new and follow up patients in order to cover a wide spectrum of rheumatoid arthritis in terms of both duration and severity. The control group consisted of patients with degenerative joint disease collected in an identical manner. By careful clinical and radiographic study with appropriate other investigations, including lung function tests in selected patients, a comparison has been made between the two series.

It is appreciated that more than one pleuro-pulmonary complication of rheumatoid arthritis may be present in the same patient. However, in the review of the literature and the presentation of the results the lesions will be dealt with separately for the sake of clarity.

II. REVIEW AND ANALYSIS OF LITERATURE

1. RHEUMATOID PLEURITIS

Although the view is widely held that pleural lesions, usually resulting in pleural effusion, may occur as an integral part of the rheumatoid process (Thompson, 1965), doubt has been expressed regarding the validity of the association (Aronoff et al., 1955). It is important, therefore to examine the evidence giving rise to this concept, which has been based on both pathological and clinical observations.

Pathological observations

Lesions regarded as rheumatoid granulomata have been described in the pleura, examined at autopsy or on biopsy, by several authors (Table 1). Although from the description given the pathological features have been divided into definite and probable, on the basis of the other information presented there seems no reasonable doubt that the lesions were rheumatoid in origin in each case. In 11 of these cases pleural effusion was present and in 9 of them this had been demonstrated on chest radiography. In one case (Bennett et al., 1940) no information was given. In one other (Castleman and McNealy, 1965) there was no clinical or radiographic evidence of pleural disease.

In addition to these lesions, various non-specific processes have also been described in the pleura in patients with rheumatoid arthritis and pleural effusion (Ball, 1954; Bevans et al., 1954; Douglas et al., 1956; Heller et al., 1956; Ward, 1961; Carr and Mayne, 1962; Mattingly, 1964; Poppius and Tani, 1964). Ball's case had both rheumatoid arthritis and polyarteritis nodosa and it is difficult to be sure of the precise pathogenesis of the pleural inflammation. However, both cases of Bevan et al. had longstanding nodular rheumatoid arthritis with widespread visceral involvement in addition to the pleural lesions. Poppius and Tani did not describe their cases in great detail and one of Mattingly's

Table 1. Rheumatoid granulation tissue in the pleura.

Year	Authors	Place	Classification	Comment
1940	Bennett et al.	Boston	Probable	Histologically more like rheumatic fever than rheumatoid arthritis.
1948	Gruenwald	New York	Probable	Diffuse rather than nodular.
1948	Raven et al.	London	Probable	Not so characteristic as some other lesions present
1954	Ellman et al.	London	Definite	
1959	Horler and Thompson	Newcastle	Definite	
1959	Lee et al.	California	Definite	
1960	Koepke	Milwaukee	Definite	Only minimal subjective evidence of arthritis.
1961	Cudkowicz et al.	Boston	Definite	No histology on pleura but sub-pleural intra-pulmonary nodules present.
1962	Schools and Mikkelsen	Michigan	Definite	
1962	Schools and Mikkelsen	Michigan	Definite	
1962	Schools and Mikkelsen	Michigan	Probable	
1965	Hindle and Yates	London	Definite	Involved visceral pleura and adjacent lung.
1965	Ropes and Castlemen	Massachussets	Definite	No clinical or x-ray evidence of pleural disease.

might have been tuberculous, but in his second as well as in the others to which reference is made there was no evidence of a cause other than rheumatoid pleuritis.

The third observation of pathological changes in the pleura in rheumatoid subjects is the high incidence of adhesions at autopsy. Fingerman and Andrus (1943) found pleural fibrosis and obliterative pleuritis in 23 out of 61 cases, and Baggenstoss and Rosenberg (1943) in 22 out of 30, although in 14 tuberculosis could have been the cause. Hench (1948) stated that of all accounts of complete autopsies in rheumatoid subjects recorded up to 1945 pleural adhesions were present in seventy three per cent. Aronoff et al. (1955) found a higher incidence of unilateral and bilateral adhesions in cases of rheumatoid arthritis compared with a control group, and Sinclair and Cruickshank (1956) and Cruickshank (1957) found the incidence to be twice that of a control group. Talbott and Calkins (1964) found 27 examples amongst 37 compared with 22 of 37 controls.

These pathological studies indicate that both specific and non-specific pleural lesions occur, the latter apparently also an integral part of the rheumatoid process, and almost invariably pleural effusion develops. The evidence from the high incidence of pleural fibrosis is much less convincing, since histologically these lesions are non-specific (Sinclair and Cruickshank, 1956) and could result from pyogenic or tuberculous infection, both of which may be more common in rheumatoid subjects (Lewis-Faning, 1950; Miall, 1955). Nevertheless, it seems much more likely that at least a proportion of the examples of pleural fibrosis are an end result of an earlier active rheumatoid process.

Clinical and radiographic observations

Evidence, then, from pathological observations for a rheumatoid

pleuritis is strong and it is surprising that some of the clinical and radiographic studies which have been undertaken have failed to show an increased incidence of pleural disease in rheumatoid subjects. For example, Aronoff et al. (1955) found 3 cases of pleural effusion in 130 but 4 in 130 controls, and the respective figures for pleural thickening were 8 and 4. This was an unselected hospital group which was carefully followed up, but chest x-rays were only taken in about one half when clinically indicated, and no doubt because of this the controls comprised cases referred to hospital for chest x-ray. Although the figures for pleural thickening are perhaps suggestive, those for pleural effusion certainly do not support the view that rheumatoid pleuritis is an entity. Stack and Grant (1965) reviewed the chest x-rays of 177 new cases of rheumatoid arthritis and found 4 with pleural thickening or a small effusion and 1 with a large effusion, compared with 10 cases with pleural thickening or small effusion in a control series of 177 cases seen at a neurological unit. On the other hand, Locke (1963) found 12 cases of pleural effusion amongst 54 with rheumatoid arthritis compared with 3 of 54 controls, and Talbott and Calkins (1964) in an autopsy series found 21 cases with effusions in 37 compared with 14 of 37 controls. In the latter series, however, the precise cause of the pleural effusions was not indicated.

Curiously the most convincing clinical and radiographic evidence for rheumatoid pleural effusion comes from uncontrolled investigations. Horler and Thompson (1959) found that five per cent of 180 patients with rheumatoid arthritis had a pleural effusion. Although the group was not unselected (only cases with an S.C.A.T. of 1 in 64 or greater were included) and was therefore not representative of rheumatoid disease as a whole, alternative causes were excluded. Such was the

case also in the series of Carr and Mayne (1962) who, however, only found effusions without possible alternative cause in 0.25 per cent of 10,000 patients, but the low incidence was probably due to the fact that only patients who actually had an effusion when seen at the Mayo clinic were included.

In summary, the evidence supporting the concept of rheumatoid pleuritis consists of pathological studies indicating that specific changes may occur in the pleura in some patients as well as non-specific inflammatory processes, regarded as due to rheumatoid arthritis. Some clinical studies have demonstrated pleural effusions without alternative cause in a significant number of patients. Despite lack of confirmation from the larger controlled radiographic investigations rheumatoid pleuritis appears to be an entity.

Incidence

Forty nine cases of rheumatoid pleural effusion have been described individually and reference has been made to a further 32 (Table 2). However, the overall incidence of rheumatoid pleuritis and pleural effusion is not known. One of the reasons for this is that no large unselected series of cases has yet been adequately studied. With present knowledge even this would only be an approximation since with the exception of positive findings on pleural biopsy in some cases and a very low glucose level in the fluid (Carr and Mayne, 1962) there are no positive diagnostic criteria.

Apart from the figures already quoted it is interesting to consider the impression of various observers as to incidence. Lodge (1956) thought they were uncommon, whereas Locke (1963) felt they were common and that more cases would be diagnosed if films were taken in the lateral decubitus position. There is support for the latter view, if one accepts that the increased incidence of pleural adhesions is mainly due to a

Table 2. Sources of cases of rheumatoid arthritis and pleural effusion.

Year	Author	Place	No. of cases	A	B
1948	Raven et al.	London	1	1	0
1948	Gruenwald	New York	1	1	0
1954	Ellman et al.	London	1	1	0
1954	Ellman and Cudkowicz	London	1	1	0
1954	Bevans et al.	New York	2	2	0
1954	Ball	Manchester	2	2	0
1955	Spence	London	1	1	0
1956	Emerson	London	6	6	0
1956	Heller et al.	Chicago	1	0	1
1957	Sokoloff and Bunim	Bethesda	2	2	0
1957	Smith and Rothermich	Ohio	1	1	0
1958	Mason and Steinberg	London	6	6	0
1959	Horler and Thompson	Newcastle	9	9	0
1959	Johnson et al.	Denver	1	1	0
1959	Lee et al.	California	2	2	0
1961	Ward	Blackburn	5	5	0
1961	Cudkowicz et al.	Boston	1	1	0
1962	Schools and Mikkelsen	Michigan	3	3	0
1962	Carr and Mayne	Rochester	25	0	25
1963	Locke	Manchester	1	1	0
1964	Mattingly	London	6	2	4
1964	Poppius and Tani		2	0	2
1965	Hindle and Yates	London	1	1	

A. Described individually.

B. Not described individually, or only mentioned.

previous rheumatoid pleuritis. On the facts available, however, Horler and Thompson's figure of five per cent, despite the minor limitations of their series, is probably nearest to the truth.

Sex and age

Although Lee et al. (1959) felt that the sexes were about equally affected, several authors have drawn attention to a striking male predominance (Mason and Steinberg, 1958; Horler and Thompson, 1959; Ward, 1961; Mattingly, 1964), and the comprehensive review of the literature amply confirms the views of these authors. Of 81 cases in which the sex was recorded 67 (83%) were men.

It is generally held that pleural effusion in rheumatoid arthritis tends to occur in older subjects and indeed Lee et al. (1959) stated that it did not occur under the age of forty five. However, patients in the decade 30 to 39 have been reported with rheumatoid pleuritis, although this is uncommon. Sixteen of Carr and Mayne's series were in fact over 50 with an overall average of 52 years. Of 43 other cases in the literature where the age of onset of the pleural effusion was either stated or could be reasonably deduced the average age of 34 men was 50 and of 9 women 51 years.

Temporal relation to rheumatoid arthritis

It is now widely known that pleural effusion may precede, occur simultaneously with or follow the onset of rheumatoid arthritis. In forty-one instances in the literature the relationship was either stated or could be reasonably deduced and this is indicated in Table 3 overleaf.

Table 3. Pleural effusion related to onset of rheumatoid arthritis

	Number of cases	Percentage	
Before	3	7%	49%
Simultaneous	6	15%	
Up to 1 yr. after	7	17%	
1 - 2 yr. "	4	10%	
3 - 5 yr. "	5	12%	
6 - 10 yr. "	6	15%	
11 - 20 yr. "	9	22%	
20 yr. + "	1	2%	
TOTAL	41	100%	

Where both began within a period of 4 weeks this has been considered as a simultaneous onset. As will be seen in seven per cent of cases the effusion preceded the arthritis and the intervals were 15 months, 6½ months and 2 months. In about one half of the cases the effusions developed either before or within two years of the onset of the arthritis. It was not possible to break down the series of Carr and Mayne (1962) in quite the same manner, but they found that the effusion preceded the arthritis by 4 months in 1 case, was simultaneous in onset in 1 case, and followed the arthritis by periods of from 1 week to 19 years in the remaining 23. It would seem then that generally pleural effusions are a relatively early feature of the disease, although they can still develop in long standing cases. The occurrence of pleural effusion before arthritis is of interest and the need to consider rheumatoid arthritis as a cause of unexplained effusion is clearly important. This was emphasized by the case described by Koepke (1960) and two of Ward's cases (1961). It is interesting to speculate whether in time these subjects will develop arthritis or whether, as Ward (1961) suggested,

pleural effusion may occur as the sole manifestation of rheumatoid disease.

Clinical features of arthritis

There were 41 patients in whom the extent of the arthritis could be assessed, 30 men and 11 women. Amongst the men the extent was mild in 13 (43%), moderate in 5 (17%) and severe in 12 (40%). The figures for women were 3 (27%), 1 (9%) and 7 (64%) respectively.

The presence of subcutaneous nodules has also been analysed. Presuming their absence when they were not mentioned, they were present in 16 (42%) of 38 men and in 6 (55%) of 11 women. In Carr and Mayne's series, all but one of whom were men, 12 (48%) of 25 had subcutaneous nodules.

Systemic lesions

It was clearly of interest to see whether there was any suggestion that pleural lesions were associated with other systemic manifestations of the disease and analysis of forty-nine cases in the literature is shown in Table 4.

Table 4. Systemic complications in rheumatoid arthritis with pleural effusion

	Men					Women						
	1	2	3	4	5	1	2	3	4	5	6	7
Ocular	+					+	+	+	+			
Neuropathy											+	+
Myopathy												
Amyloid												
Splenomegaly												
Arteritis		+	+	+						+	+	+
Cardiac	+			+	+		+	+	+	+	+	+
Others	+[1]						+[2]	+[3]				

1 = dural nodules 2 = renal lesion 3 = nodules in diaphragm

One other case, mentioned briefly, had pericarditis (Douglas et al., 1956), but the sex was not stated. As will be seen 8 per cent of the men had cardiac lesions, a figure not dissimilar from that of Cruickshank (1958), but these were present in 55 per cent of the women. Also in the women 36 per cent had ocular lesions, a figure greatly in excess of the usual frequency (Short et al., 1957). In his series of 100 autopsies Cruickshank found arteritis in the heart in 20 per cent and in other organs in 13 per cent. The present analysis shows that 8 per cent of the men had arteritis and 27 per cent of the women. Two women had neuropathy. It may be that systemic manifestations are associated with pleural effusion in women but not in men, but it should be noted that complete autopsies were done on only 9 of the 49 cases, 3 men and 6 women, and some of these were reported primarily because of cardiac lesions (Bevans et al., 1954) or arteritis (Ball, 1954; Sokoloff and Bunim, 1957; Johnson et al., 1959), rather than the pleural complications. Those in whom autopsies were done all had some systemic complication, and in fact account for almost all the recorded lesions. It is therefore safer to conclude at this stage that the associations so far recorded may be fortuitous, which is in keeping with Horler and Thompson's (1959) findings that there was no evidence of an increased incidence of other systemic lesions in their cases of rheumatoid pleural effusion. This, however, does not exclude the possibility that an association might exist with lesions that are clinically silent, especially other serous membrane involvement, and it is of interest that Baggenstoss and Rosenberg (1943), who suggested that pleural adhesions might be rheumatoid in origin, found associated pericardial adhesions in 10 of 22 cases.

Laboratory investigations

The haemoglobin levels recorded in cases of rheumatoid arthritis with pleural effusion are shown in Table 5.

Table 5. Haemoglobin levels in rheumatoid arthritis with pleural effusion

Hb. (g./100 ml.)	Males	Females
< 9.0	0	1
9.0 - 10.4	2	2
10.5 - 12.6	7	4
12.7 +	11	1
not recorded	18	3
TOTAL	38	11

Carr and Mayne's (1962) cases could not be dealt with in quite the same way but 11 of the 25 had a haemoglobin level of less than 12 g. per 100 mls. In the cases described the haemoglobin was sometimes recorded in percentage and sometimes in g. per 100 ml. No doubt different methods for estimating the haemoglobin were employed by different authors, but for purposes of comparison they have all been converted to g. per 100 ml., adopting the Haldane standard where 14.8 g. is equivalent to 100 per cent. The number of women is too small from which to draw conclusions. Of the men, however, 45 per cent had a haemoglobin of less than 12.6 g. per 100 ml., and assuming that all of Carr and Mayne's (1962) 11 cases with a haemoglobin of less than 12.0 grams were men their figure would be 44 per cent below this level. Taking the figures for men of all ages from the survey done by the Empire Rheumatism Council (Lewis-Faning, 1950) the respective percentages were 30.2 and 19.8. There is then a suggestion that a greater proportion of men with rheumatoid pleural effusion have anaemia compared with a male rheumatoid population.

The height of the recorded blood sedimentation rate (B.S.R.) is shown in Table 6 where both sexes are also combined for comparison with the series of ninety-five cases reported by Dawson et al. (1930).

Table 6. B.S.R. in rheumatoid arthritis with pleural effusion

B.S.R. mm. 1st. hr.	Males	Females	Total %	rheumatoid arthritis Dawson et al. (1930)
0 - 20	2	0	2 (7%)	21%
21 - 40	13	2	15 (50%)	23%
41 - 60	2	3	5 (17%)	27%
60 +	6	2	8 (27%)	28%
N.R.	15	4	19	
TOTAL	38	11	49 (101%)	99%

Fewer of those with pleural effusion had a B.S.R. below 20 but the figure for greater than 60 is almost identical. In the series of Carr and Mayne (1962) the B.S.R. was greater than 40 in 21 (84%) out of 25 cases, but the actual figures were not recorded. These results suggest that more cases with pleural effusion have a B.S.R. greater than 20 compared with a rheumatoid population, but there seems to be no evidence that they are more likely to have an excessively high sedimentation rate.

L.E. cells were stated to be absent in 24 men and 5 women of the 49 cases described in detail, but Carr and Mayne (1962) found 4 with L.E. cells among 24 in whom this test had been done, and regarded each of them as having rheumatoid arthritis and not systemic lupus erythematosus. There must be a natural reluctance to report cases of rheumatoid arthritis with pleural effusion in which L.E. cells are found, since it may then be impossible to be sure of the diagnosis and indeed Shaldon (1956) described a case of apparent rheumatoid

effusion which developed other features of systemic lupus erythematosus five years later. It is impossible to know the incidence of rheumatoid arthritis with L.E. cells in true rheumatoid effusions. However, accepting Carr and Mayne's figure of seventeen per cent there is nothing to suggest that rheumatoid patients with L.E. cells are more likely to develop effusions, since this figure is virtually the same as that of Kievits et al. (1956) in 100 consecutive unselected cases.

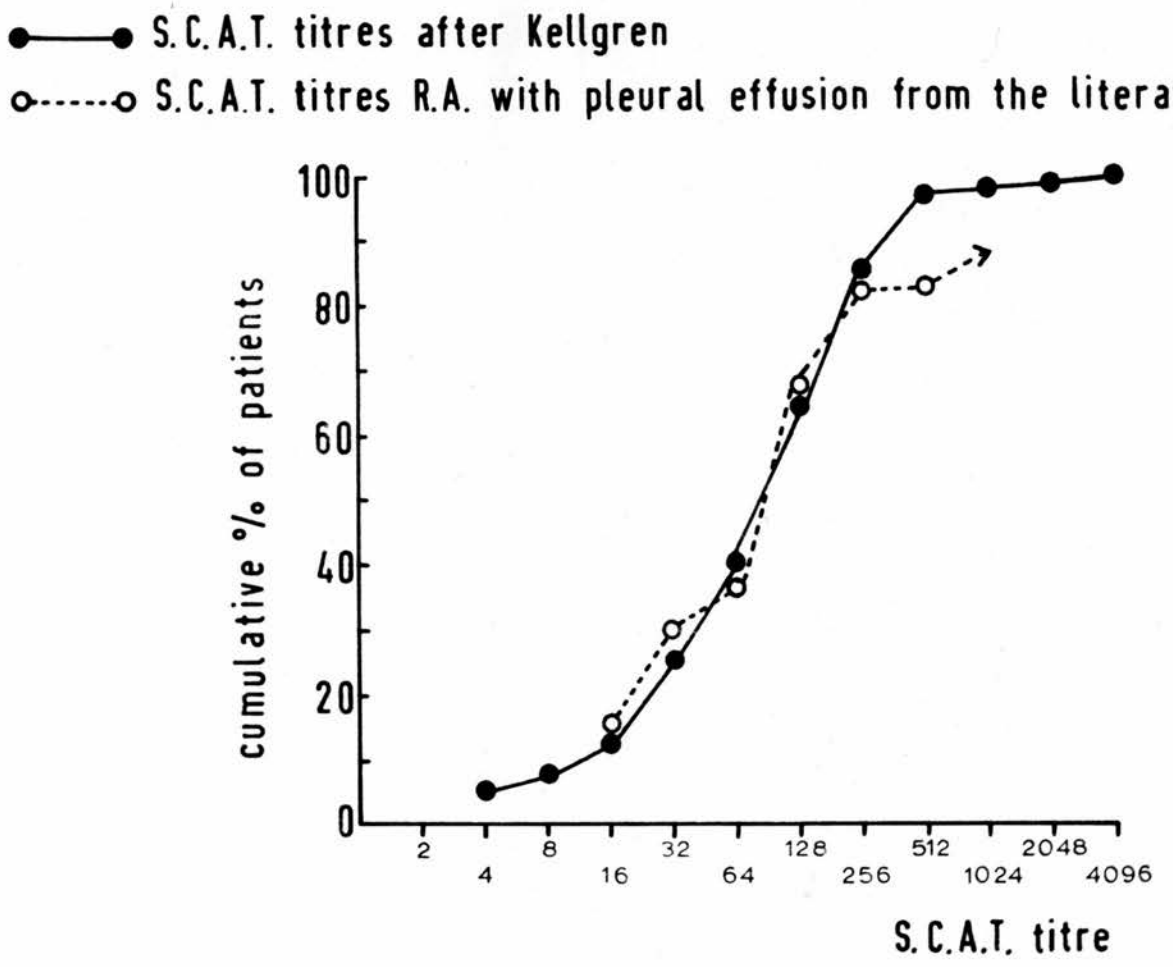
Tests for the rheumatoid factor were done in thirty nine cases and the results are shown in Table 7.

Table 7. Tests for rheumatoid factor in patients with pleural effusion and rheumatoid arthritis

S.C.A.T. (titre)							
$< 1/32$	$1/32$	$1/64$	$1/128$	$1/256$	$1/512$	$> 1/512$	positive, titre not recorded
4	4	2	8	4	-	5	5
Latex fixation test positive in 5 others. F II haemagglutination test 1:56,000 in 2 others.							

The S.C.A.T. is positive in about 85 per cent of cases of definite rheumatoid arthritis (Duthie, 1964), in 94 per cent of men and 91 per cent of women with rheumatoid arthritis confirmed radiographically, and in 94 per cent of men and 100 per cent of women with subcutaneous nodules (Hill and Greenbury, 1965). There is nothing to suggest, therefore, that effusions are more likely to occur in those with a positive S.C.A.T. Those in whom a titre for the S.C.A.T. was recorded have been charted in Figure 1 beside the results obtained by Kellgren in a rheumatoid population and quoted by Turner-Warwick and Doniach (1965). It should be noted that the titres in the pleural effusion group were from different laboratories and therefore not strictly comparable.

Fig.1 *Titre of s.c.a.t. in rheumatoid patients with pleural effusion compared with a rheumatoid population*



Nevertheless the similarity is striking and suggests that there is no correlation between pleural effusion and a particularly high titre of the S.C.A.T.

The results of the serum protein estimations have been recorded in eleven patients with rheumatoid pleural effusion and the results are shown in Table 8.

Table 8. Protein levels in the blood of 11 rheumatoid patients with pleural effusions

Albumen (G./100 ml.)	1.7*, 2.4, 3.0, 3.04, 3.1, 3.2, 3.2, 3.42, 3.5, 3.6, 6.2
Globulin (G./100 ml.)	2.1, 2.1, 2.3, 2.5, 2.5, 2.9, 3.4, 3.6, 4.3*, 4.56, 4.76

* proteinuria present

The range of normality tends to differ in various laboratories and it is not possible, therefore, to state dogmatically exactly how many of the above are abnormal. However, taking the lowest possible limit of normality for serum albumin as 3.2 g. per 100 ml., 5 of the 11 had a decreased albumin; one of these had proteinuria which could have contributed. Taking the upper limit of normal for globulin as 3.6 g. per 100 ml., the level was raised in 3 of the 11 subjects.

Joint radiographs

In twenty seven cases there was reference to x-rays of various joints. In 4 the films were normal and in 6 the changes seemed doubtful. In the remainder they were mild in 3, moderate in 1 and severe in 7. In the other six although evidence of rheumatoid arthritis was present, it was not possible to make any grading from the description given.

Aetiology

This detailed analysis of the literature revealed a higher incidence

than expected of subcutaneous nodules, of anaemia, and of a B.S.R. greater than 20 mm. 1st. hr., in subjects with pleural effusion compared with an unselected group with rheumatoid arthritis. Otherwise there were no distinguishing features, apart from some suggestion of a correlation with other systemic lesions in women. Since pleural involvement is a visceral manifestation of the disease, the positive findings might be expected, but they give no clue why men were so much more often affected than women. It seems possible that some factor additional to the disease process itself accounted for this, but Horler and Thompson (1959) were unable to find any association with previous or co-existing respiratory disease and did not feel occupational factors were likely to be responsible. However, of 49 cases described the occupation was recorded in 23, and 4 of these had been exposed to a pneumoconiotic hazard in the form of coal mining. Assuming the absence of such a hazard where there was no mention of occupation, this means that eight per cent had had contact with noxious dusts. Horler and Thompson (1959) thought that pleurisy with effusion might be "an integral male feature" of the rheumatoid process, but it is not clear why this should be so, and of course females also get similar lesions. The reason for the male predominance is as yet unknown and further studies are required to determine its cause.

Respiratory symptoms

Respiratory symptoms usually accompany a rheumatoid pleural effusion. Of 49 cases described the presence or absence of symptoms was recorded in 34. To these we can add the twenty five described by Carr and Mayne (1962). Of these 59 cases, 24 (41%) had chest pain, usually of pleuritic type, 23 (39%) had dyspnoea and 16 (27%) had a cough. Fever, sometimes said to be a common feature, was in fact only mentioned in 7 (12%).

Haemoptysis was present in two patients but this cannot be attributed to a purely pleural lesion and implies intra-pulmonary disease, which was present in one who had intra-pulmonary nodules. It is important to appreciate that there may be no symptoms attributable to the pleurisy and this was in fact the case in seventeen (29%). Apart from respiratory symptoms some authors have commented on the fact that the development of pleurisy is often associated with an exacerbation of arthritis (Emerson, 1956; Mason and Steinberg, 1958). This is apart from those cases with a simultaneous onset of pleural and arthritic disease. Carr and Mayne (1962) found that an associated exacerbation of arthritis occurred in 7 cases, was questionable in 6 and absent in 12.

Characteristics of effusions

The pleural effusion may be unilateral or bilateral. Such information was recorded in 41 of the 49 cases described in detail, and to these we may again add the 25 of Carr and Mayne (1962), as well as 1 of Poppius and Tani (1964), making a total of 67. Of these, fourteen (21%) were bilateral. Of the remainder, they occurred on the right side in thirty four (50%) and on the left side in twenty (30%). The size of the effusions varied considerably, some being very small and others quite large. The fluid itself when mentioned was described as either straw coloured or greenish yellow. In one of the specimens obtained by Carr and Mayne (1962) it was tinged with blood, but presumably this was likely to have been traumatic. The cytology has been variable, a predominance of polymorphs, of lymphocytes, of monocytes or a mixed cell population all having been recorded. Differential cell counts on the pleural fluid, therefore, are of no positive help in diagnosis. The protein content of twenty five specimens has been record-

ed, the level varying from 2.7 to 7.65 g. per 100 ml. All but one was greater than 3.0 g. per 100 ml., which merely indicated that the fluid was an exudate (Zinneman et al., 1957). The glucose content of the pleural fluid has been recorded in 12 cases, in 9 by Carr and Mayne (1961; 1962) and in 3 by Schools and Mikkelsen (1962). In an investigation of pleural glucose levels Carr and Power (1960) found very low levels in patients with rheumatoid arthritis. Carr and Mayne (1962) reported levels on 11 specimens from 9 patients and found that in 10 of them the figure was less than 17 mg. per 100 ml. Schools and Mikkelsen (1962) recorded levels of 3 mg. per 100 ml. in 1 of their cases and an absence of glucose in the other 2.

The pleural glucose level depends upon the rate of diffusion from the blood and the rate of breakdown. Durieu (1954) showed that in general when the glucose level in pleural liquid was less than in the blood, in some, but not all, cases this could be correlated with the number of cells present. Usually the count was between 1,500 and 3,000 per c.mm. when there was an important fall in pleural glucose, whereas when the pleural glucose exceeded the blood level, for example in transudates, the cell count was less than 700 per c.mm. He found that an additional factor was the speed of diffusion of the glucose, which was related more to the size of the effusion than to its cause, and he was able to show by pneumoangiography a positive correlation between the pulmonary circulation and the glucose level.

Carr and Mayne (1962) did not feel that such factors were responsible for the low levels in their cases and could offer no satisfactory explanation. They did not think that the duration of the effusion played any part, although in one of their cases the level fell significantly over a period of ten days. They pointed out that in joint

fluid the glucose level was sometimes lower than in blood and could be absent in long standing cases.

The positive diagnostic value of glucose levels in rheumatoid effusions and the reason for the very low levels, when these are present, requires further study.

In summary, the characteristics of the pleural fluid have no distinguishing features, except the very low glucose level, which, judging from the information so far available in the literature, is likely to be present in the majority of cases. There have been no studies of the titre of the S.C.A.T. in the pleural fluid and it is felt that this might be worth assessing as a diagnostic measure.

Pleural biopsy

The pathological changes which occur in these cases have already been mentioned and one might expect that at least in some cases pleural biopsy would be helpful in diagnosis. Tissue of rheumatoid origin has been obtained by needle biopsy of the pleura by Heller et al. (1956) and by Schools and Davey (1960). Indeed one gains the impression from the latter paper that this would be a frequent event, since while studying 100 consecutive cases of pleural effusion the authors reported 3 in which rheumatoid tissue was obtained and as far as could be judged these were the only patients with rheumatoid arthritis. This, however, has not been the experience of other authors who have only quoted non-specific changes by this technique (Ward, 1961; Carr and Mayne, 1962; Mattingly, 1964; Poppius and Tani, 1964). The last authors did attempt to see whether biopsy might give an indication of a connective tissue disorder rather than alternative causes for pleural effusion; Although their results were inconclusive, and they were therefore cautious in their interpretation, there was some suggestion that this might be so.

Before the true value of pleural biopsy in rheumatoid pleural effusion can be finally established a larger series of cases will need to be studied. Apart from the recovery of rheumatoid granulation tissue it would be helpful to determine whether it is possible to recognise histological changes representative of a connective tissue disorder rather than an alternative pathological process in the pleura.

Intra-pulmonary lesions

Pleural effusion is not of course always an isolated intra-thoracic complication of rheumatoid arthritis and associated intra-pulmonary lesions are not infrequently present. Those demonstrated either on chest x-ray or pathologically amongst the cases described in the literature were 3 with interstitial lung disease, 4 with intra-pulmonary rheumatoid nodules, 3 with polyarteritis nodosa, 1 with Caplan's syndrome and 1 with a localised pneumonitis considered of rheumatoid origin. In 26 cases the underlying lung was normal, and in 3 others there were conditions unassociated with rheumatoid disease. It is possible that the incidence of intra-pulmonary disease of rheumatoid origin is higher than the above figures suggest, since in two cases nodules were found pathologically when there was no obvious abnormality in the lung radiographically.

Natural history

The natural history of the pleural effusions was not always clear in the cases described in the literature. It was established that of 49 cases described in detail resolution occurred in 18, in three or four weeks in a few, but more often several months elapsed before the fluid was finally absorbed, and in some cases the period required was even longer. Residual pleural thickening of greater or lesser extent was a feature noted quite frequently. In other cases the effusions

were even more persistent continuing over periods of observation of 2 to 3 years and in one case for as long as 8 years. In Carr and Mayne's series (1962) serial x-rays were available in thirteen of their cases. In 1 resolution was rapid; it occurred between 1 and 2 months in 7, leaving pleural thickening in 4 and in the other 5 the effusion was known to persist for periods varying from 2 to 6 months. Therefore, although resolution can occur quite quickly in these cases it is more characteristic for the effusion to be more persistent, and indeed it may continue for several years.

Complications

Complications of the effusions seem to be few, apart from residual pleural thickening. However, Cudkowicz et al. (1961) found the pleural exudate to be purulent on the right side in the man they described, and subsequently he developed a left spontaneous pneumothorax with empyema. The precise cause of the latter event was not clear, but one wonders whether it could have been due to cavitation in an intra-pulmonary nodule with subsequent infection and rupture, as in the case described by Hindle and Yates (1965). Kellgren et al. (1958), while drawing attention to pyarthrosis in rheumatoid arthritis, mentioned a patient with a pleural effusion who developed empyema as well as pyarthrosis. Although the cause of the effusion was not clear in this case, by analogy with the joints it would seem reasonable to bear in mind the possibility of secondary infection in a persisting rheumatoid pleural effusion.

Treatment

There is relatively little information in the literature concerning the effects of treatment. In at least 3 cases, however, corticosteroid or corticotrophin therapy did not seem to influence the effusions (Ellman et al., 1954; Emerson, 1956; Lee et al., 1959), and in 1

intra-pleural hydrocortisone was similarly ineffective (Carr and Mayne, 1961). In 2 others the effusions appeared to improve with corticosteroid therapy (Smith and Rothermich, 1957; Ward, 1961), but in 1 of these it recurred while treatment was being maintained. In two more there was a possible response (Horler and Thompson, 1959; Ward, 1961). Chloroquine may have hastened resolution in two cases (Lee et al., 1959). It is difficult to draw any conclusion from these data and the only point which seems established is that the results of corticosteroid therapy are unimpressive.

2. INTERSTITIAL LUNG DISEASE

Ellman in 1947 was the first to suggest that an interstitial lung disease might be a systemic manifestation of rheumatoid arthritis, when he mentioned briefly a case with arthritis of rheumatoid type, as well as some features of Felty's syndrome, in which there was a diffuse chronic pulmonary process which proved at autopsy to be "a curious chronic fibrosing broncho-pneumonic lesion". The following year in conjunction with Ball (Ellman and Ball, 1948) he described in detail 3 patients, 1 man and 2 women, all of whom developed similar lung changes clinically and radiographically, 2½ years, 6 months and 9 months after the onset of polyarthritis. All of them complained of cough and dyspnoea, and one was noticed to be cyanosed. Crepitations, basal in one and diffuse in the other, were present in two and bronchial breathing was heard at the bases in the third. The chest radiographs were described as showing fine reticulation throughout both lung fields with a chronic broncho-pneumonic lesion; bilateral basal consolidation with reticular shadows in the mid-zones and widespread heavy reticulation; and apparent miliary mottling respectively. Two of these patients died and in both the interstitial lung tissue contained fibrosis and infiltration with mononuclears and some polymorphs. The intra-alveolar changes seemed to be mainly those of a terminal broncho-pneumonia. There was fibrinoid necrosis in some of the blood vessels in the kidney, in fatty tissue adjacent to the myocardium and in the lungs of one case, but the arteries in the other were normal. The third patient was still living at the time of the report. On the basis of these cases the authors suggested that the interstitial lung changes present were an integral part of the rheumatoid process.

This concept, was however, disputed by Aronoff *et al.* (1955).

Although in their series of 130 cases with chest x-rays they found 6 with diffuse pulmonary fibrosis they found evidence of a reasonable alternative cause in 4 and 1 other had some features of systemic lupus erythematosus. This left one which they preferred to regard as idiopathic diffuse interstitial pulmonary fibrosis without a relationship to rheumatoid arthritis. Other authors have also been unconvinced of the validity of the association (Dixon and Ball, 1957; Mason and Steinberg, 1958), and clearly some dispute persists. There are several reasons for this. Firstly, although interstitial lung disease can be diagnosed with considerable confidence on appropriate clinical, radiographic and physiological features, in some pathological confirmation is required and therefore it may be difficult or impossible to know the significance of certain cases. Moreover, having established the presence of an interstitial lung disease it may again be difficult or impossible to know whether an associated arthritis is truly rheumatoid or is due to another connective tissue disease. It is therefore important to analyse the evidence which has subsequently accumulated for and against Ellman and Ball's original hypothesis.

Pathological observations

In his series of 100 autopsies on rheumatoid subjects Cruickshank (1957) found 6 examples of interstitial pneumonia all of which were chronic and accompanied by diffuse or focal fibrosis. This contrasts with the work of Mallory (1948) who found 16 (0.27%) examples of interstitial fibrosis in 6,000 unselected autopsies. On the other hand, Talbott and Calkins (1964) found no difference in this respect between their series with rheumatoid arthritis and their controls, but the numbers were relatively small (thirty seven in each group), and they admitted that their study did not refute the concept that interstitial lung disease

could be a feature of the rheumatoid process. In addition to these studies cases have been reported where rheumatoid granulomata have been present in the lungs in association with interstitial lung disease (Skogrand, 1956; Cruickshank, 1959; Cudkowicz et al., 1961; Patterson et al., 1965).

Clinical observations

On the clinical side Thompson (1965) found 14 cases of interstitial lung disease amongst 643 with classical or probable rheumatoid arthritis and states that about one eighth of those seen in respiratory units also have rheumatoid disease. Patterson et al. (1965) found 8 (1.1%) in a retrospective study of 702 patients. Brannan et al. (1964) found twenty seven with definite rheumatoid arthritis and interstitial lung disease between 1950 and 1959, but did not record the total number of rheumatoid patients seen. Stack and Grant (1965) found 4 in a series of 177 new patients with rheumatoid arthritis, seen during an eighteen month period, but there were 2 in their control group of 177 patients seen at a neurological unit, a difference which was not, of course, significant.

Serological observations

Livingstone et al. (1964) and Stack et al. (1965) discussed the possibility that idiopathic interstitial lung disease might be an auto-immune disease. The work of Read (1958a and b) provided circumstantial evidence that at least some cases were dependent on immune mechanisms. Franklin et al. (1959) studied 9 patients with interstitial lung disease, in 7 of whom a positive result was obtained in at least one serological test for rheumatoid factors, although only 4 patients had convincing evidence of rheumatoid arthritis. This small series suggested that more than the expected proportion of patients

with interstitial lung disease, but without rheumatoid arthritis, had positive serological tests for the latter disease. This was subsequently confirmed by Turner-Warwick and Doniach (1965) who investigated 48 patients with interstitial lung disease, 14 of whom had rheumatoid arthritis. They found that 49 per cent of the whole series and 11 (32%) of the 34 without arthritis had a positive S.C.A.T., although 9 of the 11 had a negative latex test for rheumatoid factor. Anti-nuclear factors were present in 14 (29%) of the 48 and non-organ specific anti-bodies were present in 19 per cent, compared with an incidence of 4 per cent and 2 per cent respectively in a control group. However, Scadding (1960) did not find a positive S.C.A.T. amongst his patients with idiopathic interstitial lung disease and Stack et al. (1965) did not find anti-nuclear factor or rheumatoid factor in any of their series of cases, but they suggested that the reason for this might be that in most of them the disease had been present for a considerable time before the serum was examined and ten of their patients were receiving corticosteroid therapy.

We have, then, conflicting evidence from pathological, serological and clinical studies regarding the association between rheumatoid arthritis and interstitial lung disease. However, the findings of Cruickshank (1957) and the fact that rheumatoid granulomata may be found in the presence of interstitial lung disease are impressive. Moreover, despite the fact that the incidence of interstitial lung disease in the community is not known, it is certainly an uncommon disease and it is therefore hard to believe that the findings of Patterson et al. (1965) and Thompson (1965) are without significance.

The evidence, therefore, that interstitial lung disease may be

an integral part of the rheumatoid process is strong, if not overwhelming. This is in keeping with the opinion of most authorities on the subject, who accept the concept as a valid one.

Sex incidence

Sixty two cases were accepted for the review and the sources are shown in Table 10, overleaf. Of these 35 were men and 27 were women. In addition Brannan et al. (1964) described 27 cases, 18 men and 9 women; Patterson et al. (1965) described 4 men and 4 women, and Thompson (1965) referred to 14, 12 of whom were men. Assuming that 2 of the latter were reported by Horler and Thompson (1959) there are a total of 67 men and 42 women recorded in the literature. Considering the female preponderance in rheumatoid arthritis as a whole there is an unequivocal predominance of men affected by interstitial lung disease. Idiopathic interstitial lung disease, on the other hand, is more common in women (Stack et al., 1965).

Temporal relations

An attempt has been made to determine the age of onset of the lung disease and its relationship to the onset of rheumatoid arthritis and this is shown in Table 11.

Table 11. Relationship between onset of arthritis and lung disease

	Males		Females	
Lung disease before	3		4	
Simultaneous onset	2		2	
Lung disease after by		62%		82%
< 1 yr.	-		3	
1 - 2 yrs.	3		2	
2 - 5 yrs.	5		3	
6 - 10 yrs.	5		2	
11 - 20 yrs.	3		- (1 several yrs.)	
TOTAL	21		17	

Table 10. Sources of cases of rheumatoid arthritis with interstitial lung disease

Year	Author	Place	No. of cases
1948	Ellman and Ball	London	3
1948	Hart	London	1
1949	Yardumian and Kleinerman	Pittsburg	1
1951	Middleton	Texas	2
1954	Christie	Melbourne	1
1954	Ellman and Cudkowicz	London	1
1954	Harris	London	1
1955	Rubin	New York	4
1955	Spence	London	1
1956	Ellman	London	3
1956	Price and Skelton	London	1
1956	Skogrand	Oslo	2
1957	Dixon and Ball	Manchester	1
1957	Edge and Rickards	Lancaster	2
1957	Rubin and Lubliner	New York	2
1957	Smith and Rothermich	Ohio	1
1957	Sokoloff and Bunim	Bethesda	1
1958	Forbes	Adelaide	1
1958	Mason and Steinberg	London	4
1959	Cruickshank	Glasgow	8
1959	Horler and Thompson	Newcastle	2
1960	Ognibene	New York	2
1961	Cudkowicz *et al.*	Boston	1
1962	Doctor and Snider	Chicago	2
1962	Lee and Brain	London	2
1962	Sullivan and Miller	Buffalo	1
1963	Locke	Manchester	2
1964	Divertie	Mayo Clinic	1
1965	Stack and Grant	Edinburgh	8

Such information was by no means always clear in the case reports but it was either stated or could be reasonably deduced in 21 men and 17 women. In men the average age of onset was 48 years and in women 50 years. The average age of the series of Brannan et al. (1964) was 57 years, but this did not seem to be at the onset. Patterson et al. (1965) quoted an age range of 22 to 66 years. In 3 of the 35 men and 4 of the 27 women the lung disease preceded the arthritis by periods varying from 4 months to 5 years in 6, and in the other it seemed that the interval was as long as 20 years. In two cases in each sex the onset was approximately simultaneous. As will be seen in 62 per cent of male cases and in 82 per cent of female cases the lung disease either preceded the arthritis or occurred within five years of its onset. In the series of Brannan et al. (1964) the lung disease came first in 3 of the 27 cases by an average period of twenty months. In 5 the onset was simultaneous and in the remaining 19 the arthritis had been present for an average period of 37 months with a range of 1 month to 18 years before the lung disease became apparent. In sixteen of these cases, however, the pulmonary involvement was evident within two years of the onset of the arthritis. These findings are in accordance with the information obtained from the other cases in the literature.

Clinical features of arthritis

Omitting from consideration those in whom the data were not available the extent in the men was mild in 30 per cent, moderate in 22 per cent, and severe in 48 per cent, and in the women the figures were 19 per cent, 19 per cent and 62 per cent respectively. In the largest series of cases reported (Brannan et al., 1964) details of the extent of the arthritis were not presented, but Patterson et al. (1965) described the arthritis as severe with crippling deformity in 4, moderate

deformity in 2 and mild deformity limited to the hands and wrists in 3.

By the criteria previously defined subcutaneous nodules were present in 14 (48%) of 30 men and in 4 (20%) of 20 women. This suggests a correlation between subcutaneous nodules and interstitial lung disease in men but not in women, in which the figure is as expected in an unselected rheumatoid population. It is interesting to compare these figures with the findings of Patterson et al. (1964) in whose series all 4 men and 2 of the 5 women had subcutaneous nodules.

Systemic lesions

The systemic lesions of rheumatoid arthritis described in cases in the literature with interstitial lung disease are shown in Table 14.

Table 14. Systemic lesions of rheumatoid arthritis in interstitial lung disease

	Males							Females					
	1	2	3	4	5	6	7	1	2	3	4	5	6
Adenopathy				+								+	
Splenomegaly		+	+							+			
Hepatomegaly		+						+					
Pericarditis					+	+	+				+		
Myocarditis					+						+		
Endocarditis					+	+							+
Arteritis			+			+			+				+
Neuropathy									+				
Amyloid	+												
Nodules in striated muscle					+								

In nineteen of the patients full autopsy examination was done, and most of the others were described in sufficient detail for it to be reasonable to expect such lesions to be recorded if present. Accepting this, arteritis was present in 6 per cent, pericarditis in 6 per cent, splenomegaly in 5 per cent, and there were 2 examples each of pronounced

adenopathy, hepatomegaly, myocarditis and endocardial lesions, and 1 of neuropathy, amyloid disease and nodules in striated muscle. Of the 9 cases described by Patterson et al. (1965) 1 had keratitis sicca, 1 pericarditis and 1 rheumatoid mitral and aortic valve disease. Such figures do not suggest an association between interstitial lung disease and other systemic manifestations of rheumatoid arthritis.

Laboratory investigations

The haemoglobin levels when recorded are shown in Table 12.

Table 12. Hb. levels (g./100 ml.) in interstitial lung disease

	Male	Female
< 8.9	1	3
9.0 - 10.4	2	3
10.5 - 12.6	6	4
12.7 +	5	2
TOTAL	14	12

Included here are cases where the haemoglobin was stated to be normal, but excluded are those said to be anaemic when no actual figure was stated, and therefore the incidence of anaemia will be underestimated. Although the numbers are rather small it can be seen that 9 (64%) of the 14 men had a level of less than 12.6 g. per 100 ml. or 85 per cent. The comparable figure from the Empire Rheumatism Council's survey (Lewis-Faning, 1950) was 30.2 per cent. In the women 10 of 12 were below this level, 83 per cent, compared with 59.6 per cent in single women and 44.9 per cent in those married in the survey. In the series of Patterson et al. (1965) a mild anaemia was often present. These figures suggest that there is a positive correlation between the presence of anaemia and interstitial lung disease, and support the suggestion of Stack and Grant (1965), who thought that the develop-

ment and progression of the lung disease might depend on the degree of activity of the rheumatoid process as reflected by the presence of anaemia, which occurred in 5 of their 8 cases. These authors also thought that for the same reason there might be a correlation with the height of the B.S.R. and the results for both sexes combined are shown in Table 13, where they are compared with the figures of Dawson et al. (1930) from 95 cases of rheumatoid arthritis.

Table 13. B.S.R. in interstitial lung disease and rheumatoid arthritis

B.S.R. (mm. 1st. hr.)	Interstitial lung disease	Rheumatoid arthritis Dawson et al. (1930)
0 - 20	2 (7%)	21%
21 - 40	9 (31%)	23%
41 - 60	6 (21%)	27%
61 +	12 (41%)	28%
TOTAL	29 (100%)	99%

It will be seen that fewer cases with interstitial lung disease had a sedimentation rate less than 20 mm. 1st. hr., and more had a level greater than 40 mm. 1st. hr. Taking the latter group, 9 (31% of the total) had levels greater than 90 mm. 1st. hr. compared with 12 per cent of the group of Dawson et al. (1930).

Adding to the 62 cases the series of Patterson et al. (1965) L.E. cells were recorded as absent in 26 patients and in none were they present. The point of interest here is whether cases of rheumatoid arthritis with L.E. cells are more prone to interstitial lung disease than those without L.E. cells. However, because of the natural reluctance to ascribe cases with L.E. cells to rheumatoid arthritis and not systemic lupus erythematosus, as in rheumatoid pleuritis, no conclusion can be drawn at the present time.

There were seventeen patients in whom serum protein estimations

were recorded and the figures are shown in Table 15.

Table 15. Protein levels in the blood of 17 rheumatoid patients with interstitial lung disease

Albumin (g./100 ml.)	2.1, 2.1, 2.2, 2.6, 3.0, 3.03*, 3.1, 3.2, 3.3, 3.4, 3.6, 4.2, 4.2, 4.2, 4.2, 4.3, 4.9,
Globulin (g./100 ml.)	2.1, 2.2, 2.6, 2.8, 2.9, 3.08*, 3.3, 3.4, 3.5, 3.7, 3.9, 4.2, 4.5, 5.0, 5.7, 6.1, 6.2,

* proteinuria present

Accepting 3.2 g. per 100 ml. as the lowest possible normal for albumin there were seven patients in whom the level was decreased. Taking 3.6 g. per 100 ml. as the upper limit of normal for globulin there were eight in which it was raised. In the series of Patterson et al. (1965) the serum globulin was said to be frequently higher than normal. It is not felt that any useful conclusion can be drawn from these results at the present time.

The results of tests for rheumatoid factors are shown in Table 16, and those in which a titre for the S.C.A.T. were recorded have been charted in Figure 2, beside the results obtained by Kellgren in a rheumatoid population and quoted by Turner-Warwick and Doniach (1965). Where more than one test was done, the S.C.A.T. has been used for analysis and where more than one titre was recorded the highest has been expressed in the table and figure. It will be noted that of 33 patients in whom a test was performed a negative result was obtained in only 2, and no case had a negative S.C.A.T. The figure demonstrates that in the eighteen cases, where a positive S.C.A.T. was present, the titres were higher than in a rheumatoid population. This is in accordance with the views of Tomasi et al. (1962) who found that of 14 cases with very high latex and F II tanned cell titres 7 had diffuse pulmonary disease, whereas there were no examples of the latter amongst 14 cases

Table 16. Tests for the rheumatoid factors in interstitial lung disease with rheumatoid arthritis

	S.C.A.T.	Latex fixation test	
< 1/32	0	- ve	2
1/32	3	+ ve	1
1/64	1	strongly + ve	1
1/128	5	titre recorded	
1/256	3	1/1280	1
1/512	1	1/2560	2
1/1024	4	1/5120	2
> 1/1024	1		
+ ve no titre	6		

with moderate or low titres. Accordingly they postulated that pulmonary fibrosis might result from the precipitation of relatively insoluble complexes between rheumatoid factors and gamma globulin in pulmonary capillaries. However, if this were so one would expect all cases of interstitial lung disease to have very high titres, which is not the case, and, moreover, as Stack and Grant (1965) pointed out, the pulmonary disease may progress while only low titres are present. It seems reasonable to accept provisionally, from the relatively small number of cases so far available for consideration, that those with interstitial lung disease tend to have a higher titre for rheumatoid factors than are found in a rheumatoid population. However, that the rheumatoid factors themselves play a part in the pathogenesis of interstitial lung disease seems doubtful on present evidence.

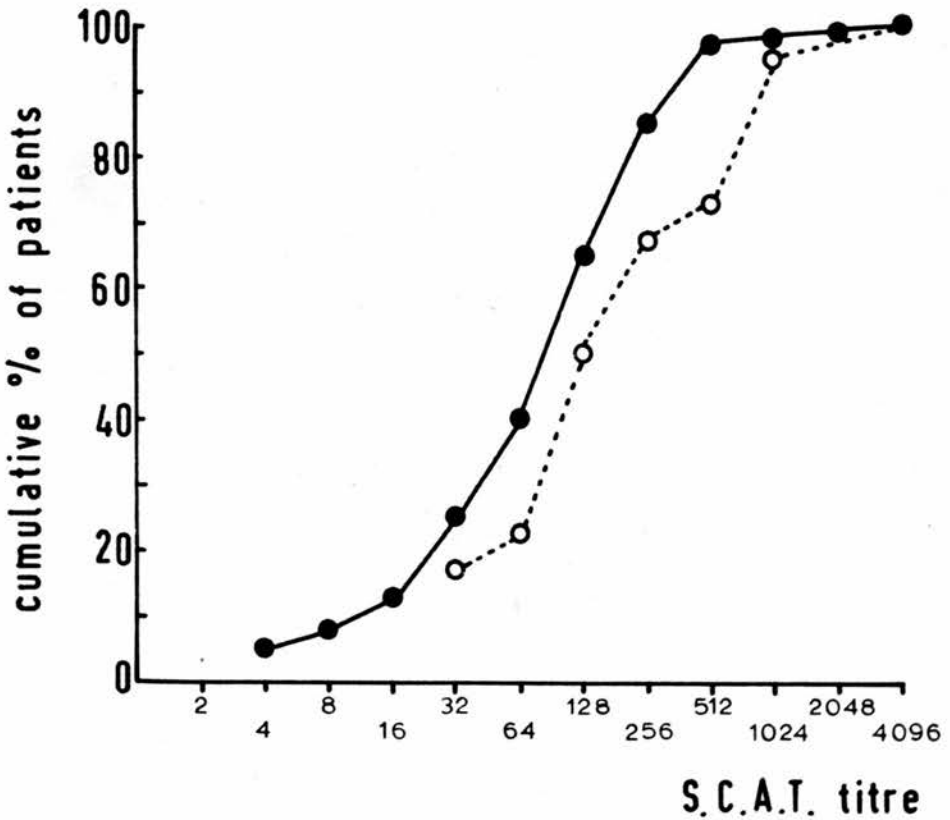
Joint radiographs

Of 22 cases in which joint x-rays had been recorded 4 were normal.

Fig.2 *Titre of s.c.a.t. in rheumatoid patients with interstitial lung disease compared with a rheumatoid population*

●——● S.C.A.T. titres after Kellgren

o-----o S.C.A.T. titres R.A. with interstitial lung disease from the literature



The changes were doubtful in 4, moderate in 3 and severe in 5 and in 6 others they were regarded as typical of rheumatoid arthritis by the appropriate authors but grading was not possible. These changes will subsequently be compared with the findings in the author's hospital population.

Respiratory symptoms and signs

Each case was carefully reviewed to determine the frequency and nature of the respiratory symptoms which could reasonably be attributed to the interstitial lung disease. In 13 patients there was no mention of symptoms and in 3 others it seemed likely that those recorded were due to alternative causes. Forty six patients remained for consideration. Of these, respiratory symptoms were absent in five (11%). Dyspnoea was the commonest symptom, being present in thirty seven (80%), and cough was also frequent, occurring in twenty eight (61%). The latter seemed to be more often unproductive, sputum being mentioned in only eight cases. Chest pain occurred in 7 cases, pleuritic in 1, non-pleuritic in 4, and uncertain in the other 2. Fever was mentioned on 3 occasions and haemoptysis was a rare symptom only occurring in 2 cases. Brannan et al.(1964) in their 27 cases found that cough occurred in 18, dyspnoea in 15, pleuritic pain in 8, and in 4 the respiratory symptoms had a febrile onset. Patterson et al. (1965) found that 2 of their 9 cases had no respiratory symptoms when the fibrosis was discovered.

In 16 cases there was no record of physical signs in the respiratory system and in 5 those mentioned seemed to be due to an alternative cause, for example pleural effusion or terminal infection. Cyanosis was recorded in 4 of the remainder, and finger clubbing was present in 15, absent in 6, and was stated to be questionable in 1. In the remainder

the presence or absence of finger clubbing was not mentioned. The lungs were stated to be clinically clear in 5 and crepitations were recorded in 32 cases. Other physical signs mentioned included dullness on percussion at the bases in 2 and bronchial breathing in 2. Pleural friction was present in 3 cases, 2 of which had pleural effusions, and the other pleural thickening.

Therefore, as expected, analysis of these respiratory symptoms and signs reveals a picture essentially the same as that described for idiopathic interstitial lung disease and is in accordance with the view of Scadding (1960), who found that his three cases with rheumatoid arthritis were indistinguishable from his series without rheumatoid arthritis. Livingstone et al. (1964) found that dyspnoea was present in all except one of their cases when first seen, but of the 42 cases of Stack et al. (1965) 9 had little or no dyspnoea and 5 of them survived for over eight years without treatment, 2 of them retaining a normal exercise tolerance. These authors wondered whether there might be a benign condition, radiographically similar to the more usual form of interstitial lung disease, which tended to occur in the older age groups. It will be recalled that the average age of onset of rheumatoid interstitial lung disease was 48 years in men and 50 years in women. Whether the twenty per cent of cases with rheumatoid interstitial lung disease without dyspnoea are explicable on this basis or whether the absence of dyspnoea is due to restriction of their activities is uncertain. The incidence of finger clubbing as obtained from consideration only of those cases in which this sign was recorded as either present or absent, and excluding the one doubtful, was seventy one per cent. This is almost certainly a true indication of the overall incidence, since it coincided closely with the findings of Stack and

Grant (1965), who recorded this sign in all of their 8 cases and found it present in 6. Moreover, it closely resembles the incidence in idiopathic interstitial lung disease (Scadding, 1960; Livingstone et al., 1964; Stack et al., 1965).

Chest radiography

Of the cases described in the literature the appearances on chest radiography were recorded in fifty four. A wide variety of terms was used to describe the abnormality present, and it has not been possible to classify them into specified groups. The two commonest appearances were reticulation and mottling. A cystic change was present in 4 and honeycombing in 3. In one the chest x-ray was normal and it is well known that this may be so in the early stages of interstitial lung disease (Livingstone et al., 1964). Enlargement of the hilar shadows was mentioned on three occasions and considered due to hilar adenopathy in one of them. Either pleural effusion or pleural thickening was present in nine cases. The pulmonary disease was always bilateral but not infrequently asymmetrical. Generally the radiographic abnormalities were most marked in the lower zones and sometimes confined to them, or, to the mid and lower zones. In a few, however, the abnormalities were most marked in the mid-zones and sometimes in the upper zones.

The descriptions of the chest radiographs and the distribution of the abnormalities present correspond closely with those in idiopathic interstitial lung disease, and clearly represent essentially the same process. The only suggestion of a distinguishing feature is the presence of pleural abnormality in seventeen per cent of the cases with rheumatoid arthritis.

Lung function tests

Tests of lung function in varying degrees of detail have been reported in these cases by Spence (1955), Rubin and Lubliner (1957), Edge and Rickards (1957), Mason and Steinberg (1958), Ognibene (1960), Cudkowicz et al. (1961), Lee and Brain (1962), Doctor and Snider (1962), Sullivan and Miller (1962), Patterson et al. (1965), and Stack and Grant (1965). Leathart and Thompson (1965) reported their results to the Heberden Society in 1965. The results have been as expected and have consisted essentially of a restrictive pattern with reduced gas transfer and arterial hypoxaemia either at rest or after exercise.

Pathology

In 39 of the 62 cases the pathological changes in the lungs were described. The tissue was obtained at lung biopsy in thirteen and at autopsy in the remainder. Cruickshank (1959) believed that the earliest change was a non-specific interstitial pneumonia consisting of the presence of lymphocytes, plasma cells and macrophages surrounding the small arteries, arterioles and bronchioles, and spreading into the adjacent walls of the interalveolar septae. He felt that this stage was reversible, and resolution probably occurred in many cases. If not, there was increasing fibrosis with dilatation of some bronchioles and alveoli to form cystic spaces, which in its extreme form became honeycombing. These spaces may be lined by a hyperplastic epithelium. Such features are those of idiopathic interstitial lung disease and are non-specific, but in 4 of the 40 cases rheumatoid granulomata have been present (Skogrand, 1956; Cruickshank, 1959; Cudkowicz et al., 1961). In two others there was a granulomatous appearance but this was not considered by the author to be characteristic of rheumatoid disease (Cruickshank, 1959). In another case the inflammatory reaction was

described as characteristic of rheumatoid disease, although there was no actual mention of rheumatoid nodules as such (Locke, 1963). In the remaining cases there was no suggestion of rheumatoid granulomata histologically. Patterson et al. (1965) also reported a case with rheumatoid granulomata in the lungs. Arterial abnormalities were described quite frequently. These were fibrosis, hyaline thickening, or elastic reduplication of the small arteries. There is some dispute as to the significance of these changes. Ellman and Cudkowicz (1954) suggested that involvement of the bronchial arteries was an essential factor in the pathogenesis of rheumatoid lung disease. Cruickshank (1959) however, after his detailed pathological study pointed out that there was no way of knowing whether it was the bronchial or pulmonary arteries, or both, which were involved and suggested that the changes might be the result of the fibrosis or a secondary factor causing permanent damage. In addition to these vascular changes, arteritis has also been reported (Ellman and Ball, 1948; Price and Skelton, 1956; Cruickshank, 1959). Apart from the changes in the lungs themselves in 3 cases the hilar lymph nodes were enlarged and in 2 of these rheumatoid granulomata were present (Skogrand, 1956);

Treatment

Of the 62 cases reviewed in detail 24 had received corticosteroid therapy after the lung disease had been diagnosed. Objective evidence of a favourable response such as improvement in tests of respiratory function or x-ray clearing, or in one case a decrease in the degree of finger clubbing, was reported in eleven cases. However, this was only temporary in four and in the remainder it was rarely prolonged. There was no evidence in the accounts of the other fourteen cases that

corticosteroids exerted a beneficial effect on the lung disease and in the series of Patterson et al. (1965) no therapy influenced the progress of the lung disease. There is virtually no information concerning the affects of any other drug treatment employed in rheumatoid arthritis. Anti-malarial therapy was only used once (Ognibene, 1960), but this was in conjunction with corticosteroids.

Stack and Grant (1965) reviewed the literature on the effects of corticosteroid therapy and treated four patients themselves. Although there was some initial improvement in 3 of their cases, rapid deterioration followed in 2 and they felt that overall the drug might have hastened the progression of the disease. They were dubious of the value of these drugs and felt they should be reserved for patients with severe progressive disability in danger of death from respiratory insufficiency.

In the acute form of the idiopathic type corticosteroid therapy may at times produce dramatic results (Livingstone et al., 1964). In this connection it is of interest to note the observations of Doctor and Snider (1962) who found that of two cases with rheumatoid interstitial lung disease the one with the more cellular reaction on lung biopsy responded to treatment much more impressively. Moreover, this was not related to the duration of the disease.

From the information so far available it would be reasonable to conclude that chronic cases without disabling symptoms should not receive corticosteroid therapy on the grounds that it is most unlikely to be beneficial and indeed may be harmful. More acute and rapidly progressive cases should receive treatment as they have a bad prognosis, and in some cases good results may be obtained. Returning to Cruickshank's

observation that the initial change is an interstitial pneumonia, one wonders whether corticosteroid therapy at this stage might increase the frequency of resolution, which he believes to occur in some cases. This emphasises the need for early diagnosis.

Natural history

The early course of the disease has been described by Brannan et al. (1964). They found that initially there were soft fluffy radiographic opacities which cleared incompletely leaving residual fibrosis. In exacerbations further soft opacities appeared and eventually over many months diffuse fibrosis resulted. They noted that in 12 of their 27 cases there were simultaneous exacerbations of arthritic and respiratory symptoms and this was also noted by Rubin (1955). In four of the cases of Brannan et al. (1964) the arthritic and respiratory exacerbations were accompanied by the rapid development of wide-spread subcutaneous nodules.

To date there has been no detailed report on the long term observation of a large series of cases, as is available for the idiopathic type (Scadding, 1960; Livingstone et al., 1964; Stack et al., 1965). It is therefore difficult to get a clear picture of the overall natural history and the prognosis of the lung disease but they are certainly very variable. Cases have died in a matter of three months (Ellman and Ball, 1948), have been asymptomatic after five years, or only slowly progressive after ten years (Patterson et al., 1965), and the latter authors commented on the widely varying course of the pulmonary disease.

Generally, those reported that have died as a result of the lung disease have done so from respiratory insufficiency often with terminal infection or cardiac failure due to pulmonary heart disease. However, Stack and Grant (1965) recently described two cases which developed

malignant pulmonary tumours and drew attention to the fact that three others had been described, to which a fourth should be added (Cruickshank, 1959). They pointed out that fourteen cases with idiopathic interstitial lung disease and bronchial carcinoma had been reported. The supposition is that malignancy may be a complication of interstitial lung disease and that this may be related to the hyperplasia of the epithelium lining the cystic space referred to earlier.

Aetiology

The precise aetiology of interstitial lung disease is unknown. As discussed earlier there is suggestive evidence of an auto-immune process. The reason why it develops in only a small percentage of cases with rheumatoid arthritis is equally obscure. Only 5 of 62 cases and 12 of the 27 of Brannan et al. (1964) had received corticosteroid therapy before the lung disease developed and therefore this certainly is not a factor, nor is there any reason to suppose that it might be. Leathart and Thompson (1965) did not find that occupational factors played any part, but it is of interest to note that 6 (17%) of 35 men described had been exposed to a pneumoconiotic hazard. This figure is derived on the assumption that when no occupation was recorded there had been no exposure to noxious dusts. Leathart and Thompson (1965) did not feel that smoking was a factor, and careful review of the previous respiratory history of the cases in the literature reveals no suggestion that there is any association with other lung disease. Ellman and Cudkowicz (1954) thought that involvement of the bronchial circulation was the essential factor, but this had not been established. Doubt also exists regarding the theory of Tomasi et al. (1962) that the condition might result from precipitation of macroglobulin complexes in the pulmonary capillaries. Cases of rheumatoid arthritis with inter-

stitial lung disease tend more often to have anaemia, a higher sedimentation rate and higher titres for rheumatoid factor when compared with a rheumatoid population as a whole. Although this might indicate that those with more active disease are more liable to have lung involvement, this is clearly not the only factor.

3. CAPLAN'S SYNDROME

In 1952 at the Thoracic Society of Great Britain Caplan first described the syndrome which has since borne his name and his work was published the following year (Caplan, 1953). He observed that of fifty one men with rheumatoid arthritis who were claimants for pneumoconiosis benefit in South Wales ninety per cent had massive fibrosis compared with only thirty per cent of claimants without rheumatoid arthritis and that in thirteen of these men (25%) the massive fibrosis was of a distinctive type. It consisted of multiple, well defined, round opacities usually about 1.0 cms. in diameter, but varying from 0.5 to 5 cms. which were distributed throughout both lung fields but particularly at the periphery. These lesions tended to appear rapidly and occurred against a background of simple pneumoconiosis of category 1 or 0 in forty five per cent. Such a radiographic picture, of course, contains several points of distinction from ordinary progressive massive fibrosis (P.M.F.).

The association between this radiographic picture in rheumatoid subjects and pneumoconiosis was established by its absence from the chest films of seventy cases who were non-miners and the association with rheumatoid arthritis was confirmed by an epidemiological study of coal miners in South Wales undertaken by the Pneumoconiosis Research Unit (Miall et al., 1953).

The syndrome was subsequently reported in coal workers in other parts of this country and in Europe (Christiaens et al., 1954; Petry, 1954; van Mechelen, 1954; Dechoux and Ruyssen, 1956; Sepke, 1957), and also in other industries. Caplan et al. (1958) and Caplan (1959) referred to cases in the potteries, in sandblasting, and in brass and iron foundries. A case was described in a boiler scaler (Campbell, 1958),

in association with pulmonary asbestosis (Rickards and Barrett, 1958; Telleson, 1961; Morgan, 1964) and in a roof-tile maker (Hayes and Posner, 1960). Colinet (1950, 1953) in Belguim had made a similar observation to that of Caplan in workers in various silica hazards and subsequent examples have also been recorded by Clerens (1953), Martin and Fallet (1953), and Van der Meer (1954).

The initial observation which led to the recognition of Caplan's syndrome was the higher than expected incidence of massive fibrosis in rheumatoid subjects. Apart from the 13 men with the distinctive appearance 21 had mixed lesions, that is, varying combinations of ordinary P.M.F., atypical P.M.F., and the characteristic round opacities; 6 cases had lesions indistinguishable from tuberculosis, 7 had typical P.M.F. and only 4 had simple pneumoconiosis. The inference was that at least a proportion of these other cases were in some way related to the rheumatoid process, and in 1962 Caplan et al. enlarged the concept of the original syndrome by demonstrating an increased incidence of rheumatoid arthritis in cases with a less characteristic radiographic appearance, although this was less than the incidence in the classical syndrome as originally described. This less characteristic group consisted of either nodular, discrete, 0.3 to 1 cm. round opacities, differing in number and distribution from a few confined to the upper zones to a snowstorm appearance, or mixed nodular and irregular opacities on a background of no pneumoconiosis or category 1 simple pneumoconiosis. The fact that the incidence of arthritis in the second group was significantly less than in the classical group suggests that the radiographic appearances were not always of rheumatoid origin. This has been confirmed by Caplan and Gough (1962) in a correlation between radiographic appearances and autopsy findings, in which although many

cases showed a rheumatoid pneumoconiosis others showed silicosis, infective nodules, P.M.F. or rarely tuberculosis.

Apart from demonstrating the incidence of rheumatoid arthritis in the various radiographic groups Caplan et al. (1962) also showed that when arthritis was absent positive serological tests for the rheumatoid factor occurred in about two thirds of those with the classical picture and in a smaller proportion of those with the less characteristic appearance, mirroring the incidence of actual arthritis in these groups. Moreover in those with ordinary P.M.F. thirteen per cent had positive tests and it is possible that some of these were rheumatoid in origin, since Caplan and Gough (1962) have shown that the end stages of some examples of rheumatoid pneumoconiosis may be indistinguishable radiographically from ordinary P.M.F. If, however, this is the explanation it is surprising that there was not a higher incidence of actual arthritis in the group regarded as ordinary P.M.F. in comparison with those with simple pneumoconiosis and no pneumoconiosis, and it is possible, as suggested by Ball (1955), that P.M.F. itself may be associated with positive serological tests in some cases.

The pathology of the Caplan's lesions was described by Gough et al. (1955) and Gough (1959). On naked eye examination the nodules consisted of concentrically arranged light and dark areas, the former being grey or yellow in colour and sometimes containing clefts. Some of the lesions were calcified. The larger masses consisted of confluence of these nodules. Histologically the lesions consisted of necrotic collagen containing lines or rings of dust with polymorphs and macrophages (some containing dust) at the periphery. Outside this zone there was circumferentially arranged collagen. Vessels at the periphery showed endarteritis.

This description differs from ordinary P.M.F. where larger lesions consist of well marked collagenous fibrosis and not confluence of nodules. Although the single rheumatoid pneumoconiotic nodules resemble the collagenous nodules, when these are affected by active tuberculosis they tend to be larger and the concentric zones are wider. Moreover tubercle bacilli cannot usually be isolated from the rheumatoid pneumoconiotic nodules whereas they almost invariably can from collagenous nodules involved by tuberculosis. Finally, although vessels show endarteritis in both, in the rheumatoid lesions the lumen contains more lymphocytes and plasma cells. The appearances of a rheumatoid pneumoconiosis are also distinct from those of classical silicosis.

The symptoms produced by a rheumatoid pneumoconiosis are in no way distinctive and are essentially similar to those occurring in other forms of massive fibrosis. In certain cases, however, there is a surprising lack of constitutional upset and only a mild impairment of respiratory function.

There is no correlation between the severity of the arthritis and the appearance of the chest radiographs in these cases (Caplan, 1953; Miall et al., 1953). Only very few opacities may be present in the chest films of those with severe arthritis whereas extensive Caplan's lesions may occur in association with only mild arthritis and in some cases only olecranon nodules are present with no peripheral arthritis (Caplan et al., 1962).

Generally speaking it appears that the lung lesions and arthritis develop at about the same time. Sometimes, however, the arthritis starts first and has been known to precede the lung lesions by up to six years. On the other hand the lung lesions may precede the arthritis

by up to ten years. This may account for those cases with the chest radiograph of a rheumatoid pneumoconiosis with or without positive serological tests and no arthritis (Caplan et al., 1962), but no long term follow up of a large series of these cases has yet been reported in order to determine what proportion of them develop arthritis. Gough (1959) mentions autopsy studies in which pulmonary nodules were present with no changes in the joints. Under certain circumstances, then, it appears that Caplan's lesions may be the only manifestation of the rheumatoid process as has been suggested for pleural effusion by Ward (1961) and as may occur in interstitial lung disease. Of interest in the group without arthritis was the observation of Miall (1955), who found that in his cases with the classical Caplan x-ray but no arthritis the familial incidence of rheumatoid arthritis was as expected in examples of this disease.

The Caplan lesions on the chest radiograph tend to increase in size with the passage of time and fresh lesions may appear at intervals of a few months, but in some cases the radiograph remains unchanged. Calcification is common and cavitation may occur which, if widespread, gives rise to a striking appearance which Caplan himself regards as almost pathognomonic. After cavitation the lesions may contract and in some instances disappear. As already mentioned in the later stages the radiographic appearance may become indistinguishable from ordinary P.M.F. Pleural effusion may develop and occurred in 7 of 56 cases (12.5%) with the classical x-ray appearance reported by Caplan et al. (1962), although there were none in the 112 in the less characteristic groups.

There is relatively little in the literature concerning the treatment of Caplan's syndrome. As tuberculosis was considered to play a

part in the development of the lung lesions it is not surprising that antituberculous chemotherapy has been tried but without benefit. Adrenal corticosteroid therapy has also by and large been unhelpful, although Caplan (1959) mentions one case in which prolonged corticotrophin therapy was accompanied by regression of some of the pulmonary opacities. Jose-Ramirez et al. (1964) described 2 cases, in which they thought corticosteroid therapy was beneficial in one and chloroquine in both. These two cases were the first recorded examples of improvement in rheumatoid pneumoconiosis with chloroquine.

The precise pathogenesis of Caplan's syndrome is unknown. Non-pneumoconiotic intra-pulmonary rheumatoid nodules are rare, as is discussed elsewhere, but amongst rheumatoid subjects with pneumoconiosis Caplan's lesions are quite common. Exposure to pneumoconiotic dust, then, is clearly of crucial importance. However, dust alone is unlikely to be the only additional factor, since uncomplicated dust nodules may be present in the lungs alongside the nodules and, moreover, characteristically the background pneumoconiosis is slight. By analogy with ordinary P.M.F. tuberculosis has been suspected to be the additional essential factor and there is some evidence to support this. Of the 16 cases described by Gough (1955) there was definite or suggestive evidence of tuberculosis in 6. Diamino-pimelic acid has been found in the lesions (Consden and Glynn, 1955) and this substance is a constituent of many organisms including the tubercle bacillus. Moreover, Miall (1955) found an increased incidence of tuberculosis in both rheumatoid miners and non-miners compared with appropriate control groups. There are however inconsistencies present. The increased incidence of tuberculosis in rheumatoid arthritis is in those of longer duration (Ball, 1955), whereas generally the rheumatoid lung lesions and the arthritis

develop at about the same time; evidence of tuberculosis is only present in a proportion and anti-tuberculous chemotherapy is ineffective.

Kellgren (1952) believed that the fundamental lesion in rheumatoid disease was an inflammatory reaction to necrotic collagen. It is thought that the necrotic collagen arises from granulation tissue and not normal tissue (Collins, 1937; Gruenwald, 1948). It would appear that the rheumatoid pneumoconiotic lesions arise as a result of an abnormal reaction to necrotic collagen which develops from the effects of exposure to dust and an additional factor. The latter may be tuberculosis but further work is required to unravel the precise mechanism.

The practical importance of the recognition of Caplan's syndrome is not inconsiderable. Patients with it have spent prolonged periods in sanatoria on the assumption that they had active tuberculosis and others have been subjected to diagnostic thoracotomy on the suspicion of other lesions, particularly malignancy (Caplan, 1959). However, the syndrome is now more widely known and such errors in diagnosis should be much less common in the future.

4. NON-PNEUMOCONIOTIC INTRA-PULMONARY RHEUMATOID NODULES

Twenty eight patients with rheumatoid nodules in the lung have been reported and their sources are shown in Table 17.

Table 17. Sources of patients with intra-pulmonary rheumatoid nodules

Name of authors	Year	Place	No. of cases	Autopsy	Biopsy	Chest x-ray only
Bevans et al.	1954	New York	1	1		
Christie	1954	Melbourne	2	2		
Ellman et al.	1954	London	1	1		
Maher	1954	Ann Arbor	1	1		
Spence	1955	London	1			1
Skogrand	1956	Oslo	3	3		
Gresham & Kellaway	1958	Cambridge	1	1		
Cruickshank	1959	Glasgow	1	1		
Flatley	1959	Rochester, N.Y.	1		1	
Horler & Thompson	1959	Newcastle	1		1	
Cudkowicz et al.	1961	Boston	1		1	
Robertson & Brinkman	1961	Detroit	1		1	
Sieniewicz et al.	1962	Montreal	2		2	
Dumas et al.	1963	Galveston	1		1	
Locke	1963	Manchester	6			6
Noonan et al.	1965	San Francisco	1		1	
Yates	1963	London	1		1	
Hindle & Yates	1965	London	1		1	
Patterson et al.	1965	Little Rock	1	1		

The initial cases were diagnosed mainly on autopsy examination but it is interesting to observe that in more recant years the diagnosis has been made in the majority on specimens resected at thoracotomy. This may reflect the increasing interest in the lungs in rheumatoid arthritis

with more wide-spread use of chest radiography leading to diagnosis in life. Two authors (Spence, 1955; Locke, 1963) have made the diagnosis from the appearances on chest radiography.

The true incidence of these lesions is not really known and indeed it would be difficult to determine in life as biopsy is not always indicated and, in addition, spontaneous resolution can occur (Sieniewicz et al., 1962). Moreover, the lesions may be very small and fail to produce an opacity detectable on chest radiography. However, the fact that only twenty eight cases have been reported over a twelve year period indicates that this is a rare complication of rheumatoid arthritis.

Eighteen of the reported cases have been men whose ages ranged from 40 to 74 years, with an average of 55 years. The age range of the women was 24 to 64 years with an average of 47 years. The duration of the arthritis at the time of diagnosis varied from 6 months to 40 years.

The size of these lesions has varied from minute up to seven centimetres in diameter, the largest so far reported (Christie, 1954). Unless they are of sizeable dimensions respiratory symptoms and signs would not be anticipated, and this in general has been the case. The symptoms recorded have more often been due to other lesions, particularly pleurisy with effusion. However, it would appear that the larger nodules may give rise to cough and in two cases haemoptysis has been recorded (Spence, 1955; Locke, 1963). However, in neither of these cases was the diagnosis confirmed pathologically. Finger clubbing has been recorded on one occasion (Hindle and Yates, 1965).

There have been descriptions of the chest radiographs in 24 of the 28 patients. The lesions have usually been described as rounded and nodular and have been single in 7 and multiple in 10. They have involved both lungs in eight. Cavitation has occurred in 3 cases with

single lesions and in 3 with multiple lesions. Pleural effusion or pleural thickening was present in 4 with multiple lesions, and in 2 with single lesions. In the remaining cases the nodules themselves did not produce a radiographic opacity. In 5 the appearances were due to an interstitial lung disease, in 1 there was a pleural effusion and in 1 pleural thickening. Thus the radiographic abnormality present may be multiple or single nodular lesions, sometimes with cavitation, and not infrequently associated with either pleural effusion or pleural thickening. Alternatively, the radiographic abnormality may be due either to interstitial lung disease or to associated pleural abnormalities without an obvious parenchymal density.

Since many of these patients died, and since in others there was no account of prolonged follow up it is only possible to obtain a picture of the natural history of these lesions from thirteen of the cases reported. In two the lesions increased either in size or number under observation. They either resolved or improved in three, one of which received chloroquine and corticosteroids, and the other corticosteroids alone. However, it is difficult to be sure whether the improvement was actually related to treatment or occurred spontaneously. In 4 cases the lesions remained unchanged over periods varying from 16 months to 8 years and in 1 cavitation was observed during follow up. In 2 there was no recurrence after excision, although a pleural effusion subsequently developed in 1 of them. Of special interest was the man described by Hindle and Yates (1965), who developed a pyopneumothorax due to rupture of a sub-pleural rheumatoid nodule. The same may have occurred in the man described by Cudcowicz et al. (1961), who developed a pyopneumothorax and broncho-pleural fistula, and who had previously been shown to have sub-pleural nodules on lung biopsy. However, no autopsy was

performed in this case, so it is not possible to be sure that rupture of the nodule was responsible.

In seventeen of these cases it was possible to grade the extent of the arthritis. It was mild in 29 per cent, moderate in 29 per cent, and severe in 41 per cent.

It would be anticipated that subcutaneous nodules would be common in these cases, and of 13 men in whom the data were recorded they were present in 10. In the women they were present in 2 of 3 in whom they were mentioned.

Since many of the systemic lesions in rheumatoid disease may be clinically silent or inconspicuous, an accurate measurement of their incidence can only be obtained by careful postmortem examination. Such examination has been recorded in eleven cases with intra-pulmonary rheumatoid nodules. A notable feature of these reports has been the high incidence of systemic lesions and these are shown in Table 18, overleaf.

Table 18. Systemic involvement in 11 patients with pulmonary nodules examined at autopsy

	male	female
cardiac	5	5
pleural	5	5
lymph gland	3	2
ocular [1]	2	2
arteritis	3	1
meninges	1	-
renal nodules	2	1
splenic capsule	-	2
spleen [2]	3	-
thrombocytopaenia	1	1
leg ulcer	-	1
neuropathy	1	1
liver nodule	1	-
oesophagus	-	1
amyloid	1	-

1. 1 F scleromalacia perforans, 1 M and 1 F episcleritis, 1 M keratoconjunctivitis sicca and iridocyclitis.

2. 1 M had a splenic nodule, 1 M amyloid.

The frequency of cardiac involvement was particularly striking, some abnormality being present in all except one case and the details are shown in Table 19, overleaf.

Table 19. Cardiac involvement in 11 patients with pulmonary nodules examined at autopsy

	male	female
pericardial nodules	1	1
pericardial effusion	-	1
pericarditis	3	5
myocarditis	2	3
myocardial nodules	1	1
endocarditis	2	1
endocardial nodules	2	-

In all but two cases a pericardial lesion was present. Two had nodules, with an effusion in one, and all the others had pericarditis or pericardial adhesions. Myocarditis was present in 5, with nodules in the myocardium in 2 others, and there was evidence of endocardial lesions in 5, these being nodular in 2. A comparitive assessment of the incidence of rheumatoid lesions of the heart can be obtained from a series of 100 autopsies reported by Cruickshank (1958). Forty nine of his cases had been admitted to hospital prior to death because of rheumatoid disease and 51 for inter-current illnesses. After excluding alternative causes he found evidence of pericarditis in 15 per cent, rheumatoid nodules in the heart in 5 per cent, myocarditis in 10 per cent and non-specific endocarditis, which he considered to be definitely of rheumatoid origin in 4 per cent, and probably so in 5 per cent. It appears, therefore, that subjects who develop intra-pulmonary nodules have a higher than expected incidence of cardiac involvement.

Haemoglobin levels were recorded in 11 men and 4 women. Amongst the men the figure in g. per 100 ml. was between 9.0 and 10.4 in 3, between 10.5 and 12.6 in 4 and 12.7 or more in the remaining 4. All

the women were anaemic, the levels being 8.9, 9.7, 10.9 and 11.5 g. per 100 ml. respectively. These numbers are of course too small from which to draw conclusions, but nevertheless, as might be anticipated, more were anaemic than would be expected in an unselected rheumatoid population.

The B.S.R. was recorded in seventeen cases and the results in both sexes combined are shown in Table 20, where they are compared with a series of patients with rheumatoid arthritis (Dawson et al., 1930).

Table 20. B.S.R. in patients with intra-pulmonary nodules and a series with rheumatoid arthritis

B.S.R. (mm. 1st. hr.)	Intra-pulmonary nodules	Rheumatoid arthritis Dawson et al. (1930)
0 - 20	0 (0%)	21%
21 - 40	12 (71%)	23%
41 - 60	1 (6%)	27%
61 +	4 (24%)	28%
TOTAL	17 (101%)	99%

As can be seen no patient with intra-pulmonary nodules had a B.S.R. of less than 20, and in most of them it was between 21 and 40. Although again, as might be anticipated, fewer of these cases had a B.S.R. of less than 20 than in an unselected rheumatoid population, there is no evidence that they tend to have an excessively high sedimentation rate.

Tests for the rheumatoid factor were recorded in 15 cases and were positive in all except 1. Actual titres were mentioned on only five occasions. These were an S.C.A.T. of 1:500, 1:128 and 1:64; a latex test of 1:5120 and an FII haemagglutination test of 1:1,764,000. It is, then as yet unknown whether there is any correlation between

the presence of intra-pulmonary nodules and high titres for the rheumatoid factor.

The peripheral blood was examined for L.E. cells in 10 cases and they were only present in 1 man (Robertson and Brinkman, 1961). There was no other suggestion of systemic lupus erythematosus in this patient, the striking feature of whom was the very large number of subcutaneous nodules.

X-rays of the joints were recorded in nine cases. They were normal in one and in the remainder there was evidence of rheumatoid arthritis of varying severity. It was not possible in this small group of cases to grade the changes.

The situation of the intra-pulmonary rheumatoid nodules has frequently been sub-pleural (Ellman et al., 1954; Flatley, 1959; Cudkowicz et al., 1961; Dumas et al., 1963; Hindle and Yates, 1965). Pathologically they have been described as firm nodular masses. In one the centre of the lesion contained sterile pus (Yates, 1963) and in another thick, yellowish green, pasty material (Noonan et al., 1963). The histological appearances have been essentially those of rheumatoid nodules encountered elsewhere. The association with other intra-thoracic complications, particularly pleural, has already been indicated.

In summary, intra-pulmonary nodules are a rare complication of rheumatoid arthritis. They have been reported more frequently in men and are often accompanied by pleural or other intra-pulmonary complications. There is a high incidence of subcutaneous nodules in these patients, who, as a group, are more anaemic and have a higher B.S.R. than an unselected rheumatoid population. Only one case has been reported with a negative test for the rheumatoid factor, which

correlates well with the results obtained in nodular rheumatoid arthritis. Other systemic manifestations, particularly cardiac lesions, are frequently associated. The radiographic appearances are in no way specific and the difficulties which may arise in diagnosis are obvious in view of the resemblance of these various appearances to tuberculosis and to primary and secondary malignant disease. Indeed, in view of the rarity of the intra-pulmonary rheumatoid nodule a patient presenting with such a radiographic abnormality would be more likely to be suffering from one of the latter conditions, and the need for pathological confirmation of the diagnosis of rheumatoid nodules in the lung requires no emphasis.

5. PULMONARY HYPERTENSION

Apart from the effects of interstitial lung disease on the pulmonary circulation pulmonary hypertension may occur as the sole intrathoracic accompaniment of rheumatoid arthritis. Wade and Ball (1957) in a series of ten cases of unexplained pulmonary hypertension described one woman with an arthritis of rheumatoid type, Raynaud's phenomenon and a positive S.C.A.T. Although no pathological examination was available, it was thought that she had an arteritis involving the pulmonary and digital vessels. In two other patients without arthritis in whom the test was done the S.C.A.T. was positive. Konn (1956) had described a similar case and the subject was reviewed with description of a third case by Gardner et al., (1957). This also was a female with rheumatoid arthritis, Raynaud's phenomenon and a positive S.C.A.T. who subsequently died from pulmonary hypertension, and autopsy revealed fibrous proliferation of the digital arteries and arterioles and similar changes in the pulmonary arterioles. These authors pointed out the importance of looking for evidence of pulmonary hypertension in rheumatoid subjects, especially when Raynaud's phenomenon was present.

Although rare, consideration of these cases is important. Raynaud's phenomenon may accompany unexplained pulmonary hypertension (Taft and Mallory, 1946; Wade and Ball, 1957) and some cases have a positive S.C.A.T. without arthritis. These features may accompany rheumatoid arthritis and these associations lend support to the view that some cases of unexplained pulmonary hypertension without arthritis may be related to rheumatoid arthritis or another connective tissue disease. It is important to look for evidence of these conditions in view of the possible benefit from corticosteroid therapy in an otherwise mortal disease.

6. PULMONARY INFECTIONS

During the last thirty years there have been occasional references to the incidence of acute and chronic infective lung disease in rheumatoid subjects. Kuhns and Joplin (1936) studied 452 selected cases with rheumatoid arthritis, ankylosing spondylitis or Still's disease (hereafter called the 'rheumatoid' group) and compared them with 198 cases with degenerative joint disease. Seventy six of the 'rheumatoid' group died and pneumonia was present in 24 per cent of them. Thirty eight of those with degenerative joint disease died, of whom 13 per cent had pneumonia. Baggenstoss and Rosenberg (1943) in an autopsy study found broncho-pneumonia in 9 (30%) of 30 cases. Fingerman and Andrus (1943) in a similar study found broncho-pneumonia in 24 (39%) of 61 cases and lobar pneumonia in 8. Bennett (1943), reporting autopsy findings in 48 cases, found pneumonia to be the cause of death in 8 (17%). Aronoff et al. (1955) described an autopsy study of 42 patients with rheumatoid arthritis and compared them with a control group. Terminal broncho-pneumonia was found in 21 per cent of the patients with rheumatoid arthritis and in 14 per cent of the controls. Brannan et al. (1964) found broncho-pneumonia in 31 (41%) in an autopsy series of 76 rheumatoid subjects, and Talbott and Calkins (1964) in a similar series of 37 cases found that 4 died as a result of pneumonia compared with 1 in their control series. At death, then, the incidence of pneumonia, although variable, has in general been quite high, and has exceeded the incidence in control groups where these have been studied.

During life one would anticipate an increased incidence of pneumonia in rheumatoid arthritis in view of the above findings and the studies of Lewis-Faning (1950) and Cobb (1953), both of whom reported an increased susceptibility to infections of all kinds in rheumatoid subjects. Short

et al. (1957) did indeed find a higher frequency of pneumonia when compared with a control group, but most of the attacks took place well before the onset of the arthritis. This finding was not in accordance with that of Lewis-Faning (1950), who found no significant difference in the incidence of pneumonia before the onset of rheumatoid arthritis compared with a control group. Talbott and Calkins (1964), from their finding of a higher incidence of non-specific increased densities and pneumonitis radiographically, believed that pulmonary infections were more frequent in rheumatoid subjects. Stack and Grant (1965) found pneumonic changes in 3 of their rheumatoid group and in 1 of their control group in a radiographic study.

Considering chronic infections, Fletcher and Lewis-Faning (1945) found the frequency of pulmonary tuberculosis to be 4.3 per cent amongst 254 rheumatoid patients and the study of Short et al. (1957) revealed an incidence of 5.5 per cent in their 293 patients. Kuhns and Joplin (1936) and Miall (1955) reported an increased frequency of pulmonary tuberculosis in controlled observations, but both Aronoff et al. (1955) and Stack and Grant (1965) found less in their rheumatoid patients than in their control groups.

Kuhns and Joplin (1936) found no examples of bronchiectasis amongst the 76 cases in their 'rheumatoid' group, whereas this disease was present in 2.6 per cent of those with degenerative joint disease. Baggenstoss and Rosenberg (1943), however, found 3 with bronchiectasis amongst 30 rheumatoid subjects studied at autopsy. Bach (1948) stated that he had the impression that there was more than a chance association between bronchiectasis and rheumatoid arthritis, particularly in men past middle age, and he described twelve examples. Aronoff et al. (1955) found that bronchiectasis was present in 6 of 253 cases of

rheumatoid arthritis, and in their x-ray study of 130 of these patients there were 4 with bronchiectasis compared with 2 in the control group. In their autopsy series of 42 patients, 5 with bronchiectasis were found in the rheumatoid group compared with none in the control group. Brannan et al. (1964) found 4 cases amongst 76 on which autopsy was performed. Stack and Grant (1965) found 12 with chronic inflammatory changes, including bronchiectasis, amongst 177 patients with rheumatoid arthritis compared with 4 in their control group. Short et al. (1957) found 4 cases amongst 293 with rheumatoid arthritis.

Aronoff et al. (1955) suggested as one possible explanation for their finding that it might be due to an increased susceptibility to infection in patients with rheumatoid arthritis. It is therefore of interest to review the temporal relationship between the onset of the two diseases in the patients reported. Of the 3 cases mentioned by Baggenstoss and Rosenberg the pulmonary symptoms preceded the arthritis in 1, followed the arthritis in 1 and in the third no details were given. Of the 12 described by Bach (1948) the arthritis preceded the lung symptoms in 2, but the relationship in the remainder was not clear. Of the 4 cases mentioned by Short et al. (1957) the pulmonary symptoms preceded the arthritis in 3. The relatively little attention that has been devoted to this point does not permit any firm conclusion.

Aronoff et al. (1955) found that 41 of their 253 patients had chronic bronchitis. In their comparative autopsy study the figures for bronchitis were 16 and 7 and for emphysema 10 and 9 respectively. Brannan et al., found 7 cases of bronchitis in their autopsy group of 76.

Stack and Grant (1965) found no difference in the incidence of

emphysema in their rheumatoid group compared with the control group.

In general there is relatively little information concerning pulmonary infections in rheumatoid arthritis. The studies on the frequency of pneumonia are interesting but conflicting. There is some evidence of an association between bronchiectasis and rheumatoid arthritis, but the relationship, if any, between the two diseases is not clear. There have been no detailed studies on the incidence of chronic bronchitis or of the possible effects of chronic lung infection on the natural history of the arthritis.

III. MATERIAL AND METHODS

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Two groups of patients have been studied.

1. The first group consisted of 516 patients who fulfilled the criteria for the diagnosis of definite or classical rheumatoid arthritis laid down by the American Rheumatism Association (Ropes et al., 1959). The object was to study a large population selected only by the factor of having been referred to hospital because of arthritis. Both new and follow up patients were accepted for the series in order to include cases of long standing. The series therefore comprised consecutive new cases and follow up cases attending the Rheumatism Clinic at the Leeds General Infirmary under one consultant (Dr. V. Wright) between January 1964 and June 1965. Also included were direct admissions to hospital for treatment of rheumatoid arthritis during the same period.

2. As a control group 301 patients with degenerative joint disease (D.J.D.), either primary or secondary osteoarthrosis or disc degeneration, were collected in a manner identical with the rheumatoid patients.

A third small series of patients, not included for purposes of comparison except where indicated, was referred by other physicians because of suspected pleuro-pulmonary manifestations of rheumatoid arthritis.

In each case a full history was taken and a complete clinical examination done. The proforma used for the recording of special information is shown in Appendix 1. A record was made of the age of onset of articular symptoms and their duration. Functional capacity was divided into 5 grades as defined by the Empire Rheumatism Council (1960) in their controlled trial of gold therapy in rheumatoid arthritis.

Depending on the number of joints involved in the upper and lower limbs and taking no account of small joint involvement the severity of the arthritis was divided into three grades as follows:-

mild	=	one or two large joints
moderate	=	three or four large joints
severe	=	more than four large joints

Joint involvement was defined as either deformity or the presence of two of the following three features, namely swelling, tenderness and limitation of movement. The presence or absence of subcutaneous nodules was noted, but if absent at the time of review they were considered present if they had been previously recorded by a physician. A careful note was made of any evidence of systemic complications, which are enumerated in the proforma. Treatment already received was noted. This included corticosteroid therapy, its duration and dose, as well as gold, anti-malarials or phenylbutazone.

In the respiratory system symptoms were noted and evaluated and special enquiry was made regarding previous respiratory diseases, including pneumonia, pleurisy, haemoptysis, pulmonary tuberculosis or other chest illness. The presence or absence of chronic bronchitis was also recorded, the condition being defined in this review as a cough productive of sputum on most days throughout periods of 6 months for at least 2 consecutive years without alternative cause.

Bronchiectasis, when present was divided into three grades:-

(a) Definite

1. If proven by bronchography.

2. In the presence of a history of continuous or intermittent cough, productive of purulent sputum with repeated haemoptysis or repeated

respiratory infections with physical signs consistent with the diagnosis and an abnormal chest x-ray due to localised collapse or shrinkage, definite cystic change or diffuse shadowing.

(b) Probable.

1. In the presence of a strongly suggestive plain x-ray, but without a typical history.

2. A typical history without the abnormalities on chest x-ray as listed above.

(c) Possible.

Localised shrinkage on chest x-ray without symptoms suggestive of the diagnosis.

Other previous illnesses were recorded as volunteered by the patient, unlike previous respiratory illnesses where their presence or absence was recorded in every case.

A record was made as to whether the patient was a smoker or non-smoker, and if the former whether he had stopped or still smoked. Smokers were grouped into those who smoked a pipe and those who smoked cigarettes. The daily consumption of cigarettes and the duration were recorded as indicated in the proforma. Present and previous occupations were noted and divided into those known to be associated with a pneumoconiotic hazard and those not so associated.

The haemoglobin level, white cell count and blood sedimentation rate were performed on each patient either at or within three months of the time of review. The Rose-Waaler differential agglutination of sensitised sheep cells (S.C.A.T.) was done on all the patients using the technique of Greenbury (1957). Again this was usually done at the time of review, but where previous readings were available the highest titre recorded was used for analysis. Routine examination of the urine

was done on all patients. L.E. cells in the peripheral blood were looked for in 248 patients. Serum proteins were estimated in 212 patients by a biuret method (Kingsley, 1940; Martin et al., 1950; Weischelbaum, 1956). Normal levels in our laboratory for albumin are 3.4 to 4.8 g. per 100 ml., and for globulin are 1.7 to 3.2 g. per 100 ml. Electrophoresis of the serum was done in 166 patients, using paper strips 5 X 12 cms. with a current of 0.2 mA./cm. width for 16 hours.

All patients had an x-ray of the chest. This was usually done at the time of review, but if a film had been taken within the previous twelve months and there had been no respiratory symptoms or illnesses since then the x-rays were not repeated. All these films were read personally without knowledge of the group to which they belonged and the abnormalities were recorded on the proforma. The presence or absence of pleural thickening was noted in every case, and in addition to obvious interstitial lung disease or diffuse parenchymal shadowing of alternative cause the lung markings were carefully scrutinised. Initially it was intended to attempt to distinguish between an increase in the vascular pattern and the presence of very slight interstitial shadowing but it rapidly became apparent that it was not possible to differentiate the latter with certainty from prominence of the fine pulmonary vessels. The attempt was therefore abandoned and the films were classified as showing lung markings increased, doubtfully increased or normal. Special note was also made of the presence or absence of pulmonary tuberculosis, including evidence of old primary infection, or cardiac size, and of fractured ribs.

All rheumatoid subjects had films taken of their hands and feet,

and those in the control group had films taken of the major joints involved. These films were read jointly (with Dr. V. Wright). Rheumatoid changes in the hands and feet were graded as normal, doubtful, mild, moderate or severe, and when assessing them films of both hands or both feet were taken into consideration. The criteria used were as follows:-

1. Severe.

   Four or more major erosions

   or deformity and at least two major erosions

   or bony ankylosis.

2. Moderate.

   Two or three major erosions

   or one major erosion and deformity.

3. Mild.

   one major erosion

   or unequivocal minor erosions.

4. Doubtful.

   juxta - articular rarefaction only.

Agreement was reached between the two observers in at least 90 per cent of cases. In those in which there was disagreement the films were discussed and a decision taken as to grade which was mutually acceptable.

Tests of lung function were performed on 54 patients who were divided into 5 groups.

Group 1.

Six of the patients with interstitial lung disease detected during study of the rheumatoid population and 3 others seen out of the series.

Group 2.

Six patients with interstitial lung disease not associated with rheumatoid arthritis apparently of the idiopathic type, who were referred for evaluation to the Respiratory Function Laboratory (General Infirmary at Leeds), while the author was working there.

Group 3.

Eighteen patients in the series, in whom chest x-ray was considered to show an increase in the lung markings.

Group 4.

Fifteen patients with a doubtful increase in lung markings.

Group 5.

Miscellaneous. There were 6 patients in this group, 2 with Caplan's syndrome, 1 who had had bilateral pleural effusions, 2 with normal x-rays and unexplained dyspnoea and 1 with known obstructive airways disease and dyspnoea for evaluation.

The following tests were employed:-

1. Minute Volume (M.V.). This was measured with a Wright's vane anemometer.

2. Lung Volumes. The residual volume was determined by the closed circuit helium dilution method (Gilson and Hugh-Jones, 1949). A Godard 'Pulmotest' was used for this determination, as well as for the other lung volume measurements.

3. The Forced Expiratory Volume in one second (F.E.V.) was also estimated using the Godart 'Pulmotest'.

4. Gas Transfer was measured by the carbon monoxide uptake test using the single-breath method by the technique described by Ogilvie et al. (1957).

5. Blood gas studies. The arterial carbon dioxide tension was

estimated by the re-breathing method of Campbell and Howell (1960) in the majority of cases. In a few blood was taken by needle puncture from the femoral artery and the oxygen tension was measured using a Beckman oxygen electrode. When arterial blood was taken the carbon dioxide tension was measured with the Astrup micro-electrode (Astrup et al., 1960).

Gas volumes were converted to B.T.P.S. (body temperature and pressure saturated). When expressed as a percentage of normal the latter was taken from the data of Needham et al. (1954) as modified by Comroe et al. (1962). Predicted normal values for gas transfer were obtained from the formulae of Ogilvie et al. (1957).

Pleural biopsy was performed under local anaesthesia using the Abrams punch (Abrams, 1958).

IV. RESULTS

IV. RESULTS

1. FEATURES OF RHEUMATOID AND CONTROL GROUPS

Sex and age

The sex distribution in the two populations is shown in Table 21. Of the rheumatoid patients 73 per cent were female and of the control patients 79 per cent.

Table 21. Sex distribution in patients with rheumatoid arthritis (R.A.) and degenerative joint disease (D.J.D.)

Sex	R.A.	D.J.D.
Male	140	62
Female	376	239
TOTAL	516	301

The age distribution is shown in Figure 3. The two groups were reasonably comparable, and in both, the majority of cases were in the fifth and sixth decades.

Clinical features of rheumatoid group

The age of onset and duration of the arthritis are shown in Figures 4 and 5.

The functional grading at the time of examination is shown in Table 22. The men were better functionally than the women.

Table 22. Functional grading in rheumatoid population (percentage in parenthesis).

	Grade					TOTAL
	1	2	3	4	5	
Male	22(16)	54(39)	46(33)	17(12)	1(1)	140
Female	23(6)	108(29)	170(45)	67(18)	8(8.2)	376
TOTAL	45(9)	162(31)	216(42)	84(16)	9(2)	516

Fig.3 *Age distribution of patients with R.A. and D.J.D.*

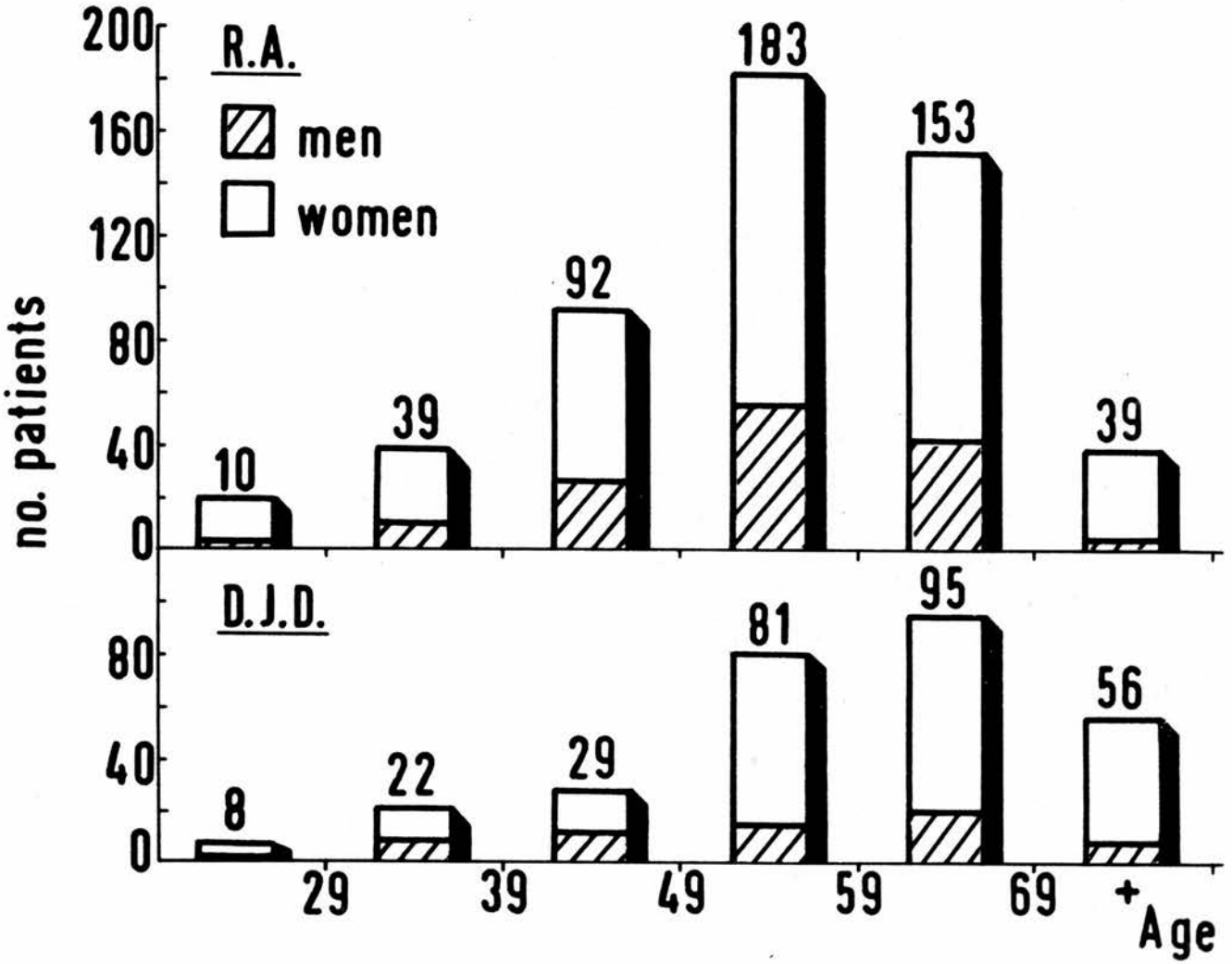


Fig. 4

Age of onset of rheumatoid arthritis

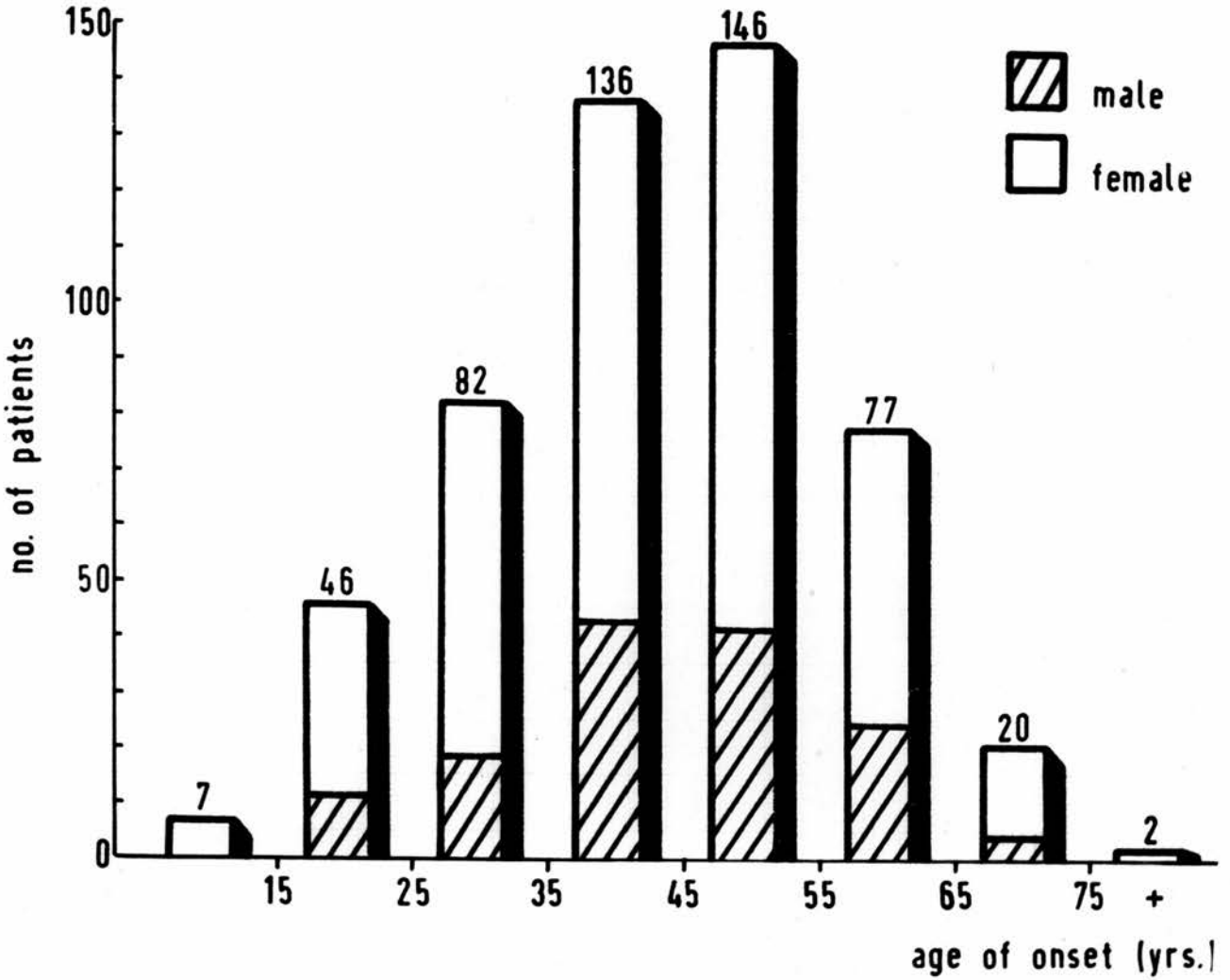
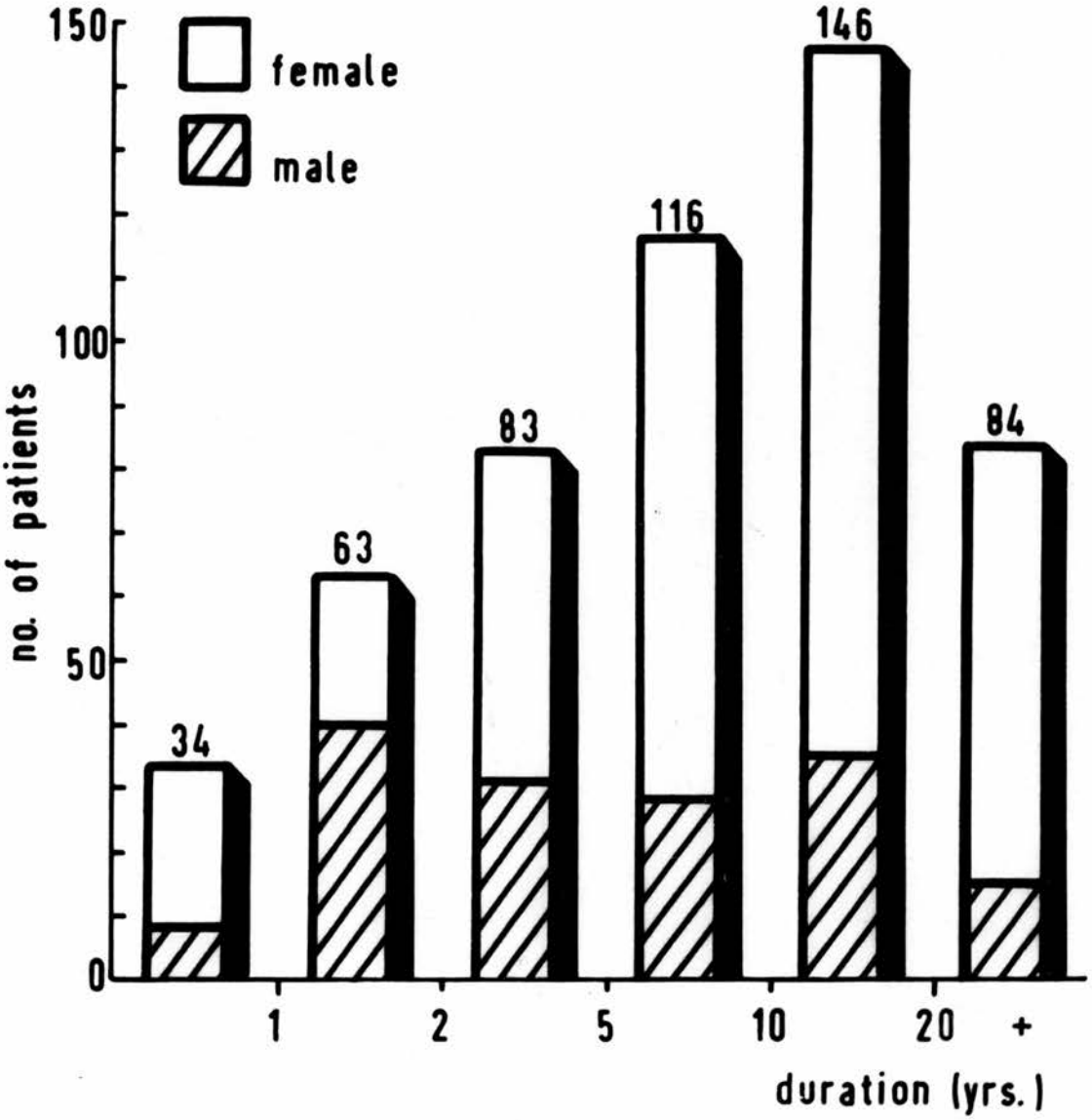


Fig. 5 *Duration of rheumatoid arthritis*



The extent of the arthritis was somewhat less in men (Table 23), a finding in keeping with the functional grading.

Table 23. Extent of rheumatoid arthritis in each sex (percentage in parenthesis).

	Extent of arthritis		
	Mild	Moderate	Severe
Male	41 (30)	36 (26)	62 (45)
Female	88 (24)	90 (24)	197 (53)

The extent was not recorded in 1 of each sex.

Subcutaneous nodules were present in 44 per cent of the men and in 25 per cent of the women. Leg ulcers were present in 12 rheumatoid patients, 10 of them women. In one woman they were undoubtedly due to ulcerated nodules, but in the others it was difficult to be sure of their precise pathogenesis. A leg ulcer was only present in one of the control group. A history of either superficial or deep venous thrombosis in the legs was obtained from 10 patients, 9 of them women, in the rheumatoid group compared with only 2 women in the control group. Thus the increased incidence of leg ulcers in the rheumatoid group does not necessarily imply that these were a specific feature of the rheumatoid process.

Ocular lesions were present in 17 women, episcleritis in 9, kerato-conunctivitis sicca in 4, iritis in 2 and corneal ulcers in 2. Three men had ocular lesions, episcleritis in 2 and kerato-conjunctivitis in 1. No special examination was done for kerato-conjunctivitis sicca unless symptoms were present which suggested this diagnosis. Splenomegaly was present in 17 patients, 3.4 per cent of the total; 6 were men (4%) and 11 were women (3%). Neuropathy was present in 8 cases and myopathy in 6. Electro-myography was done in all these patients and motor

point muscle biopsy in most of them. Pericarditis was present in 7 patients, 3 men and 4 women. The diagnosis was confirmed at autopsy in 2 of the men.

Valvular heart disease was present in 15 of the rheumatoid subjects (2.9%) and in only 4 of the control series (1.3%). This finding was of interest, particularly in view of the fact that a previous history of rheumatic fever or chorea was obtained from 3.5 per cent of the rheumatoid group and 4.8 per cent of the control group. Moreover, aortic valve disease was present in 8 rheumatoid subjects, compared with 2 in the control group. These findings suggest that at least some of the valvular lesions were rheumatoid rather than rheumatic in origin, and this may have applied particularly to those with aortic disease.

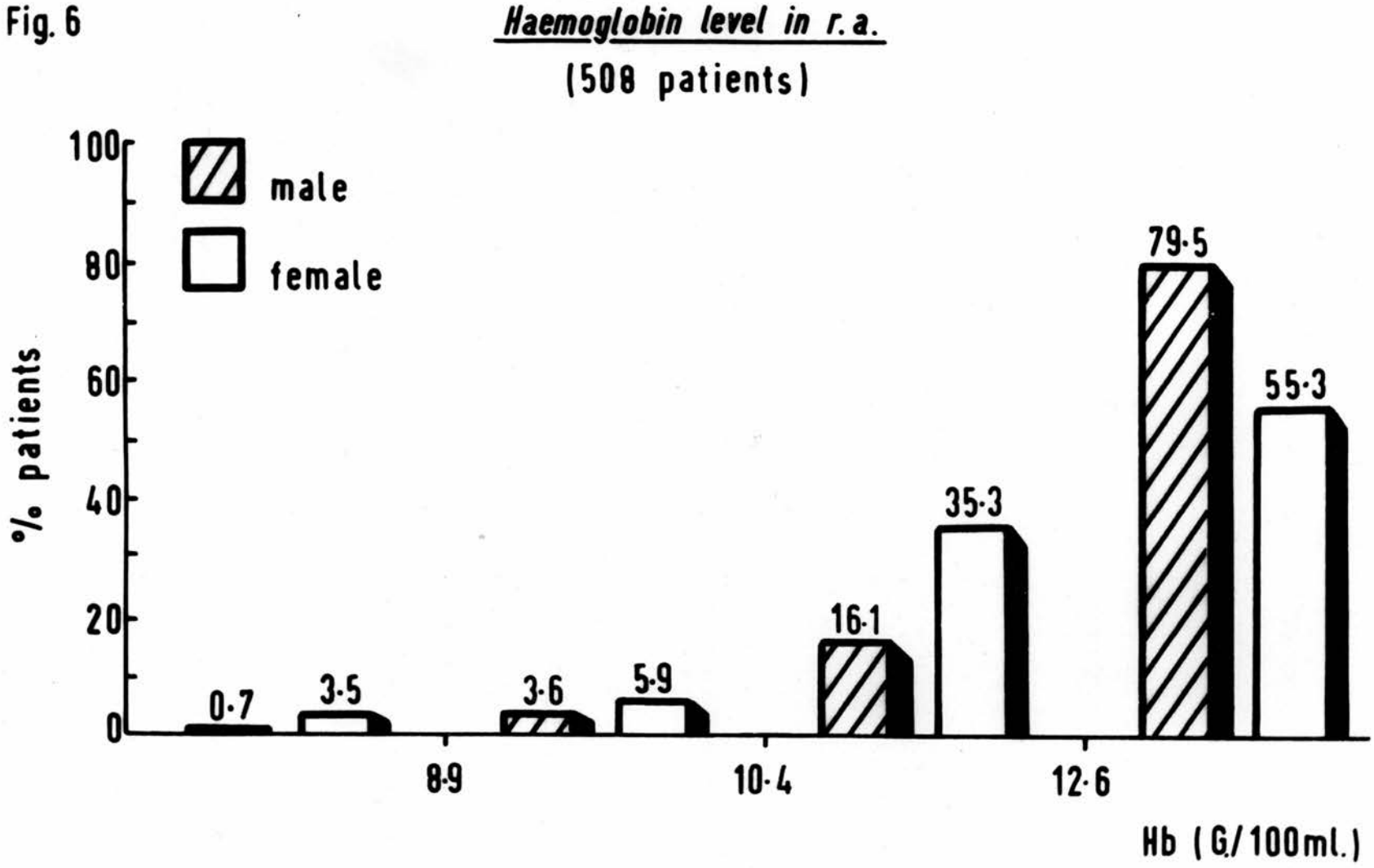
Laboratory investigations

The haemoglobin levels in 508 of the rheumatoid patients are shown in Figure 6. Anaemia was more frequent in the women than in the men. These figures can be compared with the control group in which 55 (93%) of 59 men, in whom the haemoglobin was recorded, had a level greater than 12.6 g. per 100 ml. Of 236 female controls, who had the haemoglobin estimated, 194 (79%) had a level greater than 12.6 g. per 100 ml. These results are in keeping with the well established fact that anaemia is a feature of rheumatoid arthritis and is more common in women than in men.

Table 24. B.S.R. in patients with rheumatoid arthritis (percentage in parenthesis).

	B.S.R. (mm.1st.hr)				TOTAL
	0-20	21-40	41-60	61+	
Male	41(29)	41(29)	28(20)	29(21)	139
Female	90(24)	107(29)	107(29)	64(17)	368
TOTAL	131(26)	148(29)	135(27)	93(18)	507

Fig. 6


Haemoglobin level in r.a.
(508 patients)
male
female
% patients
100
80
60
40
20
0
0·7
3·5
3·6
5·9
16·1
35·3
79·5
55·3
8·9
10·4
12·6
Hb (G/100ml.)

The levels of the blood sedimentation rate (B.S.R.) are shown in Table 24. They are fairly comparable with the series of Dawson et al. (1930), although a greater percentage of his cases (28%) had a level greater than 60 mm. 1st. hr. and rather fewer had a level less than 20 mm. 1st. hr. These differences can probably be explained by the introduction of various methods of treatment which lower the B.S.R. since Dawson and his colleagues investigated their cases.

The white cell counts in 429 of the rheumatoid patients are shown in Table 25.

Table 25. White blood count in rheumatoid arthritis (429 patients)

	male	female	TOTAL
< 3,000	-	1	1
3-5,000	10	51	61
5-10,000	89	231	320
10-15,000	19	24	43(10%)
15,000 +	-	4	4(0.9%)

The distribution of the titres of the S.C.A.T. is shown in Figure 7. A titre of less than 1:32 was present in 28 per cent of the women and 16 per cent of the men and a titre of 1:512 or greater was obtained in 37 per cent of the men and 26 per cent of the women. In the control group none of 51 men tested had a titre of more than 1:16. In the women ten (4.8%) of those tested had a titre of 1:32 or greater. This figure in the women is in keeping with the findings in a random population (Ball, 1964).

L.E. cells were looked for on at least one occasion in 248 of the rheumatoid patients, and were present in 14 (6%), see Table 26.

Fig. 7

Titre of rheumatoid factor (s.c.a.t.) in r. a.

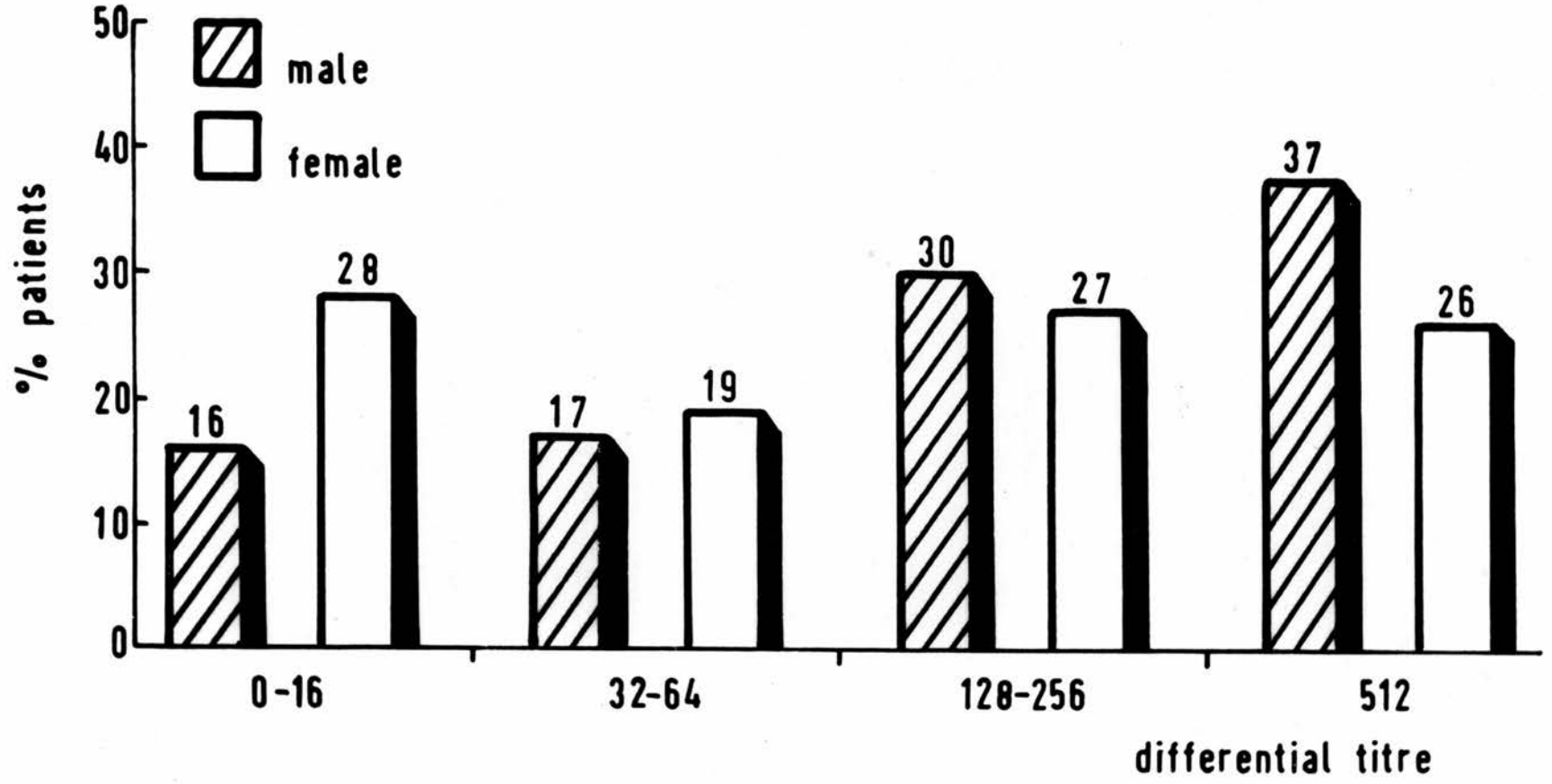


Table 26. L.E. cells in rheumatoid arthritis (248 patients)

	male	female	TOTAL
numerous	1	7	8(3.4%)
scanty	1	5	6(2.6%)
absent	57	177	234

Serum protein estimations were done in 212 patients and the electrophoretic pattern in 166 (Table 27). The common abnormalities on electrophoresis were an increase in the alpha 2 or gamma globulins.

Table 27. Serum protein changes in rheumatoid arthritis

	male %	female %	total %
low albumin	26	16	19
high globulin	32	23	26
abnormal electrophoresis	74	65	68

Radiographs of the hands were available in 503 cases of rheumatoid arthritis and of the feet in 486 and the findings are summarized in Tables 28 and 29.

Table 28. X-ray grade in hands of rheumatoid patients (percentage in parenthesis).

	X-ray grade					
	Normal	Doubtful	Mild	Moderate	Severe	TOTAL
Male	13(10)	16(12)	30(22)	22(16)	52(39)	133
Female	26(7)	32(9)	73(20)	48(13)	191(52)	370
TOTAL	39(8)	48(10)	103(21)	70(14)	243(49)	503

Table 29. X-ray grade in feet of rheumatoid patients (percentage in parenthesis).

	X-ray grade					TOTAL
	Normal	Doubtful	Mild	Moderate	Severe	
Male	17(13)	12(9)	28(22)	25(19)	47(36)	129
Female	35(10)	20(6)	93(26)	72(20)	137(38)	357
TOTAL	52(11)	32(7)	121(25)	97(20)	184(38)	486

Previous drug therapy

In those with rheumatoid arthritis 65 per cent of the men and 71 per cent of the women were receiving or had previously received corticosteroid therapy. In only 23 of these had the dose exceeded the equivalent of prednisolone 10 mg. daily. Of 89 men in whom the information was available 67 had received corticosteroid therapy for longer than 6 months, and for women 225 of 259 had also received this treatment for longer than 6 months. Gold had been administered to 203 patients, anti-malarial therapy to 114, either hydroxy-chloroquine or chloroquine, and 290 had received phenylbutazone.

Previous medical history

Of the rheumatoid patients 2.5 per cent had ischaemic heart disease, diagnosed on the basis of a history of angina pectoris or of myocardial infarction, compared with 3.6 per cent of the control group. Gall bladder disease was present in 4.5 per cent of the rheumatoids and in 5 per cent of the controls. Hiatus hernia producing symptoms and confirmed by barium meal was present in 2.9 per cent of the rheumatoids and 2 per cent of the controls. These patients were all women except one male rheumatoid. The incidence of peptic ulceration in the stomach or duodenum was 6.8 per cent in the rheumatoid group and 4.6 per cent in the control group. The only striking difference

between the two groups in this respect was that 2.3 per cent of the rheumatoids had a gastric ulcer compared with 0.3 per cent of the controls. The gastric ulcers were confirmed by barium meal. It should however be stated that the relationship between peptic ulceration and the onset of the arthritis or any possible effects of therapy was not specifically studied.

Thyroid disease including hyperthyroidism, hypothyroidism, Hashimoto's disease and simple goitre was present in or had occurred in 3.9 per cent of the rheumatoids and 2.3 per cent of the controls. All these patients were women except for one male rheumatoid.

The comparitive incidence of various infective processes in the two groups is shown in Table 30. These do not include chest infections which are considered separately. Under chronic infection have been included any condition of an infective nature with symptoms which were more than temporary, and examples of these were sinusitis, pyelonephritis, osteomyelitis and mastoiditis. There was no significant difference in the incidence of any of those listed with the exception of herpes zoster.

Table 30. Incidence (per cent) of infections in patients with rheumatoid arthritis and those with degenerative joint disease.

	chronic infections	diphtheria	malaria	infective hepatitis	herpes zoster
R.A.	3.9	2.3	0.9	1.9	2.9
D.J.D.	4.0	2.3	1.3	1.0	0.7

Smoking habits

Comparison of the smoking habits in the two groups showed no difference in the women (Table 31). In the rheumatoid group 60 per

cent were non-smokers compared with 65 per cent of the women in the D.J.D. group.

Table 31. Smoking habits in women with r.a. and d.j.d. (percentage in parenthesis).

Duration (yrs.)	Cigarettes/day					
	1 - 10		11 - 20		> 20	
	r.a.	d.j.d.	r.a.	d.j.d.	r.a.	d.j.d.
0 - 10	30(8)	18(8)	3(0.8)	6(3)	-	1(0.4)
11 - 20	25(7)	13(5)	9(2)	4(2)	-	2(1)
> 20	61(16)	22(9)	19(5)	13(5)	3(0.8)	2(1)

Of the men, however, only 10 (7%) of 140 with rheumatoid arthritis compared with 12 (19%) of 62 with D.J.D. were non-smokers. The difference was significant ($t = 2.54$, $n = 202$, $P < 0.02$). Analysing the male smokers the difference between the two groups fell mainly in those who smoked 11 - 20 cigarettes daily for more than 20 years (Table 32).

Table 32. Smoking habits in men with r.a. and d.j.d. (percentage in parenthesis).

Duration (yrs.)	Cigarettes/day					
	1 - 10		11 - 20		> 20	
	r.a.	d.j.d.	r.a.	d.j.d.	r.a.	d.j.d.
0 - 10	3(3)	3(5)	3(3)	-	-	11(18)
11 - 20	7(5)	2(3)	5(4)	2(3)	6(4)	-
> 20	30(21)	13(21)	46(33)	12(19)	19(14)	9(15)

For pipe smoking the figures were 7 per cent in the rheumatoid group

and 10 per cent in the D.J.D. group.

Only two of the men in the rheumatoid group started smoking after the onset of arthritis.

2. PREVIOUS AND CONCURRENT RESPIRATORY ILLNESSES

A. PLEURISY

Incidence

The number of patients giving a history of pleurisy in the two groups is shown in Table 33.

Table 33. Episodes of pleurisy in R.A. and D.J.D. (percentage frequency in parenthesis).

	Male	Female	TOTAL
R.A.	39 (28)	68 (18)	107 (21)
D.J.D.	4 (6)	32 (13)	36 (12)

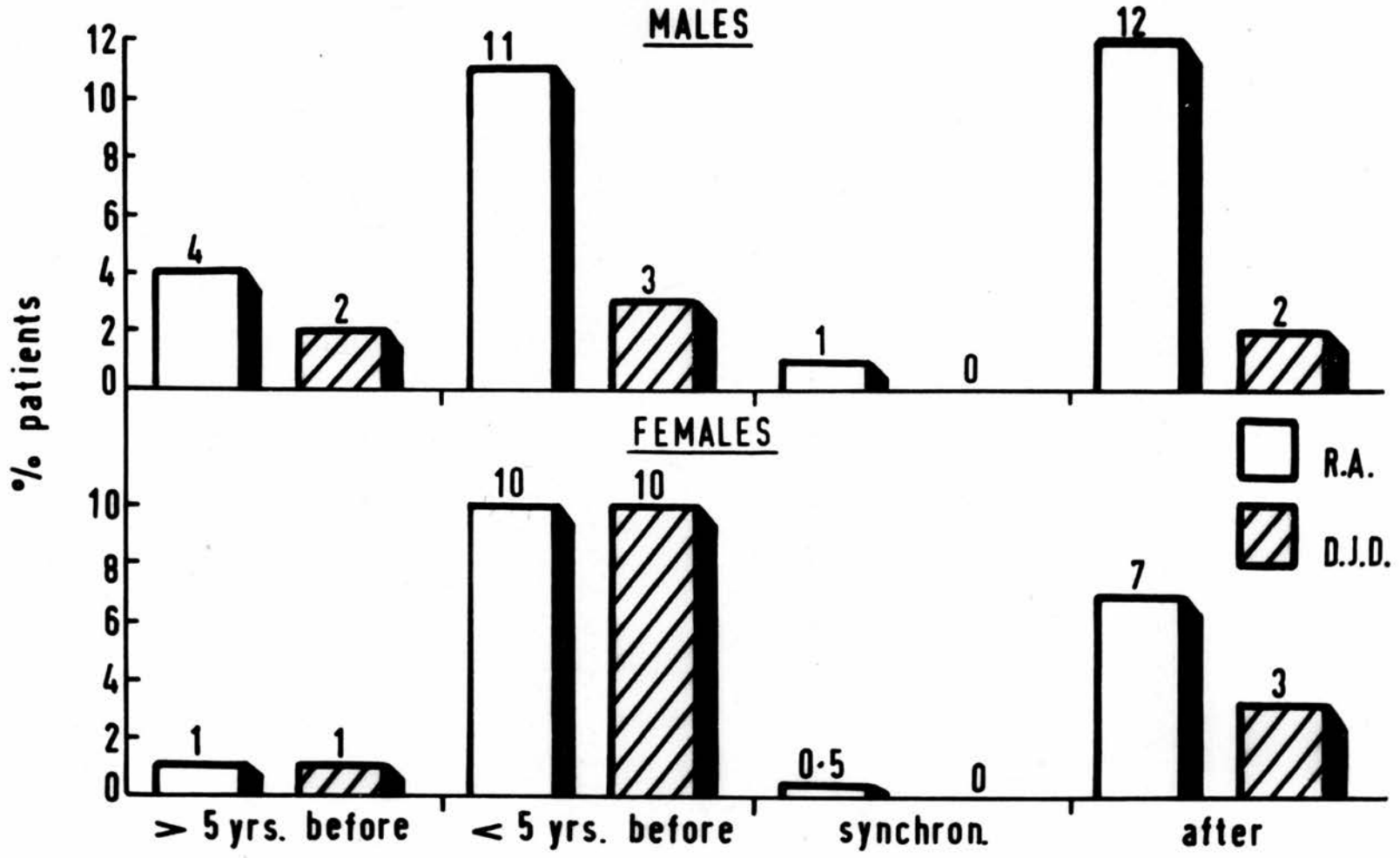
Pleurisy was more common in the rheumatoid group, and in the men the difference was significant ($\chi^2 = 10.5$, $P < 0.01$).

Temporal relationship

The distribution of the attacks of pleurisy in relation to the onset of arthritic symptoms in the two groups is shown in Figure 8. There was no difference in the incidence of pleurisy occurring more than five years before the onset of arthritis. Within five years of the onset of arthritis, however, although there was no difference between the two groups in women, attacks of pleurisy were more common in the men with rheumatoid arthritis. One per cent of the men and 0.5 per cent of the women with rheumatoid arthritis gave a history of pleurisy synchronous with the onset of arthritis. Such a history was not obtained from any patient in the D.J.D. group. After the onset of arthritis pleurisy was more common in the rheumatoid group in both sexes, the difference being particularly striking in the men. In the rheumatoid group 2 men and 2 women had an exacerbation of arthritis coincident with an attack of pleurisy, whereas this did not occur in the D.J.D. group.

Fig. 8

Relation of pleurisy to onset of arthritis



Comment

These figures revealed that attacks of pleurisy occurred more frequently in the rheumatoid group than in the D.J.D. group. They were more common in the men (28%) compared with the women (18%). The association was emphasised by the fact that in men attacks of pleurisy were 4 times more common within 5 years of the onset of arthritis, and 6 times more common during the course of the arthritis in the rheumatoid group compared with the D.J.D. group.

B. PLEURAL SHADOWING

The incidence of pleural abnormality on the chest radiographs is shown in Figure 9. This included pleural effusion and varying degrees of pleural thickening, including obliteration of the costo-phrenic angle. There was a significant difference in the incidence in both sexes between the rheumatoid and D.J.D. groups. Patients with apparent pleural thickening were then divided into those who had a possible cause for the radiographic abnormality and those who did not. The conditions accepted as possible causes were as follows:-

1. Pneumonia at any time.
2. X-ray evidence of tuberculosis (primary or secondary).
3. Fractured rib on the same side as the pleural abnormality.
4. Bronchiectasis.
5. A history of pulmonary infarction.
6. The presence of congestive cardiac failure when the film was taken.

A history of pleurisy itself was not accepted as a cause for the pleural abnormality, since some cases in the rheumatoid group might have had a rheumatoid pleuritis and evidence of this was being sought. The division of patients into those with pleural thickening without a cause and those with a cause is shown in Figure 10. In both sexes in the D.J.D. group and in the female patients with rheumatoid arthritis about half had a cause, but among men with rheumatoid arthritis a greater percentage remained unexplained. The figure also shows a difference between the incidence of unexplained pleural shadowing in the men with rheumatoid arthritis compared with the D.J.D. group, and this was statistically significant ($P < 0.02$).

The incidence of unilateral and bilateral pleural shadowing is shown in Figure 11. Unilateral pleural abnormality was more common in the rheumatoid than in the D.J.D. group.

Fig. 9 *Incidence of pleural shadowing (total)*

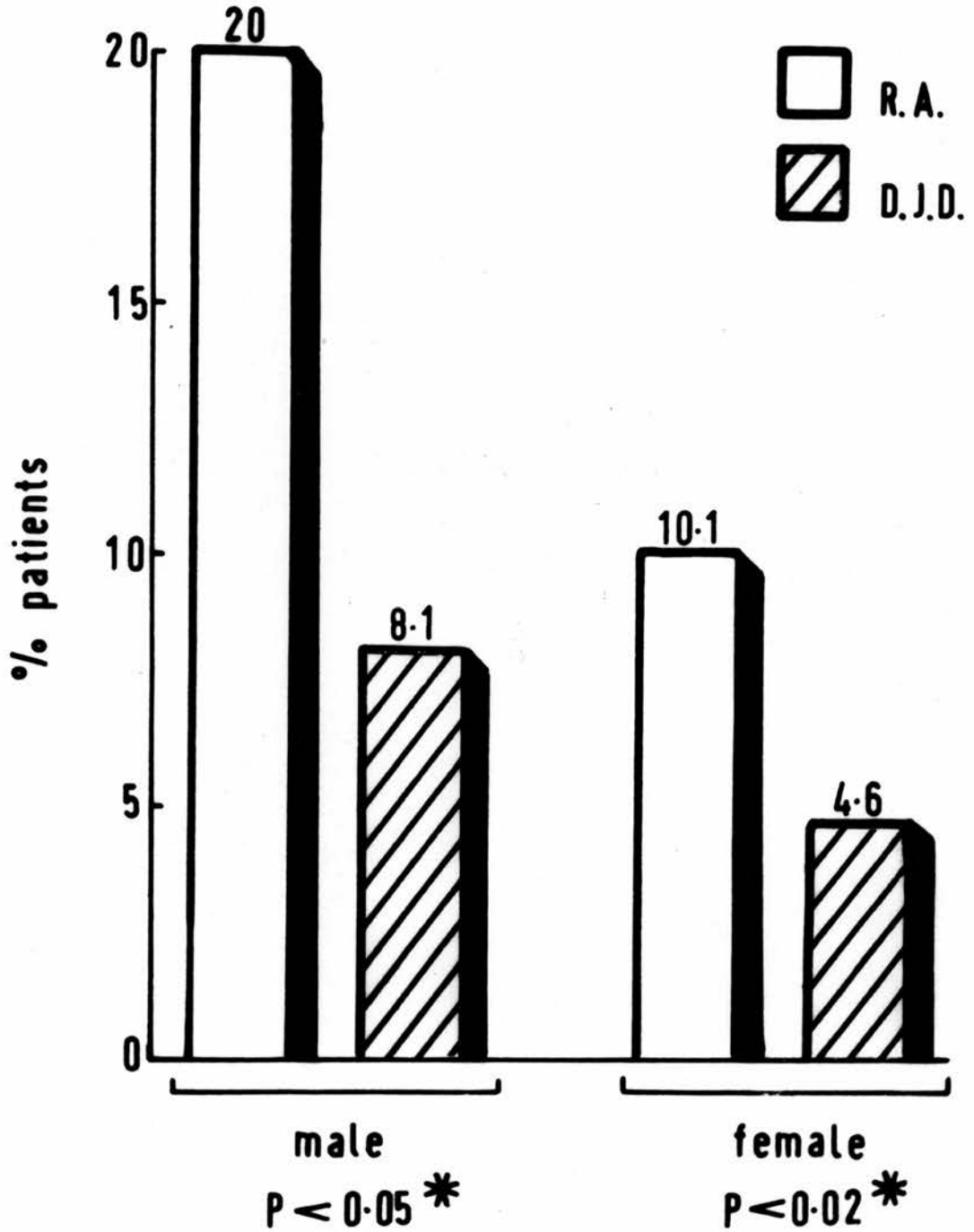


Fig. 10 *Incidence of pleural shadowing*

(with & without an alternative cause)

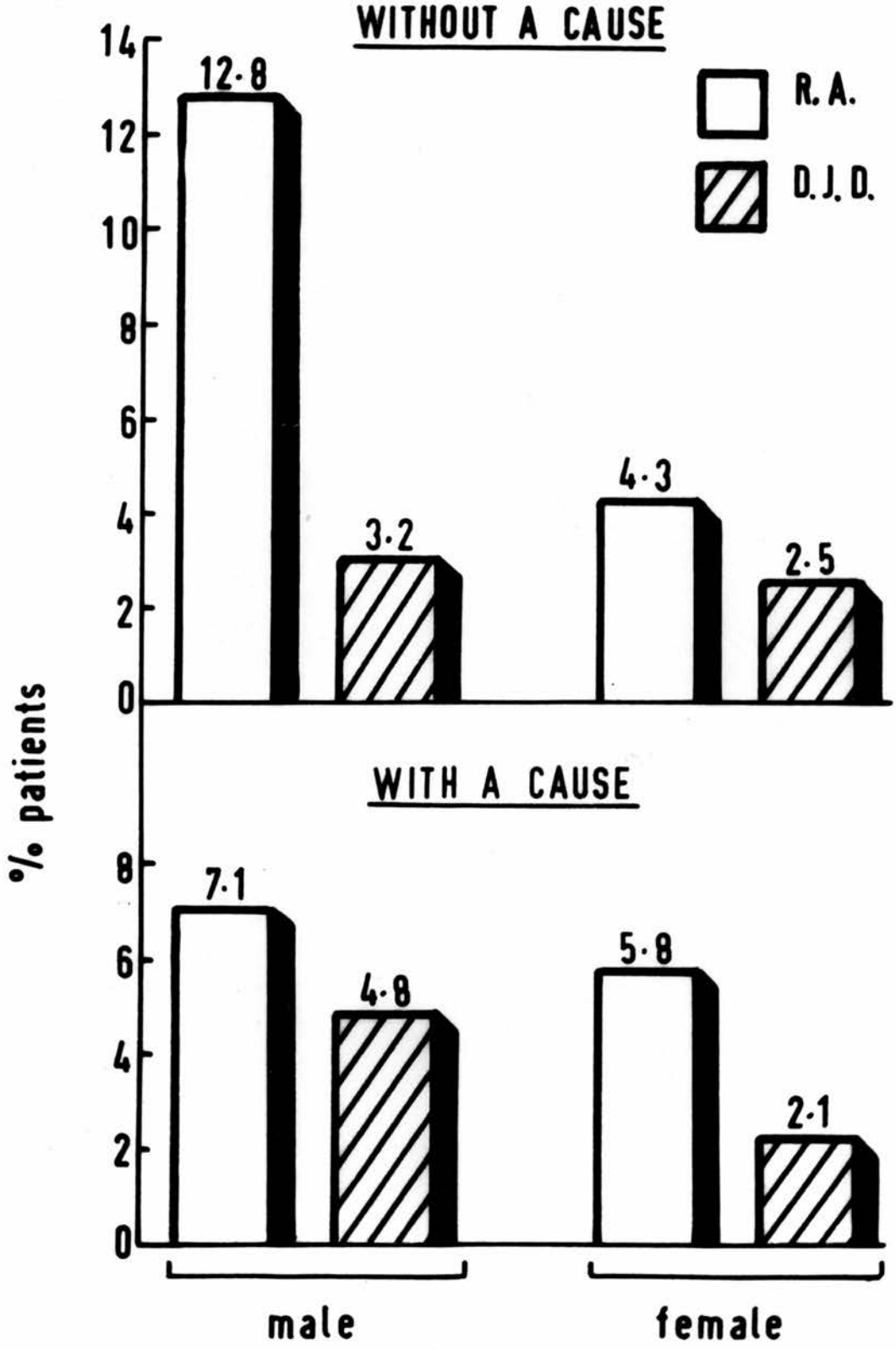
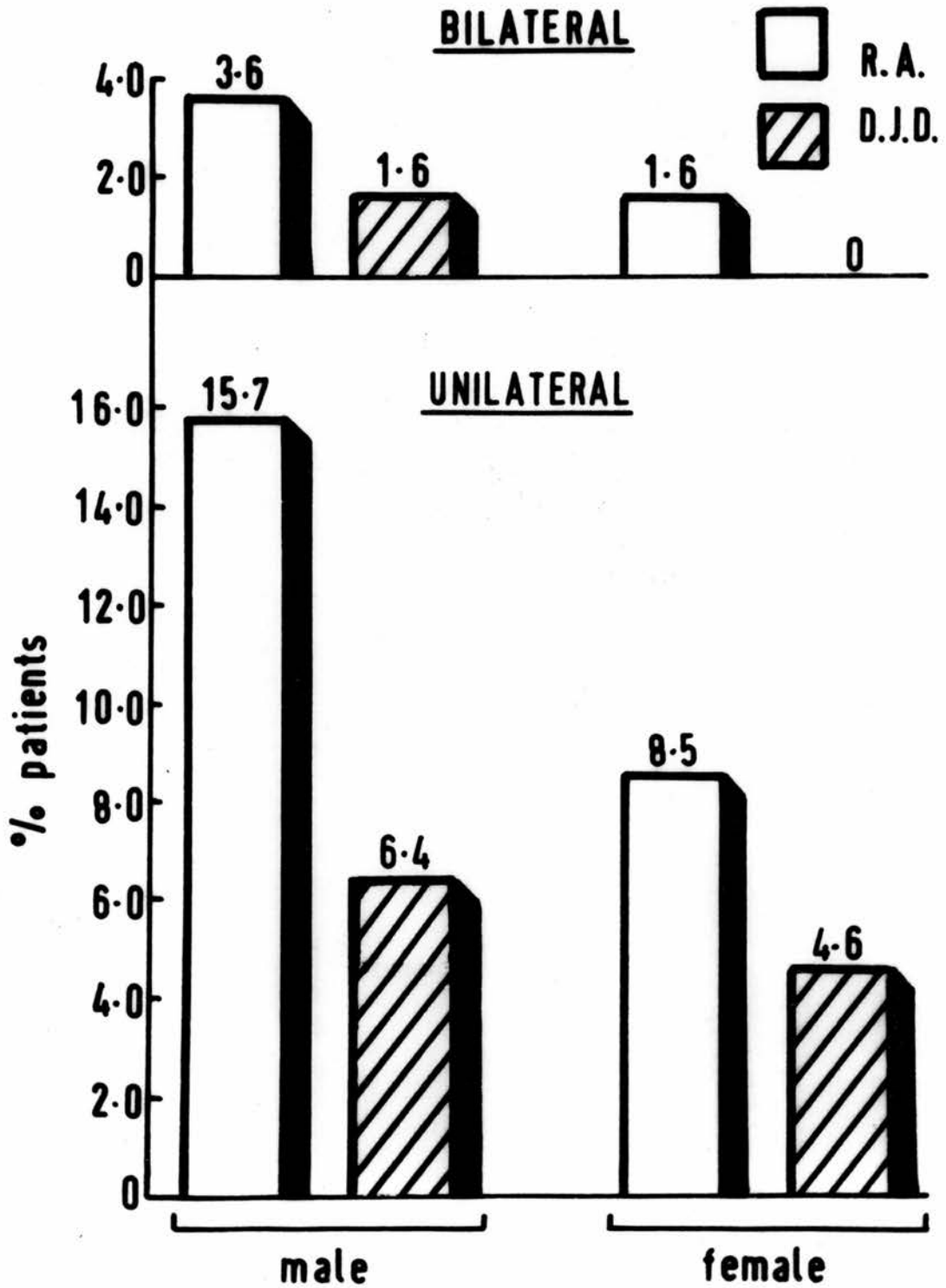


Fig. 11

Incidence of unilateral & bilateral pleural shadowing (total)



C. PLEURAL EFFUSION

The cases now to be considered and labelled the pleural effusion group were those who had a pleural effusion at the time of examination, or those with a history of a pleural effusion during the course of their rheumatoid arthritis. They were accepted as rheumatoid pleural effusions when there was no evidence of an alternative cause such as tuberculosis, carcinoma, pulmonary embolism, cardiac failure or evidence of underlying pneumonia. The majority of these cases had been fully investigated personally, and when this was not so the case records were carefully scrutinized for evidence of the above conditions.

Incidence

Eleven of the men with rheumatoid arthritis and 6 of the women had a pleural effusion considered due to the rheumatoid process. The incidence in the whole group was 3.3 per cent, in the men 7.9 per cent and in the women 1.6 per cent. There were two rheumatoid patients who had a pleural effusion for which there was an alternative cause. In the D.J.D. group there were 2 women who had a pleural effusion and in 1 of them there was no convincing evidence of any of the causes listed above. The difference in the incidence of unexplained pleural effusion in the rheumatoid group compared with the D.J.D. group was statistically significant ($\chi^2 = 6.1$, $P < 0.02$).

Clinical features of arthritis

There were too few women for any conclusion to be drawn regarding the age of onset of the arthritis. In the men 46 per cent of those in the effusion group developed arthritis before the age of 45 years compared with 51 per cent of the rheumatoid male population. The age of onset in other decades corresponded quite well with the rheumatoid population.

Combining the sexes in the effusion group there was no difference functionally compared with the entire rheumatoid population. The extent of the arthritis was similar in the pleural effusion group and the rheumatoid population (Table 34).

Table 34. Extent of arthritis (percentage figures) in patients with pleural effusions and the rheumatoid group.

	Mild	Moderate	Severe
Effusion group	12	35	53
R.A.	25	24	52

The duration of arthritis in those with effusion was slightly more prolonged than in the group as a whole, and therefore there is no evidence to suggest that pleural effusion was more likely to occur in severe arthritis.

Subcutaneous nodules were present in 8 men and 2 women in the pleural effusion group, 73 per cent and 33 per cent respectively. In the rheumatoid population 44 per cent of men and 25 per cent of women had subcutaneous nodules.

Systemic lesions

None of the women in the pleural effusion group had any systemic manifestation of rheumatoid arthritis. Of the 11 men, 1 had splenomegaly compared with 5 of the remaining men in the rheumatoid population; 1 had a myopathy compared with 3 other proven cases; 3 had pericarditis, 1 of them a year after his effusion, and these were the only 3 examples of pericarditis encountered amongst men in the whole series.

Laboratory investigations

There was no difference in the haemoglobin levels of the men with effusions compared with the male rheumatoid population. A haemoglobin

of less than 12.6 g. per 100 ml. was present in 27 per cent of men with effusions and in 20 per cent of the rheumatoid group. In the women a haemoglobin level of less than 12.6 g. per 100 ml. was present in 67 per cent of the effusion group compared with 44 per cent of the rheumatoid group, but there were only six with pleural effusions. There was no difference in the B.S.R. Of those with effusions 41 per cent had a B.S.R. of greater than 40 mm./1st hr., and in the rheumatoid group 45 per cent.

Comparing the results of the S.C.A.T. in the pleural effusion group with the rheumatoid population as a whole no significant difference was apparent.

Eighteen per cent of the pleural effusion group had L.E. cells in the peripheral blood compared with 6 per cent of the rheumatoid group. However, it should be noted that all of the effusion group were examined for L.E. cells, whereas only 48 per cent of the rheumatoid population had this investigation.

A low serum albumin was more common (9 of 14, 64%) in the effusion group than in the total rheumatoid population (41 of 212, 19%). This was a significant difference ($\chi^2 = 15.1$, $P < 0.01$). The serum globulin levels were similar in the two groups. They were raised in 31 per cent of the effusion group, compared with 26 per cent of those examined in the rheumatoid population. An abnormal electrophoretic pattern was present in 86 per cent of those with effusions, compared with 68 per cent of the total who had this examination done.

Joint radiographs

There was no difference in the severity of the changes in the hands or feet between the two groups.

Other respiratory diseases

Chronic bronchitis occurred in 36 per cent of the men with effusions as opposed to 22 per cent of the total male rheumatoid population but neither this nor other respiratory diseases were significantly more frequent in the pleural effusion group.

Smoking histories

In the pleural effusion group four (24%) were non-smokers compared with 45 per cent of the rheumatoid population as a whole. The men who smoked heavily were divided into groups according to the number of cigarettes smoked and the duration. The distribution of smoking habits amongst the men who smoked more than ten cigarettes daily was similar in the pleural effusion group and the total male rheumatoid population (Table 35).

Table 35. Smoking habits given as percentage in rheumatoid men with pleural effusions compared with the male rheumatoid population.

	No. of cigarettes daily and duration		
	> 10 11-20 yrs.	11-20 > 20 yrs.	> 20 > 20 yrs.
Effusion group	9	36	18
Total R.A. group	8	33	14

Occupation

Only one in the effusion group had been exposed to noxious dusts (a furnace cleaner in an iron foundry), compared with 10 per cent of the total rheumatoid population.

Temporal relations

Nineteen patients (13 men and 6 women) were considered, 17 from the series and 2 specially referred. The relationship between the time of development of the effusion and the onset of the arthritis is shown in Table 36.

Table 36. Onset of effusions related to onset of R.A. - 22 episodes in 19 patients.

	Before	Synchronous	Years after			
			< 5	6-10	11-20	> 20
Male	1	2	5	2	4	2
Female	0	2	1	1	1	1
TOTAL	1	4	6	3	5	3

The effusion came first in one man, preceding the arthritis by a period of at least 6 weeks. In four (18%) the effusion occurred synchronously with the arthritis. The onset was regarded as synchronous if either occurred within four weeks of the other. In exactly half of the cases the effusion either preceded or developed within five years of the arthritis. The remainder occurred after varying intervals and some developed in very long-standing cases. In 4 there was an exacerbation of the arthritis at the time the effusion developed, and in 1 it occurred very shortly after the appearance of subcutaneous nodules.

Respiratory symptoms

In 1 man and 1 woman there were no symptoms attributable to the pleural effusion, both being detected by routine chest radiography. Either unilateral or bilateral pleuritic pain occurred in 10 men and 5 women. Dyspnoea of varying severity occurred in 7 men and 3 women, 3 men and 3 women had cough, and in 1 man and 1 woman fever was

definitely known to occur. In the majority of cases, therefore, symptoms did occur, pleuritic pain being the commonest.

Characteristics of effusion

The effusion was bilateral in 4, on the left side in 6, and on the right side in 12. The size of the effusions was variable. For example, in one case the collection of liquid (proven at aspiration) did little more than produce obliteration of the costo-phrenic angle, whereas in others the fluid produced a radiographic opacity involving about half of the hemi-thorax. In the main there was a moderate amount of fluid involving between one third and one half of the hemi-thorax.

In all but two cases the fluid on aspiration was serous, straw coloured liquid. In one the fluid seemed slightly blood stained, but it is likely that this was traumatic. In the other the fluid on initial aspiration was purulent.

Differential cell counts were done on the pleural fluid in 13 cases. The fluid was predominantly lymphocytic in 6, polymorphs predominated in 3, and in the remaining 4 there was a mixed cell population.

The glucose levels in 12 specimens of pleural fluid from 8 patients are shown in Table 37.

Table 37. Glucose levels in the pleural fluid.

Patient	mg./100 ml. glucose
E.B.	112, 122, 105
L.H.	0
W.S.	65
E.S.	120
G.W.	16
W.H.	40, 60
N.D.	80, 85
J.J.	60

In one case no glucose was present and in another the level was very low at only 16 mg. per 100 ml. In a third the initial level was 40 mg. per 100 ml., but two and a half months later the level had increased to 60 mg. per 100 ml. In the remainder the initial level was 60 mgs. or more. In one case the level was followed serially over a period of 10 months. It was above 100 mg. per 100 ml. on each occasion.

Protein levels were done on the pleural fluid in seven cases. The levels varied from 3.7 to 5.5 g. per 100 ml. These figures were consistent with the fact that the effusion was an exudate in each case.

In eight patients the S.C.A.T. was done on both the blood and the pleural fluid. The titres are shown in Table 38.

Table 38. S.C.A.T. in pleural fluid and blood.

Patient	Pleural	Blood
E.B.	512, 512, 256	128
L.H.	negative	negative
W.S.	256	256
G.W.	1024	256
N.D.	negative	negative
A.G.	512	32
E.S.	512	512
J.J.	negative	negative

In three cases the S.C.A.T. was negative in both the blood and the pleural fluid. In 3 of the remaining 5 there was more than a one tube difference in the titres, that in the pleural fluid being higher than in the blood in each case. In the remaining two there was no difference in the titres.

Pleural Pathology

Punch biopsy of the parietal pleura was performed in 11 patients considered to have a rheumatoid pleural effusion, 9 of them in the series. The investigation was done in 2 additional patients, one of whom had pleural thickening only. In the other the diagnosis of systemic lupus erythematosus was thought to be more likely than rheumatoid arthritis on other grounds and this case was not included in the series.

All thirteen specimens were examined by two general pathologists (A and B) independently. Pathologist A had reported on the sections routinely and was informed of the clinical details. Pathologist B was presented with 12 of these specimens. To these were added 8 which Pathologist A regarded as showing no specific changes; these were taken from patients with pleural effusion of other cause who had no arthritis. Pathologist B was asked to state in each case whether, if the patient had rheumatoid arthritis clinically, he would regard the changes as those of a rheumatoid pleuritis, as consistent with rheumatoid pleuritis or completely non-specific. Pathologist B was unaware of the number of patients with clinical rheumatoid arthritis. The results of the observations of the two pathologists on the specimens taken from patients with arthritis are shown in Table 39, overleaf.

Agreement was complete in 10 of the 12 specimens examined by both pathologists and there was only definite disagreement in 2 (M.L. and L.H.). Of the 10, both pathologists regarded the changes as rheumatoid in origin in 2 (Figure 12 a, b, c,) and in 2 others consistent with this diagnosis. An example of the latter is shown in Figure 12 d. Of the 8 specimens reviewed by Pathologist B as controls there was agreement in 7, the changes being regarded as non-specific.

Table 39. Observations by two pathologists on pleural biopsies.

Patient	Pathologist A	Pathologist B
G.W.	Non-specific	Non-specific
R.S.	Non-specific	Non-specific
A.G.	R.A.	R.A.
D.H.	R.A.	R.A.
M.L.	Consistent with	R.A.
N.D.	Non-specific	Non-specific
N.C.	Non-specific	Non-specific
W.H.	Non-specific	Non-specific
W.S.	Consistent with	Consistent with
J.G.	Non-specific	Non-specific
J.J.	Consistent with	-
E.S.	Consistent with	Consistent with
L.H.	Consistent with	Non-specific

The other, however, was considered to be a non-specific granulomatous lesion by Pathologist A but regarded as rheumatoid by Pathologist B. The diagnosis was subsequently proven to be tuberculosis.

Treatment

In 2 of the 19 cases oral corticosteroid therapy was given specifically because of the pleural effusion. In both resolution occurred shortly afterwards. In one case intra-pleural corticosteroid therapy was given without any obvious benefit. Single or repeated aspirations were employed for treatment purposes in nine cases.

Natural history

In 13 the effusion resolved within 3 months, but in 1 of these there was a recurrence 12 months later. In four cases the effusion was unduly persistent. In one the duration so far has been over a year with only temporary improvement after aspiration. In a second the effusion persisted for 18 months before finally resolving. In one man the effusion

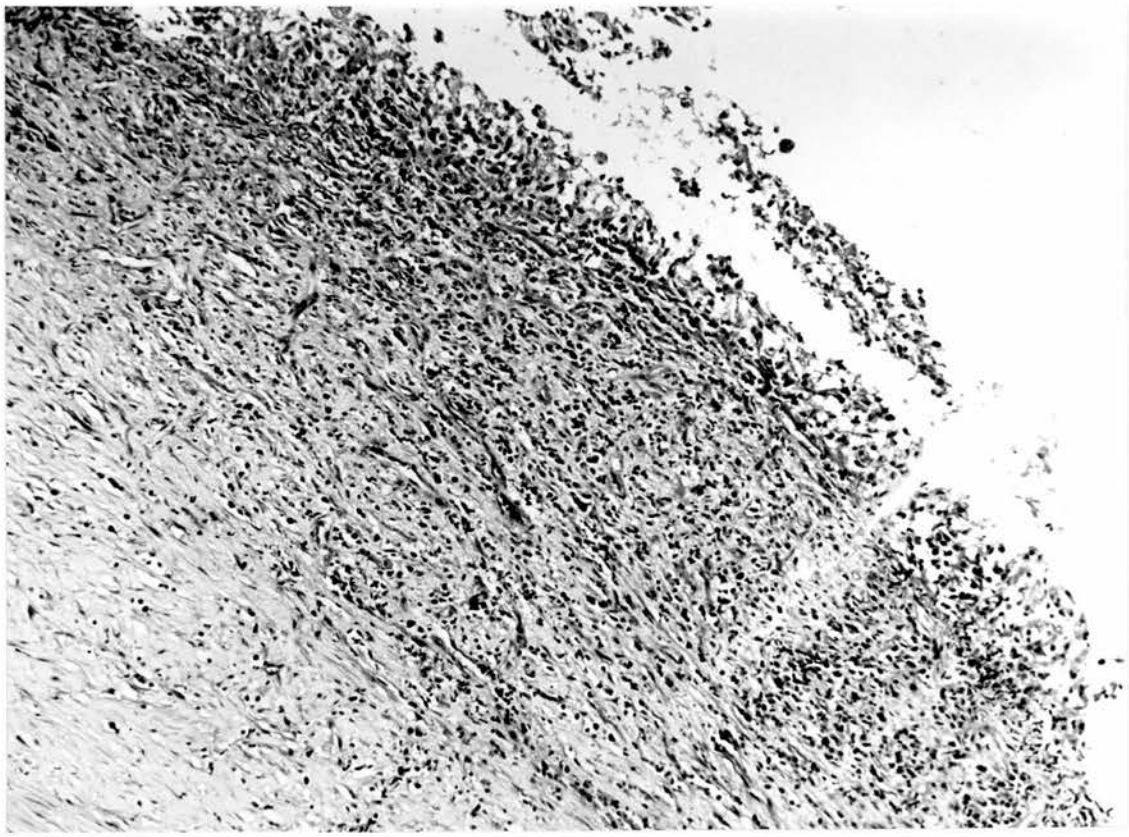


Figure 12a.

Pleural biopsy from case D.H. showing epithelioid cells overlying a fibrotic pleura. There are small areas of fibrinoid necrosis and a slight tendency to palisading. H. and E. × 150.

Figure 12b.

Pleural biopsy. Same case as Figure 12a. Shows epithelioid cells with focal areas of fibrinoid necrosis. H. and E. x 150.

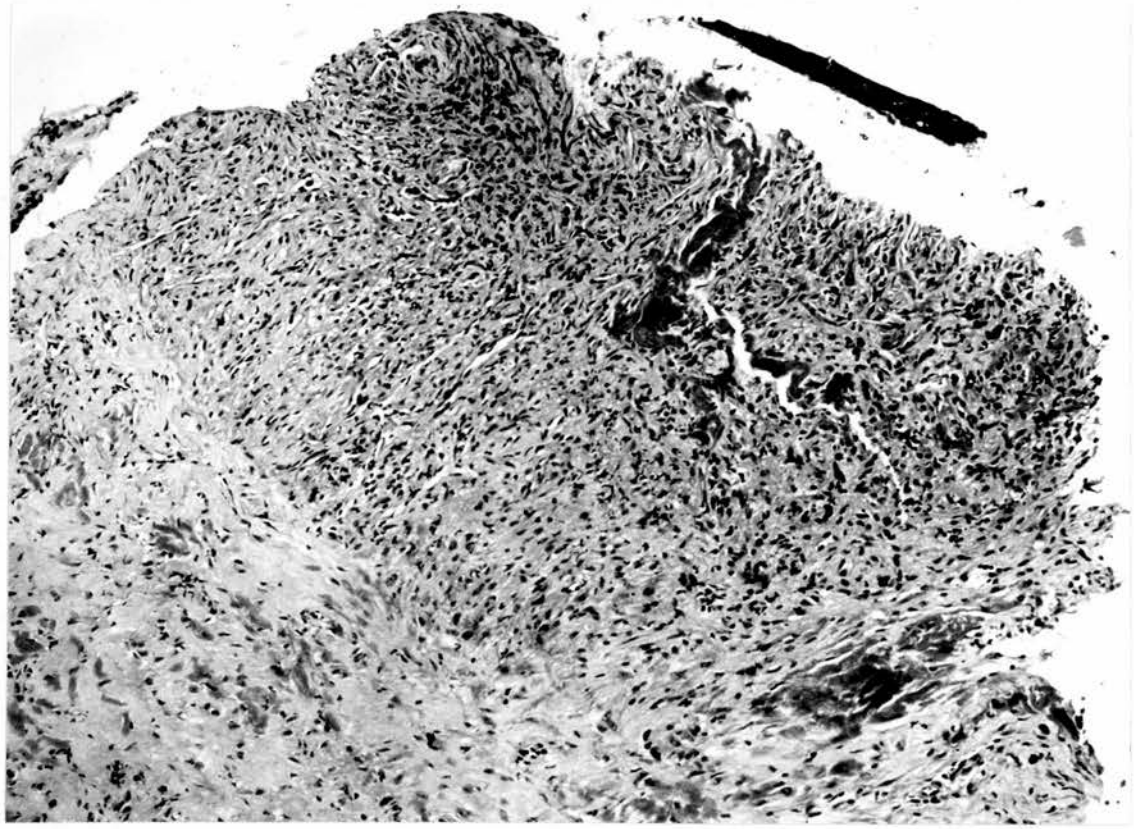


Figure 12c.

Pleural biopsy showing a large irregular focus of fibrinoid necrosis and epithelioid cells overlying a fibrotic pleura. H. and E. x 150.

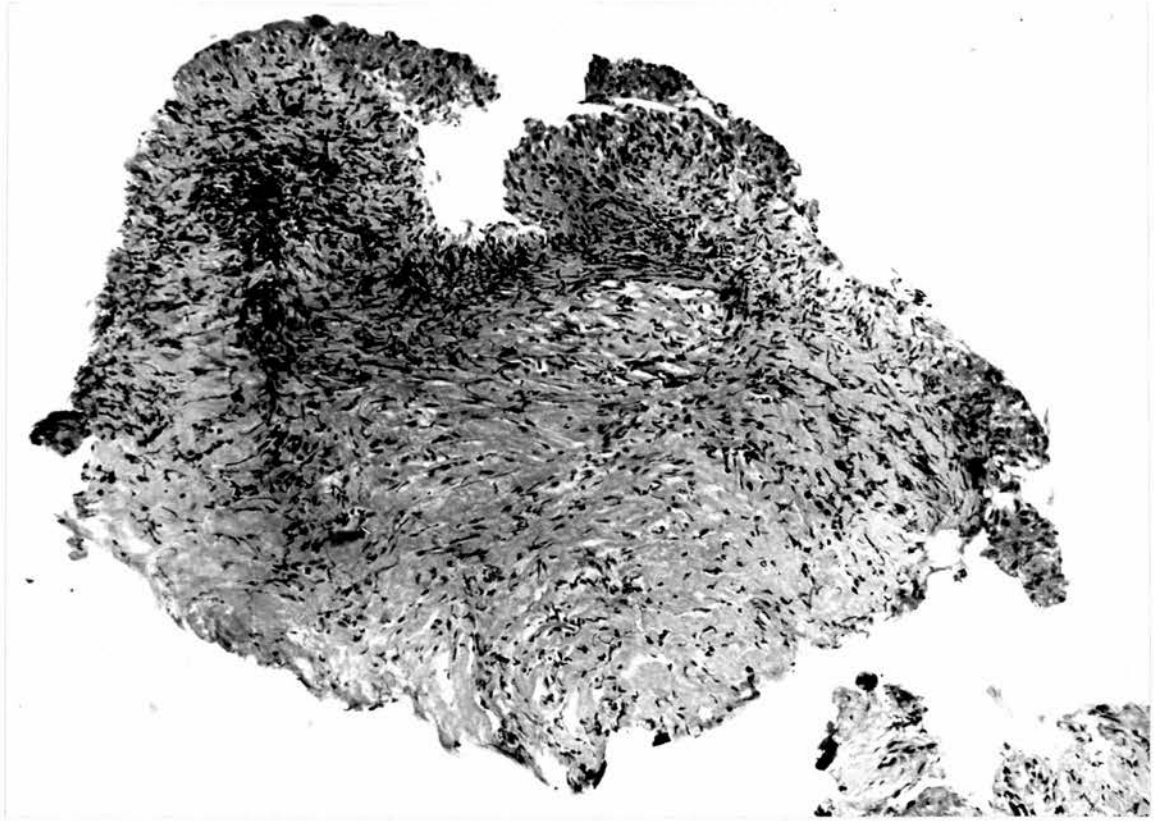


Figure 12d.

Pleural biopsy. Shows a thick surface layer of epithelioid cells, tending to palisade, overlying a fibrotic base. H. and E. × 150.

persisted for 15 months and during this time he developed severe pleural thickening which resulted in gross restriction of respiratory movement on that side and associated dyspnoea. Decortication had to be performed, which relieved him of his symptoms. A fourth patient, a man with empyema, had persistent pleural fluid for five years, until he died as a result of renal papillary necrosis. Two more of the 19 patients also died, the first as a result of cardiac tamponade from a pericardial effusion, and the second from lobar pneumonia on the opposite side to that of the effusion. At autopsy in the latter case it was established that the effusion had resolved. Brief case summaries of two examples of pleural effusion are given in Appendices 2 and 3.

Associated pulmonary lesions

These were present in 4 cases - 1 patient had interstitial lung disease, 1 had Caplan's syndrome. One had a proven, intra-pulmonary, rheumatoid nodule on the opposite side. The fourth patient had an intra-pulmonary lesion on the same side, detected at thoracotomy, which was regarded as a probable rheumatoid nodule.

Comment

There was a significantly higher incidence of pleural effusion and pleural thickening in the rheumatoid group compared with the D.J.D. group. Both were more frequent in men. In the pleural effusion group subcutaneous nodules were more common in both sexes than in the remainder of the rheumatoid population, but otherwise there was no clinical difference in the arthritis. Pericarditis was present in three patients. The haemoglobin levels and blood sedimentation rates were similar. Two in the effusion group had L.E. cells in the peripheral blood. A decreased serum albumin was more frequent in the effusion

group. The joint radiographs were similar.

Half of the effusions occurred either before or within five years of the onset of the arthritis and they were bilateral in 20 per cent. Glucose levels in the pleural liquid were 40 mgs./100 ml. or less in 3, and in the same number the S.C.A.T. was higher in the fluid than in the blood. Changes regarded as due to rheumatoid pleuritis or consistent with this diagnosis were found on pleural biopsy from some patients. Four patients had intra-pulmonary disease of rheumatoid origin. The effusion persisted for more than 12 months in 4 and empyema was present in 1.

D. INTERSTITIAL LUNG DISEASE

Of the 516 patients with rheumatoid arthritis reviewed, 8 (1.6%) were found to have interstitial lung disease. Three others were specially referred, and the total of 11 cases (8 men, 3 women) will be compared with the rheumatoid population as a whole.

Diagnostic criteria

The criteria for diagnosis were:-

1. an abnormal chest radiograph with appearances consistent with interstitial lung disease.
2. the absence of an alternative cause after clinical examination and appropriate investigations.

Figure 13 shows an illustrative example, of which the case history is given in Appendix 4.

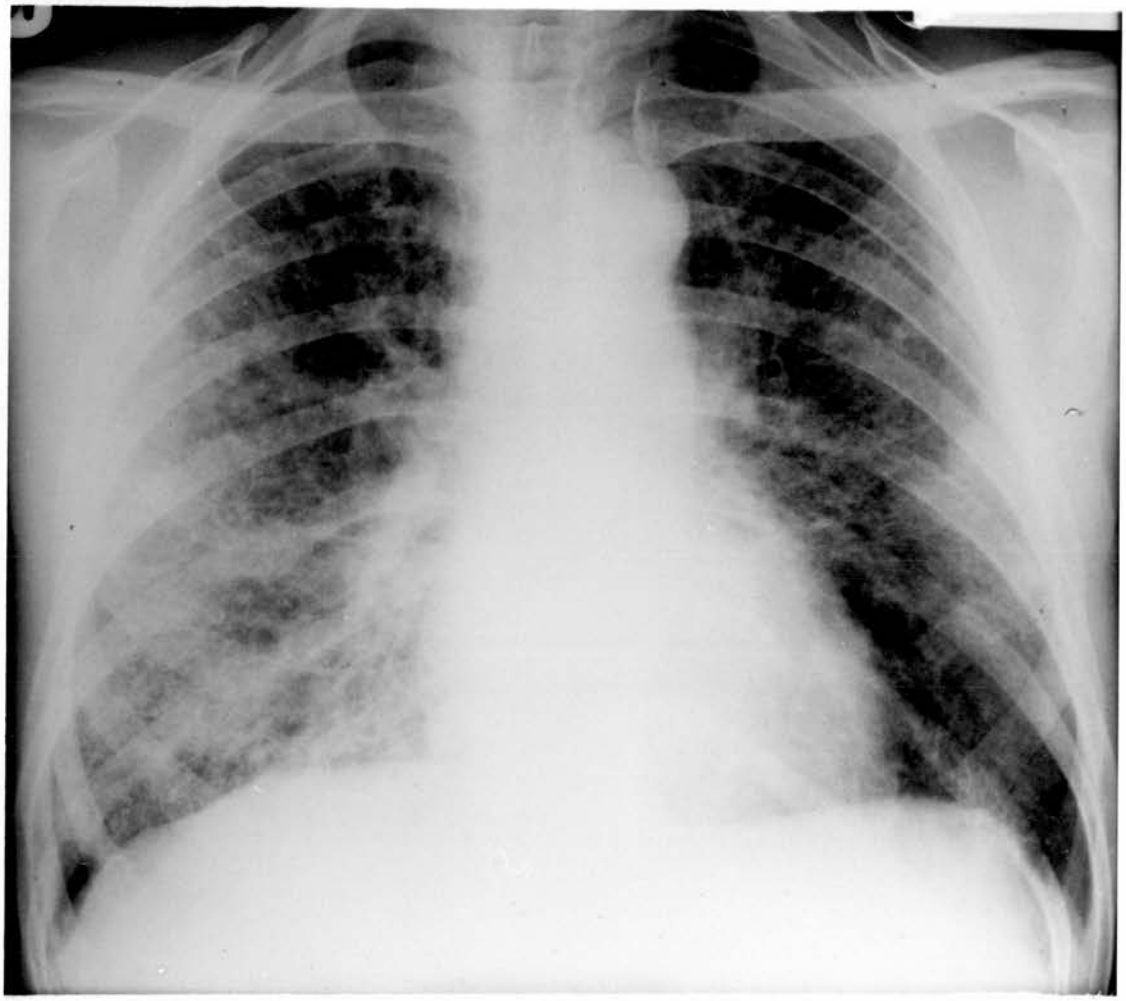
Clinical features of arthritis

At the time of review all were in the sixth or seventh decade, the mean age being 60.2 years (range 54 - 66). Only 1 patient in the group with interstitial lung disease developed arthritis before the age of 46 years, compared with 52 per cent of the rheumatoid population as a whole. The mean age of onset of arthritis was 53.2 years (range 40 - 61). In 1 case the lung disease preceded the arthritis and in a further 2 it was present within 2 years of the onset.

There were 6 patients in functional grade 2, 4 in grade 3, and 1 in grade 5. This was a distribution similar to that in the rheumatoid population as a whole. The extent of the arthritis in those with lung disease was essentially the same as in the rheumatoid population as a whole. The percentages of mild, moderate, and severe were 27, 27 and 46 compared with 25, 24 and 52 respectively.

Eight of the 11 patients with lung disease had subcutaneous nodules,

Figure 13.



6 men and 2 women. This was a higher incidence than in the rheumatoid population as a whole, in which 44 per cent of the men and 25 per cent of the women had subcutaneous nodules. The only definite example of systemic manifestations of rheumatoid arthritis in the series with lung disease was one man with pericarditis.

Laboratory investigations

Four of the patients had a haemoglobin level between 10.5 and 12.6 g. per 100 ml., 2 of whom were women. The remainder all had haemoglobin levels of over 12.6 g. per 100 ml. There was no suggestion of an increased incidence of anaemia in those with lung disease. Nine (82%) of the 11 patients with lung disease had a B.S.R. greater than 40 mm. 1st. hr. compared with 45 per cent of the rheumatoid population as a whole.

Rheumatoid factor was present in the blood of 10 of the 11 patients with lung disease. Two had a positive latex slide test. In the remaining 8 patients the S.C.A.T. was positive in a titre of 1:32 in one, in 1:512 or greater in 4, and 1:128 or 1:256 in the remaining 3.

Two patients both with nodular rheumatoid arthritis had L.E. cells in the peripheral blood. They were absent from the remaining nine.

In the group with lung disease 3 had a decreased serum albumin, and 5 an increased serum globulin amongst the 10 examined. This compared with an incidence of 19 per cent and 26 per cent respectively in the rheumatoid population as a whole. Eight (89%) of the 9 in whom electrophoresis was performed had an abnormal pattern, compared with 68 per cent of those in the rheumatoid population. The changes observed were essentially those seen in uncomplicated rheumatoid arthritis, and consisted of an increase in the gamma and alpha 2

globulins, and less commonly a decreased albumin and increased alpha 1 and beta globulins.

Joint radiographs

There was no essential difference in the radiographic severity of rheumatoid changes in the hands and feet between the group with lung disease and the rheumatoid population as a whole.

Treatment

None of the patients had received corticosteroid therapy because of their lung disease. Seven had received such therapy for treatment of their arthritis, an incidence identical with that in the rheumatoid population as a whole.

Smoking history

Two of the female patients in the group were non-smokers. The remaining patients had all smoked for more than twenty years. One woman and 2 men smoked from 1 - 10 cigarettes daily, 3 men smoked from 11 - 20 daily, and 3 men smoked more than 20 cigarettes daily. Sixty per cent of the women in the rheumatoid population were non-smokers. Looking at the men in the total rheumatoid population 21 per cent had smoked 1 - 10 cigarettes daily for more than 20 years compared with 25 per cent in the group with interstitial lung disease; 33 per cent had smoked 11 - 20 cigarettes daily for more than 20 years compared with 37,5 per cent, and 14 per cent had smoked more than 20 cigarettes daily for more than 20 years compared with 37.5 per cent.

The occupational histories of the patients did not suggest that exposure to an irritant atmosphere had been operative in the production of interstitial lung disease.

Clinical features

The symptoms and duration, when this could reasonably be deduced,

of interstitial lung disease in the eleven cases are shown in Table 40.

Table 40. Symptoms and duration of interstitial lung disease

Case	Duration (years)	Cough	Haemoptysis	Dyspnoea grade	Chest pain
T.J.	$1\frac{1}{2}$[1]	present	absent	2	absent
M.D.	5	present	absent	1	absent
W.E.	4	present	absent	0[2]	present
D.C.	4	absent	absent	1	absent
B.R.	5	present	absent	1	absent
W.W.	10[3]	present	absent	2	absent
J.W.	uncertain	absent	absent	0[5]	absent
J.K.	$2\frac{1}{2}$	present	absent	1	absent
H.T.	3[4]	present	present	0[5]	absent
F.P.	$7\frac{1}{2}$	absent	absent	1	absent
E.S.	uncertain	present	present	3	absent

1. Abnormal x-ray 18 months previously and prior to onset of dyspnoea.
2. Bedridden because of arthritis.
3. X-ray reported as showing basal fibrosis 10 years previously, and clubbing recorded then.
4. X-ray abnormal 3 years previously.
5. Activities restricted.

Dyspnoea grade - 0 = absent 1 = on slight exertion
2 = moderate exertion 3 = at rest

The shortest duration of symptoms was five weeks, but this man had had a chest x-ray 18 months previously, which contained well marked changes consistent with interstitial lung disease. The case with the longest duration was a man who ten years previously had had a chest x-ray reported as showing basal fibrosis (the film was not available for personal review), and at that time finger clubbing was recorded. In the remaining cases the duration has been dated from the onset of symptoms attributable to interstitial lung disease, or from the date of an abnormal x-ray, if symptoms at that time were not present. The mean duration was 4.7 years.

Cough was present in 8 and haemoptysis occurred in 2. In one of the latter this was attributed to interstitial lung disease, which was proven by lung biopsy. In the other, however, mitral stenosis was

present, which was much more likely to have been responsible. Interstitial lung disease and pericarditis, considered of rheumatoid origin, were found at autopsy.

In this group of cases dyspnoea, although prominent, was not, in general, a severe symptom and it was absent in three. However, as might be anticipated, all these cases had restricted activities, because of arthritis, and one was actually bedridden. One had had chest pain of pleuritic type for four years.

Table 41 (overleaf) shows that 9 of the patients had finger clubbing, slight in 3, moderate in 2 and gross in 4. Crepitations were audible over the lungs, usually basal in distribution, in all but two patients.

Chest radiographs

The radiographic abnormalities have been described as fine or coarse mottling, reticulation or streaky shadowing, and the type, present alone or in combination, is shown in Table 41. In two, small cystic spaces were also apparent. Two cases had pleural abnormalities in the form of pleural thickening in one and a small effusion in the other.

Corticosteroids were employed as treatment for the lung disease only in the presence of rapidly progressive or disabling dyspnoea. The one patient with dyspnoea at rest died soon after being seen. One case, T.J., was treated with corticosteroids specifically for his lung disease and Cases M.D. and H.T. received anti-malarials for reasons discussed later. Case H.T. died suddenly at home, presumably from a myocardial infarction, 3½ months after starting treatment with hydroxychloroquine. No autopsy was performed. He had been seen three months after treatment was started, at which time the follow up chest x-ray

Table 41. Clubbing and radiographic findings in patients with interstitial lung disease.

Case	Clubbing	Type of shadowing	X-ray		
			Distribution	Zones with maximum involvement	Pleural
T.J.	gross	fine mottling & streaky	diffuse	mid and lower	nil
M.D.	absent	coarse reticular	diffuse	mid and lower	nil
W.E.	gross	coarse mottling	lower zones	R. lower	thickened on right
D.C.	slight	fine reticular	mid and lower zones	mid and lower	nil
B.R.	absent	streaky	diffuse	all	nil
W.W.	gross	reticular	lower zones	lower	nil
J.W.	gross	coarse mottling	diffuse	lower	nil
J.K.	slight	fine mottling	both lower and L. mid-zone	lower and L. mid	nil
H.T.	slight	fine reticular & coarse mottling	L. lung and R. mid and lower zones	L. mid and both lower zones	nil
F.P.	moderate	coarse reticular	diffuse	all except apices	nil
E.S.	moderate	fine mottling	diffuse	mid and lower zones	small effusion on right

was unchanged, and his respiratory symptoms were also unchanged. He, however, was one of the cases without dyspnoea. Follow up lung function tests were not performed in this case, but were available in Cases T.J. and M.D. Serial readings of the vital capacity and gas transfer are shown in Table 42.

Table 42. Serial readings of vital capacity and gas transfer in two cases of interstitial lung disease with R.A. under treatment.

	Pre-treatment	Corticosteroids	
		for 3 months	for 7 months
Case T.J.			
V.C.	2.98, 2.85	2.95	2.9
G.T.	14.5, 13.0	8.1	10.3
		Hydroxy-chloroquine *	
		for 3 months	for 4½ months
Case M.D.			
V.C.	2.04, 1.94	2.2	1.7
G.T.	10.1, 10.6	14.8	11.9

V.C. = vital capacity in litres.

G.T. = Gas transfer by the CO uptake test in ml./min./mm. Hg.

* Hydroxychloroquine 200 mgm. q.i.d. for 1 month, followed by 200 mgm. b.d.

In Case T.J., who received corticosteroids, the vital capacity did not change throughout the period of observation. The gas transfer had fallen at 3 months and risen slightly at 7 months, although remaining below the pre-treatment level.

In Case M.D. after 3 months treatment with hydroxy-chloroquine both the vital capacity and gas transfer had increased slightly, whereas after 4½ months the vital capacity had fallen below the pre-treatment figure and the gas transfer had also again fallen. One other patient with interstitial lung disease and a positive test for the rheumatoid factor, but without rheumatoid arthritis, was also treated with hydroxy-chloroquine in the same dosage with considerable symptomatic improvements. The results of her tests before treatment and after three months are shown in Table 43.

Table 43. Serial figures for V.C. and G.T. in patient with interstitial lung disease without R.A. treated with hydroxy-chloroquine.

	Pre-treatment	After 3 months treatment
V.C.	1.31	1.52
G.T.	5.9	6.8

V.C. = Vital capacity in litres
G.T. = Gas transfer by the CO uptake test in ml./min./mm. Hg.

Lung function tests

The results of selected tests of lung function in 9 of the 11 patients are shown in Table 44.

Table 44. Lung function tests in 9 patients with rheumatoid interstitial lung disease.

Initials	Sex	V.C.	T.L.C.	F.E.V.	CO uptake mls./min./mm.Hg.
T.J.	M.	2.98	3.8	2.4	14.5 (61)
M.D.	F.	2.04	2.98	1.85	10.1 (42)
W.E.	M.	3.44	5.11	2.72	10.2 (42)
D.C.	M.	2.94	4.58	2.19	18.2 (58)
B.R.	F.	2.44	3.1	1.97	7.9 (34)
W.W.	M.	4.3	6.55	2.67	14.5 (61)
J.W.	M.	3.73	4.97	2.88	13.5 (46)
J.K.	M.	4.48	6.4	2.37	13.5 (40)
H.T.	M.	2.83	4.44	2.03	17.5 (70)

V.C. = Vital capacity in litres.
T.L.C. = Total lung capacity in litres.
F.E.V. = Forced expiratory volume in 1 second in litres.
Figures in parenthesis are percentages of predicted normal values.

Only one had a vital capacity below the normal range (Case D.C.). The gas transfer was significantly reduced in 8 and in the other the figure was at the lower limit of normal, namely 70 per cent. In this case the arterial oxygen tension remained normal after exercise and, although the latter could not be strenuous because of his arthritis,

it was sufficient to provoke definite dyspnoea. The diagnosis of interstitial lung disease was subsequently confirmed by lung biopsy.

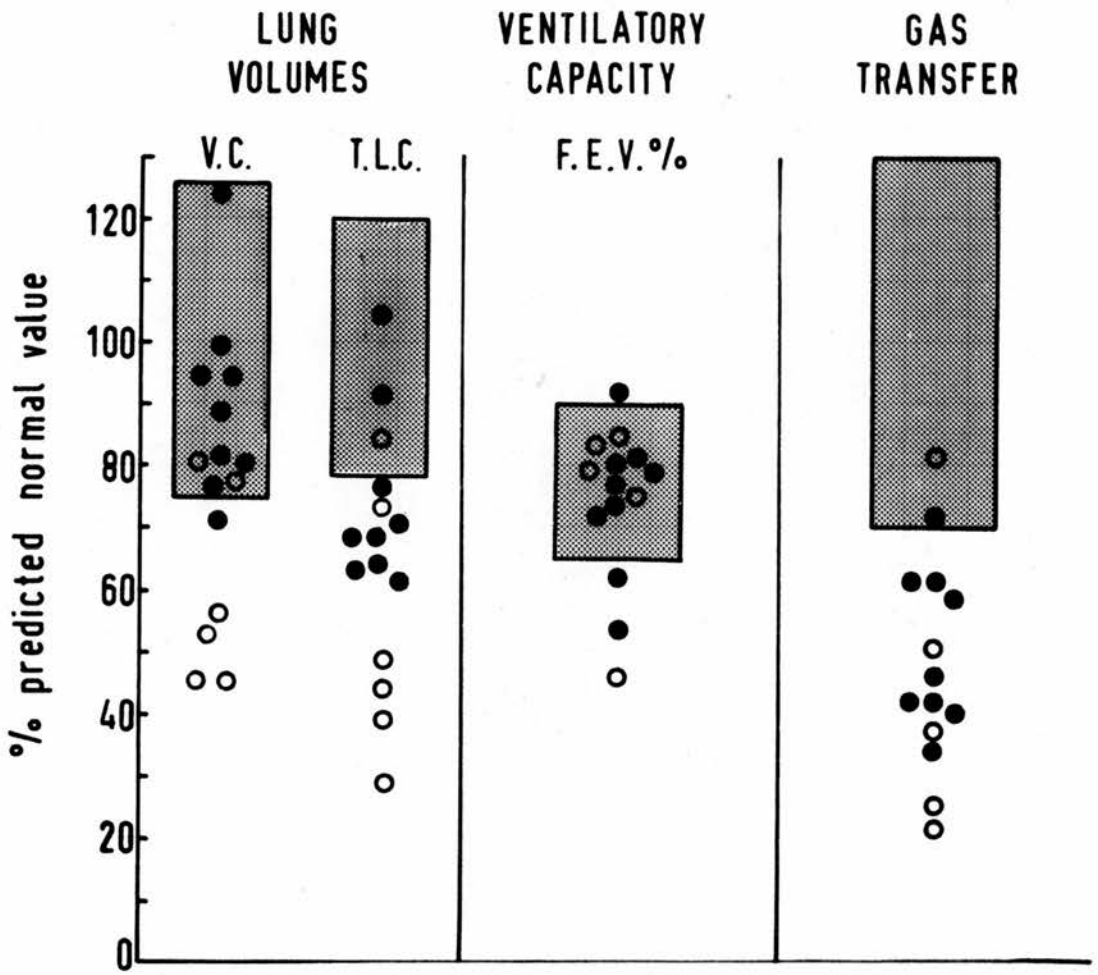
Table 45. Lung function tests in 6 patients with interstitial lung disease without rheumatoid arthritis.

Sex	V.C.	T.L.C.	F.E.V.	CO uptake in mls./min./mm. Hg.
F.	1.31	2.29	1.09	5.9 (25)
M.	2.67	3.32	2.24	14.5 (50)
M.	1.71	2.22	1.36	5.7 (21)
M.	3.33	5.4	1.53	10.8 (37)
F.	1.0	1.67	-	- *
F.	1.99	2.8	1.5	18.4 (81)+

V.C. = Vital capacity in litres.
T.L.C. = Total lung capacity in litres.
$F.E.V_1$ = Forced expiratory volume in 1 second in litres.
Figures in parenthesis are percentages of predicted normal values.
* Inadequate V.C. for test to be done. Arterial oxygen tension = 49 mm.Hg at rest.
+ Arterial oxygen tension at rest = 88 mm.Hg; after exercise = 45 mm. Hg.

These results show less lung restriction than usually encountered in cases with interstitial lung disease. It should, however, be recalled that all these cases were seen primarily because of their arthritis, and by way of contrast the results obtained in six cases with interstitial lung disease, apparently idiopathic, are shown in Table 45. The results are compared with the rheumatoid group in Figure 14, where they are expressed as a percentage of predicted normal (the shaded areas on the scattergram representing the normal range). The dominant complaint of the patients without rheumatoid arthritis was breathlessness. Lung restriction was much more marked, in this group, the volumes being mainly less than the lower limit of normal. Gas transfer was considerably impaired in 4 of the 5 cases in which this

Fig.14 *Lung function tests in R.A. with interstitial lung disease and interstitial lung disease without R.A.*



V.C. = vital capacity T.L.C. = total lung capacity

F.E.V. = forced expiratory volume in 1sec. as % of V.C.

was tested. In the one in which the figure was within the normal range arterial oxygen tension fell significantly on exercise. In the one patient in whom the test was not possible, because of a very reduced vital capacity, the arterial oxygen tension was considerably reduced at rest.

Pathology

Specimens for pathological examination were obtained from 3 patients, 2 by lung biopsy and 1 at autopsy. The clinical features of case T.J. are presented in appendix 4 and his chest radiograph is shown in Figure 13. His biopsy specimen was interpreted as showing diffuse interstitial fibrosis with obliteration and gross distortion of alveolar spaces (Figure 15a). Case H.T. gave a history of haemoptysis and had not noticed dyspnoea. His chest radiograph was consistent with interstitial lung disease and review of a film taken three years previously revealed a similar but less marked abnormality. His lung biopsy (Figure 15b) revealed diffuse interstitial fibrosis with cellular infiltration, consisting mainly of lymphocytes, but with some plasma cells. There were numerous distorted air passages filled with macrophages.

Case E.S. had had rheumatoid arthritis for 12 years and finger clubbing had been present for 8 years. He had developed haemoptysis 1 year before review and dyspnoea 4 months later. At that time his chest radiograph, taken elsewhere, showed fine mottling in both lung fields. He subsequently developed a pleural effusion. Mitral stenosis had been suspected from the cardiac outline on chest radiography, but neither the author nor a cardiologist were able to elicit confirmatory physical signs. He died from lobar pneumonia. An autopsy section from the lung (Figure 15c) showed diffuse fibrosis with partial obliteration of respiratory passages and thickening of residual alveolar walls.

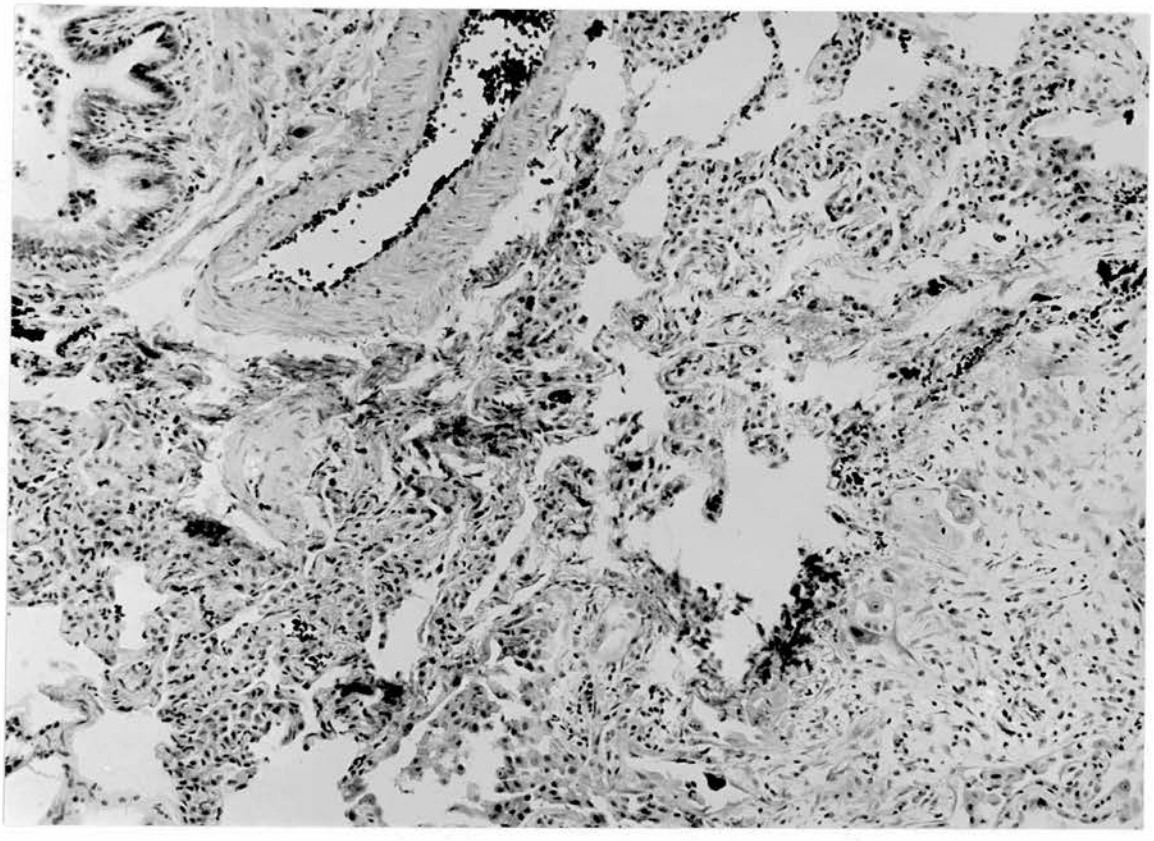


Figure 15a.

Section of lung (biopsy specimen). H. and E. x 150.

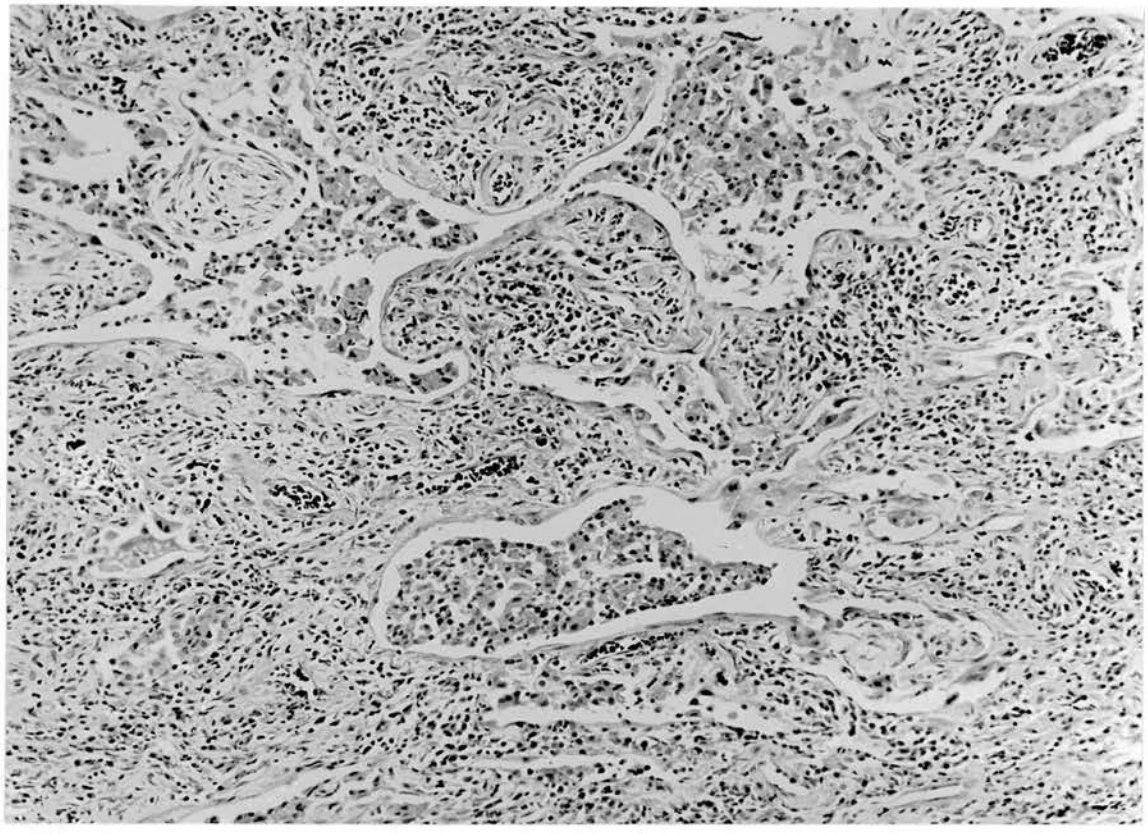


Figure 15b.

Section of lung (biopsy specimen). H. and E. × 150.

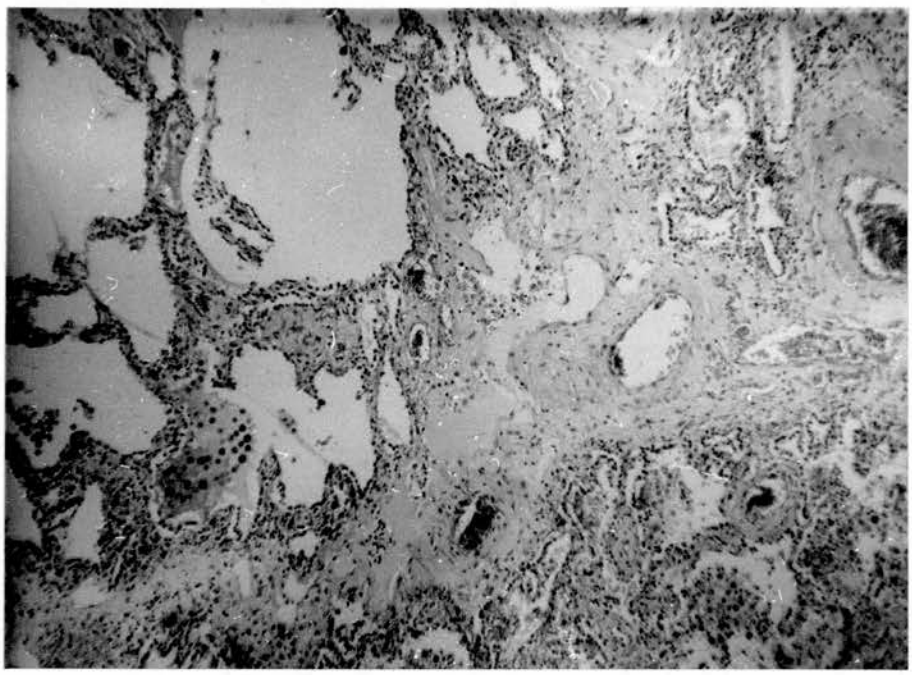


Figure 15c.

Autopsy section from lung showing diffuse fibrosis with partial obliteration of respiratory passages and thickening of residual alveolar walls. H. and E. × 30.

The pleura and pericardium were thickened and showed extensive fibrinoid necrosis. Mitral stenosis was present but unfortunately histological examination was not performed on the valve. There were no specific features of rheumatoid arthritis in any of the three specimens of lung tissue.

Comment

In the group with interstitial lung disease there were more men than women, their age at review was greater, and arthritis developed later than in the rheumatoid population. The duration of arthritis at review was rather less than in the population as a whole, and in 45 per cent the lung disease either preceded or was apparent within 5 years of the onset of arthritis. Subcutaneous nodules were more frequently present in both sexes than in the rheumatoid population. The group also had a higher B.S.R., the figure being greater than 40 in 82 per cent compared with 45 per cent of the rheumatoid population. Only one of the group with lung disease had an absence of rheumatoid factor and more had serum protein abnormalities than were found in the rheumatoid population. Two of the patients had L.E. cells in the peripheral blood. The extent of the arthritis and functional grade were both very similar to the rheumatoid population, and this also applied to the radiographic changes in the hands and feet. A similar proportion in each group had received corticosteroid therapy. There was no evidence that cases with lung disease were more likely to have anaemia. All the men had smoked for more than 20 years, but 2 of the women were non-smokers.

The duration of the lung disease varied from 1½ to 10 years. Three patients had not experienced dyspnoea. Finger clubbing was present in 9. The chest radiographs showed mottling, reticulation

or streaky shadowing with maximum involvement in the lower zones or in the mid and lower zones in all but two cases. Pleural abnormalities were present in two. Corticosteroid therapy was given to one patient as treatment for his lung disease. Two others received hydroxychloroquine. As a group the patients with rheumatoid interstitial lung disease had less impairment of respiratory function than a group of six patients with idiopathic interstitial lung disease. Specimens for histological examination were available from 3 of the 11 patients.

E. INCREASED LUNG MARKINGS

In view of the likelihood of observer error in the interpretation of chest films from the point of view of an increase or doubtful increase in lung markings 114 films were read a second time after an interval.

Of the 66 cases originally classified as normal, on re-reading 62 were again classified as being within normal limits, a reproducibility of 94 per cent. Of 24 films originally classified as showing a definite increase in lung markings on re-reading only 1 was considered normal, a reproducibility of 96 per cent. Of the 24 films originally read as showing a doubtful increase in lung markings 7 were re-read as normal, a reproducibility of only 71 per cent.

Incidence

In view of the expected poor reproducibility in the doubtful category these have been discarded for purposes of comparison.. In the rheumatoid group 27 (5%) had an increase in lung markings compared with 12 (4%) of the D.J.D. group.

Clinical aspects

Examination of the clinical data, and in some cases further investigation, revealed evidence of a possible cause for the radiographic finding in 14 of the patients with rheumatoid arthritis and 5 of those with D.J.D. These included bronchiectasis, chronic bronchitis, and cardiac failure. The number of patients with increased markings for which there was no apparent cause was 13 (2.5%) in the rheumatoid group and 7 (2.3%) in the D.J.D. group.

Lung function tests

These were performed in 18 patients, 2 with D.J.D. and 16 with rheumatoid arthritis. The results obtained are shown in Appendix 5.

Some abnormality was present in 10 of the 16 patients with rheumatoid arthritis. These were due to obstructive airways disease in 5 and to asbestosis in 1. One other case had severe obstructive airways disease as well as lung restriction, but a normal carbon monoxide uptake test (Case M.D.). Three had a reduced gas transfer, only just below the lower limit of normal in 1, but unequivocally reduced in 2, without other abnormality, and a similar finding was present in both cases with D.J.D.

Lung function tests were also performed in 15 cases with a doubtful increase in lung markings and the results are shown in Appendix 6. An abnormality was present in 4, obstructive airways disease in 2, and a slightly reduced gas transfer in 2 others.

Of the 33 cases in the above two groups examined with lung function tests, 6 had an abnormal gas transfer without other abnormality. In none of them was there any evidence clinically of interstitial lung disease. One of them was carefully reviewed for over 12 months. She did not develop either dyspnoea or cough, and follow up testing showed an identical result in gas transfer.

There were six further rheumatoid patients whose tests are shown in Appendix 7. Case A.C. had bilateral pleural effusions and Cases B.C. and G.W. had unexplained dyspnoea. Cases J.F. and G.W. had Caplan's syndrome and Case J.W. obstructive airways disease. There was no suggestion of unexpected interstitial lung disease in any of them.

Comment

Of 18 patients with a definite increase in lung markings tests of lung function revealed an abnormality in 12. In most of them there was an explanation other than interstitial lung disease. An abnormal carbon monoxide uptake test as an isolated finding was present in 3 rheumatoid patients and in 2 with D.J.D. Of 15 patients with a doubtful

increase in lung markings pulmonary function was abnormal in 4, resulting from obstructive airways disease in 2. In the two others carbon monoxide uptake was decreased without other abnormality.

F. INTRA-PULMONARY NODULES

One patient in the series had an intra-pulmonary opacity thought to be due to a rheumatoid nodule and this was subsequently proven at autopsy (Appendix 8). A similar lesion was suspected in one other patient but no pathological examination has yet been done so the diagnosis remains doubtful. A further patient in the series with a pleural effusion had a small ill defined opacity in the right upper lobe not thought to be a rheumatoid nodule radiographically. Thoracotomy was performed for decortication when the intra-pulmonary lesion was found to be a rounded mass with central softening. Histology revealed a necrotic lesion with very little cellular reaction and no evidence of tuberculosis. It was considered by the pathologist (Dr. J. B. Lynch) to be compatible with a rheumatoid nodule.

Therefore in the series there was 1 definite, 1 probable and 1 possible example of intra-pulmonary rheumatoid nodules. One additional case has been seen and is described in Appendix 9.

G. INDUSTRIAL LUNG DISEASE

In the rheumatoid population twelve men had been coal miners. Of these 3 had Caplan's syndrome, 2 had ordinary P.M.F., 2 had simple pneumoconiosis, and the remaining 5 chest radiographs were passed as normal. In the D.J.D. group 11 men had been coal miners, of whom 4 had simple pneumoconiosis and the remaining films were considered to be normal.

In an additional twenty cases in the rheumatoid group there was a history of exposure to a pneumoconiotic hazard other than coal mining. One patient, a foundry worker, had Caplan's syndrome; 1 had asbestosis, and 5 had x-ray appearances of simple pneumoconiosis, their occupations being a stone mason in 1, a foundry worker in 1, a boiler scaler in 1 and a welder in 2. The films of the remaining thirteen patients were normal. In the D.J.D. group there were seven patients with a history of a pneumoconiotic hazard, other than coal mining, and their chest films were normal.

H. CHRONIC BRONCHITIS

Incidence

Chronic bronchitis was present in 31 (22%) of 140 men and in 17 (4.5%) of 376 women with rheumatoid arthritis. In the group with D.J.D. 6 (10%) of the men and 16 (7%) of the women had chronic bronchitis. In both groups, as expected, more men than women had chronic bronchitis. The incidence of chronic bronchitis in the male rheumatoid group was significantly greater than in the corresponding control group (Figure 16). In the women there was no significant difference in this respect between the two groups.

Temporal relationship

In 12.1 per cent of men with rheumatoid arthritis symptoms of chronic bronchitis preceded those of arthritis (Figure 17). In 5.7 per cent the arthritis began first. In some the precise relationship between the onset of the two diseases was uncertain. In the D.J.D. group the bronchitis started first in 3.2 per cent and the arthritis first in an equal number. Of the females with rheumatoid arthritis the bronchitis started first in 2.4 per cent and the arthritis first in 0.8 per cent. Of the females with D.J.D. the bronchitis started first in 3.3 per cent and the arthritis first in 0.4 per cent. It should be noted that the figures in the male D.J.D. group were very small, the lung disease starting before in 2, after in 2 and in 2 more the relationship was uncertain.

Smoking habits

Of the men with chronic bronchitis 87 per cent smoked cigarettes and none were non-smokers. Of the 130 smokers in the male rheumatoid series 24 per cent had chronic bronchitis. Amongst the women with chronic bronchitis 53 per cent smoked cigarettes and of the 151 women

who smoked in the rheumatoid series 6 per cent had chronic bronchitis compared with an incidence of 3.6 per cent in the non-smokers.

Comment

In this population, as expected, there were more men than women with chronic bronchitis. Although the incidence in the total rheumatoid group was only slightly greater than in the D.J.D. group, in the men the difference was two fold and was statistically significant. There was a striking difference in the incidence of chronic bronchitis starting before the onset of rheumatoid arthritis in men compared with the incidence before the onset of D.J.D., whereas the bronchitis occurred with similar frequency after the onset of joint disease in both groups. Of those in the rheumatoid group with chronic bronchitis all of the men and 53 per cent of the women were smokers.

Fig. 16 *Incidence of chronic bronchitis*

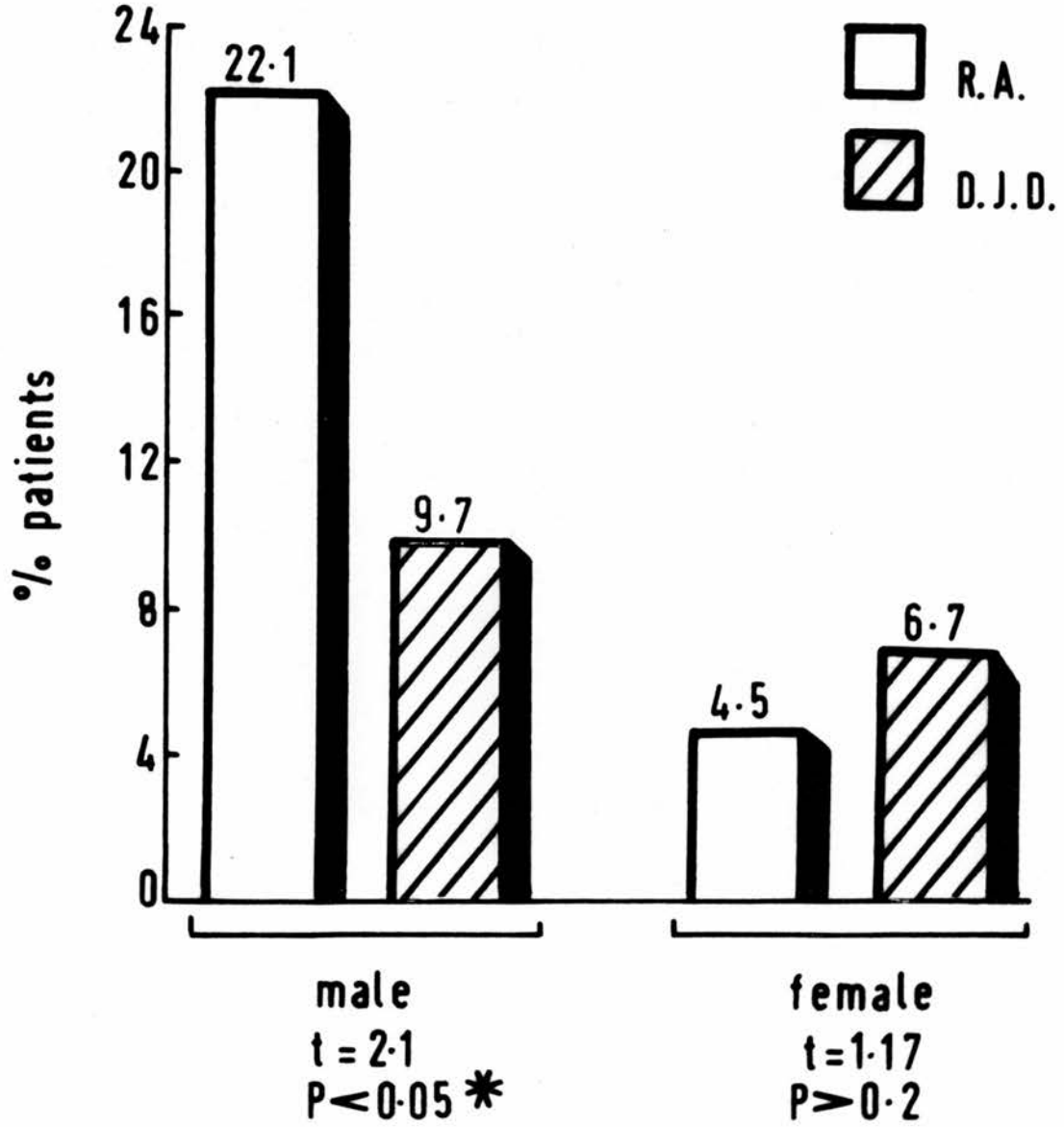
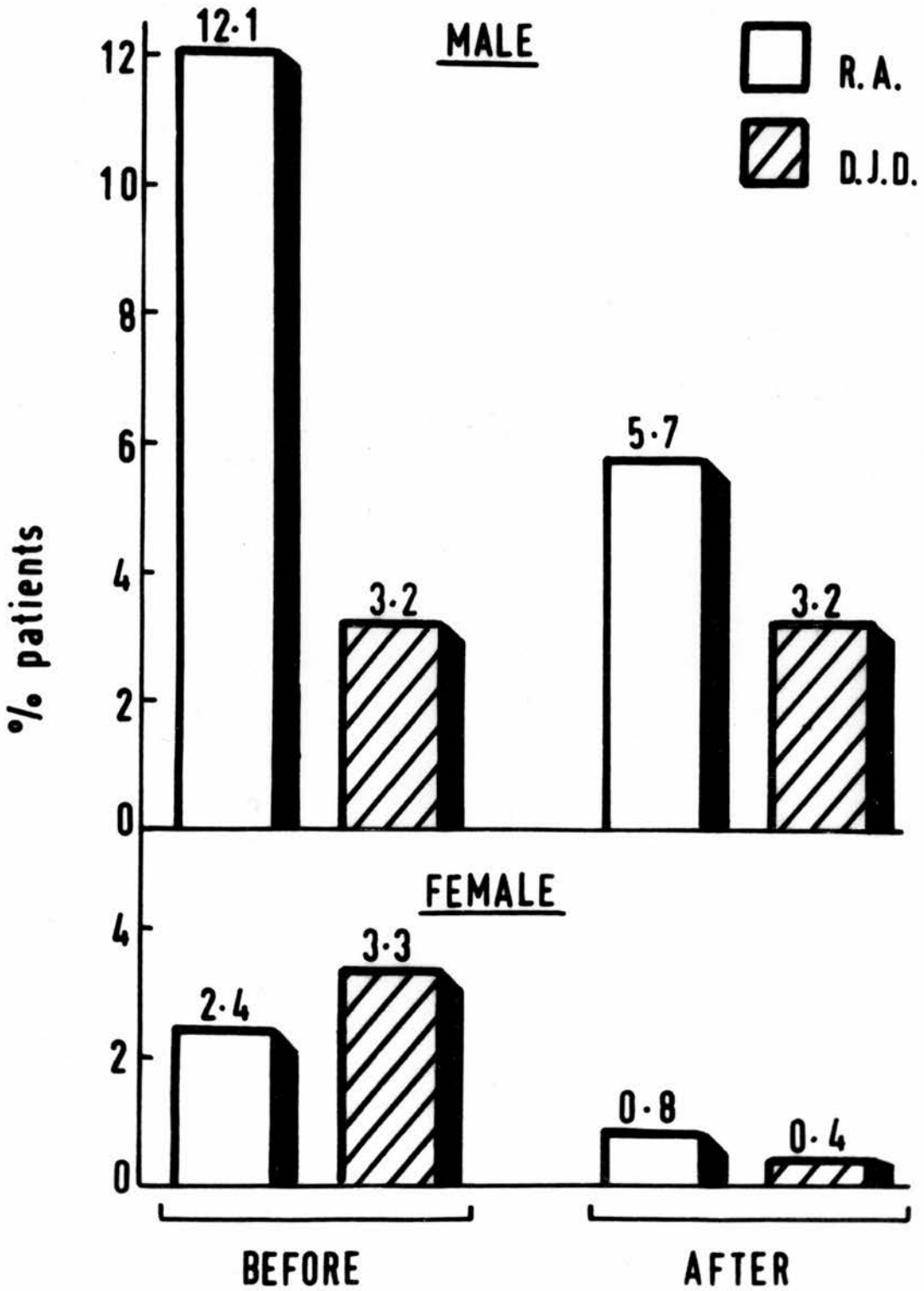


Fig. 17

Incidence of chronic bronchitis related to onset of arthritis



I. PNEUMONIA

The frequency of a history of pneumonia in the two groups is shown in Figure 18. More cases in the rheumatoid group had had pneumonia, but only in the men was the difference significant ($t = 2.68$, $n = 202$, $P < 0.05$) and most of the attacks had occurred before the onset of the arthritis (Table 46).

Table 46. Occurrence of pneumonia in relation to the onset of rheumatoid arthritis.

	Male	Female	TOTAL
Pneumonia before	32	54	86
Pneumonia after	5	23	28
TOTAL	37	77	114

Rheumatoid features

A comparison was made between those rheumatoid patients without a history of pneumonia, those with pneumonia before and those with pneumonia after the onset of arthritis. It should be noted that the number of men who had pneumonia after the onset of arthritis was only five and too few from which to draw conclusions. Comparing the three groups there was no difference between the age of onset, or the extent, or radiographic severity of the arthritis, the presence of subcutaneous nodules, systemic complications, haemoglobin levels, or the B.S.R. The pereentages who had received corticosteroid therapy were almost identiaal (Table 47, overleaf).

Comment

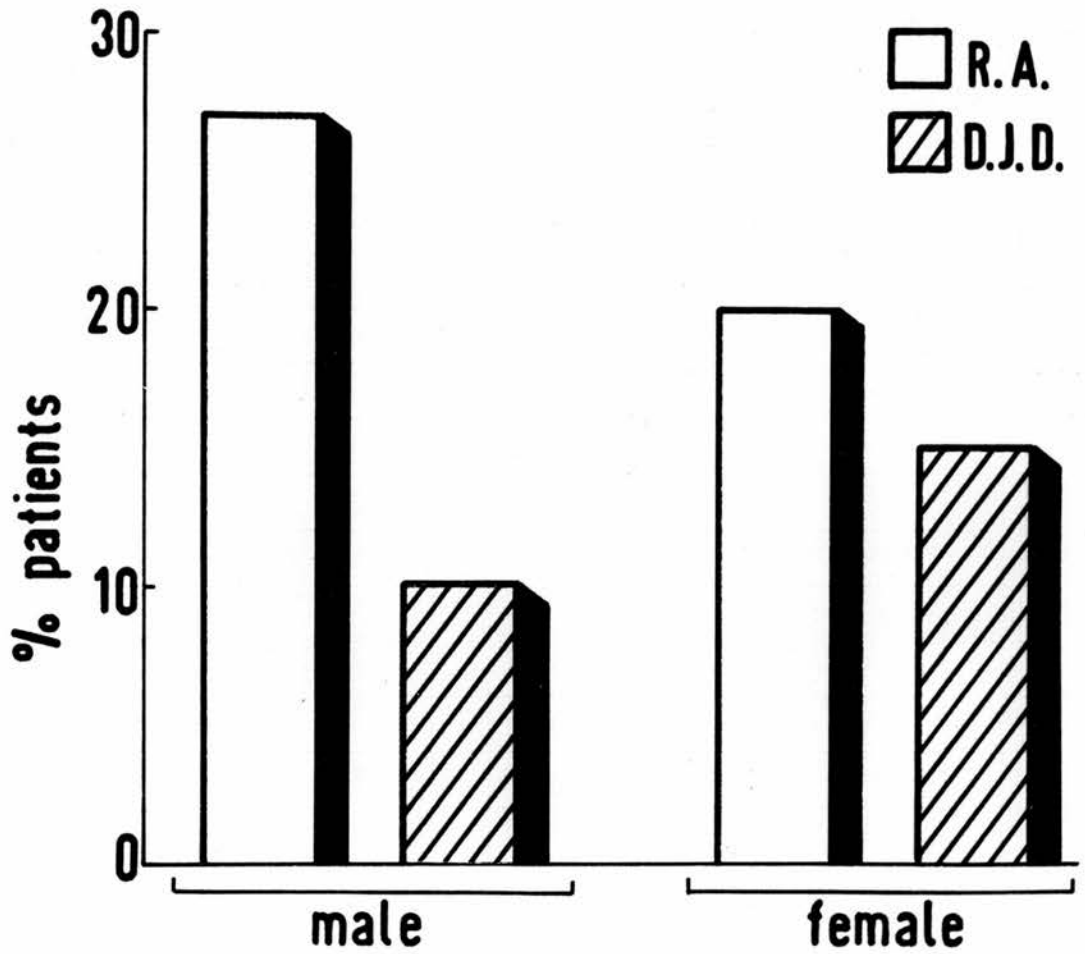
A history of pneumonia was more frequent in those with rheumatoid arthritis than in those with D.J.D. In men six times as many attacks of pneumonia occurred before the onset of arthritis. Comparison between those without a history of pneumonia and those with pneumonia

Table 47. Patients with R.A. receiving corticosteroid therapy, related to the development of pneumonia (percentage in parenthesis).

	Male	Female
Pneumonia before	19/32 (59)	37/54 (67)
Pneumonia after	3/5 (60)	17/23 (68)
No pneumonia	68/102 (67)	213/298 (72)

before arthritis and after arthritis showed no essential differences. The percentage of those in the three groups who had had corticosteroid therapy was very similar and did not suggest that this treatment predisposed to attacks of pneumonia.

Fig.18 *Incidence of pneumonia in R.A. and D.J.D.*



J. BRONCHIECTASIS

In the group with rheumatoid arthritis definite bronchiectasis was present in 16 cases, probable bronchiectasis in 2 and possible in 8. In the D.J.D. group there was one case each in the three categories. For the purpose of comparison between the two groups probable and possible cases have been excluded, making an incidence of 3.1 per cent in the rheumatoid group and 0.3 per cent in the D.J.D. group. Of the 16 cases in the rheumatoid group 9 were confirmed by bronchography, one at autopsy, and 6 on the clinical features and the appearance of the straight x-ray. The diagnosis was made in the one case in the D.J.D. group on the clinical features and the appearances on the straight x-ray. In the rheumatoid group there were 5 men and 11 women, and the one case in the D.J.D. group was a woman. The total incidence was significantly greater in the rheumatoid group (Table 48).

Table 48. Incidence of bronchiectasis in R.A. and D.J.D. groups.

	male	female	total
R.A.	5 (3.6%)	11 (2.9%)	16 (3.1%)
D.J.D.	0	1 (0.4%)	1 (0.3%)
statistical comparison	$\chi^2 = 1.22$ $P > 0.2$	$\chi^2 = 3.56$ $P > 0.05$	$\chi^2 = 5.86$ $P < 0.02^{*}$

To ascertain whether the increased incidence of bronchiectasis was due to the fact that patients with bronchiectasis and arthritis were followed up more closely, the incidence was determined in patients newly referred to the clinic during the period of study. It was found that the incidence of bronchiectasis was 6 (3.2%) of 189 patients with rheumatoid arthritis, an incidence exactly the same as in the total rheumatoid population, compared with 1 (0.4%) of 221

patients with D.J.D.

Dating the onset of the bronchiectasis from the patients' history, the lung disease preceded the onset of rheumatoid arthritis in 13 patients, followed the arthritis in 1 patient, and in the remaining 2 the precise temporal relationship between the conditions could not be determined with certainty. Taking only those in whom the bronchiectasis preceded the arthritis and comparing them with the incidence in the D.J.D. group, the frequency was still significantly greater at the five per cent level (Table 49).

Table 49. Incidence of bronchiectasis (onset before arthritis).

	R.A.	D.J.D.
with bronchiectasis	13 (2.5%)	1 (0.3%)
without bronchiectasis	503	300
total	516	301
statistical comparison	$\chi^2 = 4.86$ $P < 0.05^*$	

Three additional patients were seen with bronchiectasis and rheumatoid arthritis, who were not included in the series, since they were specially referred because of the co-existence of chronic lung disease and arthritis. Since the series was closed two further subjects with rheumatoid arthritis and bronchiectasis have been seen. There were, then, for consideration a total of 21 cases of rheumatoid arthritis and bronchiectasis, 5 men and 16 women. In 1 man the temporal relationship between the two diseases was uncertain but in the remaining 4 symptoms of bronchiectasis preceded those of arthritis by between 24 and 50 years with a mean of 36.5 years. Of the 16 women the temporal relationship

was uncertain in 1, in 1 the lung disease definitely followed the arthritis by a period of 3 years but in the remaining 14 symptoms of bronchiectasis came first by between 12 and 54 years with a mean of 28.5 years.

Features of arthritis

The 21 cases of definite bronchiectasis and rheumatoid arthritis have been compared with the rheumatoid population, excluding those with definite, probable or possible bronchiectasis. The age of onset of the arthritis is shown in Figure 19. The arthritis started before the age of 45 years in relatively more patients with bronchiectasis than without, but the difference was not great.

There was no significant difference in the functional grading between the two groups, and the extent of the arthritis was similar (Table 50).

Table 50. Extent of arthritis in patients with and without bronchiectasis (percentage in parenthesis).

	mild	moderate	severe
with	4 (19)	4 (19)	13 (62)
without	122 (25)	121 (25)	245 (50)

The extent was not recorded in 2 patients without bronchiectasis.

The incidence of subcutaneous nodules in those with and without bronchiectasis was virtually identical.

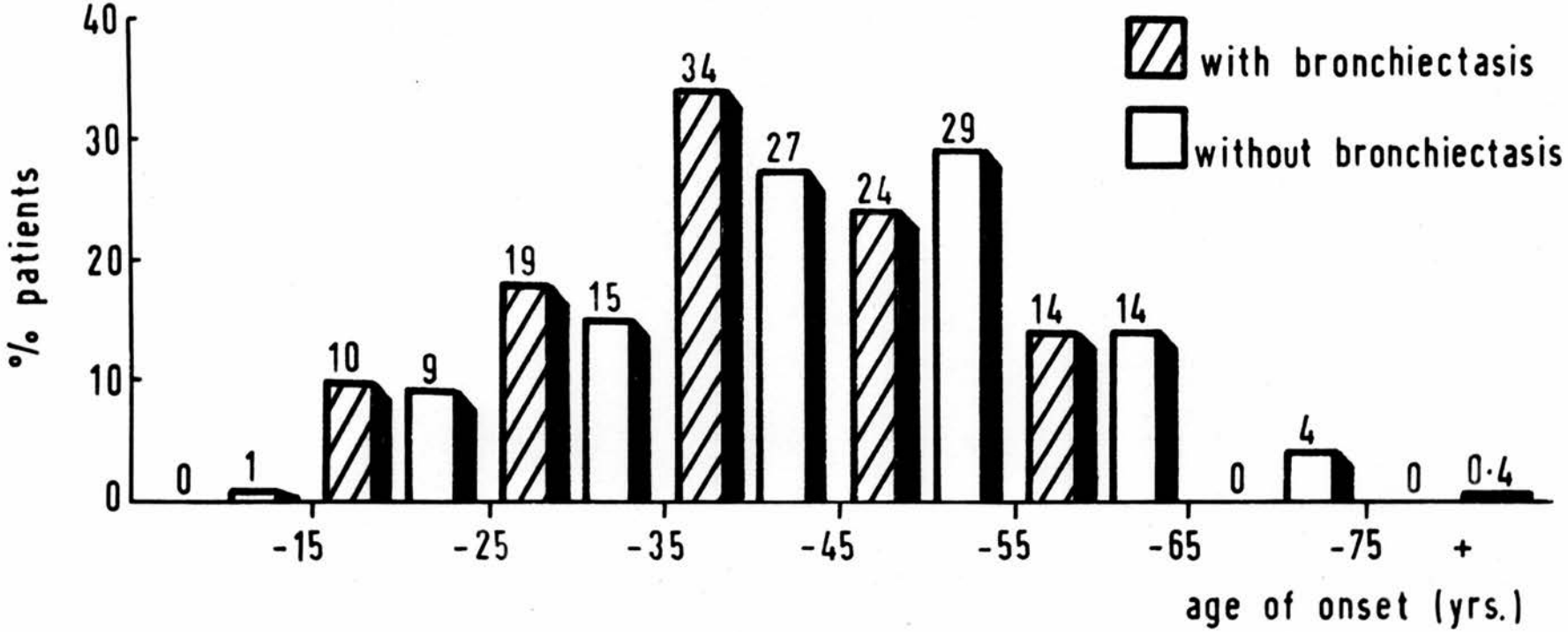
Systemic lesions

In the group with bronchiectasis 2 had splenomegaly, 1 woman had a leg ulcer and 1 man arteritis and ocular lesions.

Corticosteroid therapy

Forty three per cent of the group with bronchiectasis had received

Fig. 19 *Age of onset of r.a. in patients with and without bronchiectasis*



corticosteroid therapy, compared with 70 per cent of those without bronchiectasis. The difference was probably due to a reluctance to employ corticosteroid therapy in the presence of pulmonary infection.

Features of bronchiectasis

Symptoms began before the age of 10 years in 12 patients and between 11 and 20 years in 3. In the remainder symptoms started in adult life. Eleven patients dated the onset of their symptoms to an attack of pneumonia, which followed whooping cough in 1, and was complicated by empyema in 2. In one symptoms began after a post-operative chest complication and another described the initial illness as pleurisy.

In fifteen cases cough had been persistent and in the remainder intermittent. Thirteen raised purulent sputum every day; the others did so only episodically. Fourteen had had haemoptysis, repeated in 10.

Excluding initial episodes of pneumonia, 5 had had repeated attacks and 1 had had a single further attack. Four had had repeated episodes of pleurisy, and 7 had had single episodes.

Seven had finger clubbing and the majority had crepitations over the involved areas of the lungs. The distribution of the bronchiectasis was assessed from bronchograms or pathological examination. In patients where neither of these were available the plain films were used. The disease was unilateral in seven. Involvement was diffuse in two and localised in the remainder. The left lower lobe was involved in 16, the right lower lobe in 12, and the lingula in at least 6. When significant organisms were cultured from the sputum either a pneumococcus or haemophilus influenzae or both were isolated, except for 1 case with a staphylococcus aureus and 1 with a haemolytic streptococcus.

Only one patient had had surgical treatment.

Laboratory investigation

Comparing the haemoglobin levels of those with and without bronchiectasis the incidence of anaemia was similar in both. The B.S.R. in those with and without bronchiectasis is shown in Table 51. Although there was no difference in the percentages with a rate above 60 mm. 1st. hr., in the remainder the rate tended to be higher in those with bronchiectasis.

Table 51. B.S.R. in patients with and without bronchiectasis (percentage in parenthesis).

	b.s.r. (mm. 1st. hr.)			
	0-20	21-40	41-60	61+
with	2 (10)	6 (28)	9 (43)	4 (19)
without	127 (26)	141 (29)	125 (26)	88 (18)

The result was not available in 9 patients without bronchiectasis.

The titre of the S.C.A.T. was less than 1:32 in 1 man and 2 women in the group with bronchiectasis (Table 52). Three of the remaining 4 men had a titre of 1:512 or greater. More of the women with bronchiectasis had a titre of 1:32 or 1:64 compared with those without bronchiectasis, but there was no essential difference between the two groups when the higher titres were considered.

L.E. cells were absent in 6 women and 4 men in whom this investigation was done.

Serum protein abnormalities were looked for in 14 cases with bronchiectasis. A low albumin was found in 2 (14%) compared with 38 (19%) of 196 patients without bronchiectasis. A high globulin was found in 5 (35%) of 14 with bronchiectasis compared with 49 (25%) of 194 without. An abnormal electrophoretic pattern was present in 7 (58%) of 12 patients with bronchiectasis compared with 105 (68%) of 154 of

Table 52. S.C.A.T. in patients with and without bronchiectasis (percentage in parenthesis).

	S.C.A.T.			
	0-1:16	1:32, 1:64	1:128, 1:256	> 1:256
MALE				
with	1 (20)	1 (20)	-	3 (60)
without	20 (16)	23 (18)	41 (32)	45 (35)
FEMALE				
with*	2 (13)	7 (48)	3 (20)	3 (20)
without	100 (29)	64 (18)	95 (27)	90 (26)

*One other had a positive latex slide test.
The result was not available in 12 patients without bronchiectasis.

the remainder.

Joint radiographs

Table 53 shows the comparison between the radiographic severity of changes in the hands and feet in those with and without bronchiectasis. The radiographs of the hands revealed no essential difference between the two groups. Although rather more with bronchiectasis were graded as severe in the feet, there was no significant difference from the group without bronchiectasis. The duration of the arthritis in the group with bronchiectasis was very similar to the rheumatoid population as a whole, and would not therefore bias the results.

Comment

There was a significant increase in the incidence of bronchiectasis in the rheumatoid group compared with the D.J.D. group.

These cases were in the main examples of localised bronchiectasis, resulting from bronchial obstruction and infection, which usually occurred in childhood. They were representative of this type of bronchiectasis

Table 53. Radiographic comparison of severity of changes in the hands and feet in patients with and without bronchiectasis (percentage in parenthesis).

	x-ray grades				
	normal	doubtful	mild	moderate	severe
HANDS					
with	1 (5)	3 (14)	3 (14)	3 (14)	11 (52)
without	37 (8)	43 (9)	101 (21)	65 (14)	231 (48)
FEET					
with	2 (10)	-	7 (35)	-	11 (55)
without	49 (11)	31 (7)	111 (24)	97 (21)	173 (38)

films of the feet were not available in one man with bronchiectasis, and 29 without bronchiectasis, and of the hands in 13 without bronchiectasis.

and did not seem to have any unusual features. In the majority symptoms of bronchiectasis preceded those of arthritis by many years.

The arthritis in those cases did not differ significantly from those without bronchiectasis. Rather more had a moderately raised B.S.R., probably due to the effect of pulmonary infection.

K. MISCELLANEOUS

Clinical

In the rheumatoid group 4.3 per cent of the men and 7.7 per cent of the women gave a history of one or more attacks of acute bronchitis. In the D.J.D. group the figures were 1.6 per cent and 9.2 per cent respectively. These were patients without chronic bronchitis. One woman in the rheumatoid group and 4 in the D.J.D. group had bronchial asthma. Four men and 3 women in the rheumatoid group had had empyema compared with 1 in each sex in the D.J.D. group.

Radiographic

Radiographic evidence of pulmonary tuberculosis, including old primary lesions, is shown in Figure 20. There was no significant difference in this respect between the two groups.

Opacities considered to be due to old or recent inflammatory lesions were present in 2.1 per cent of the rheumatoid group and in 2 per cent of the D.J.D. group. Other abnormalities noticed in the rheumatoid group were a retrosternal goitre in 2, a left ventricular aneurysm in 1, radiation fibrosis in 1, a diaphragmatic hernia in 1 and a probable pleuro-pericardial cyst in 1. In the D.J.D. group there was 1 with an aortic aneurysm, 1 with a secondary deposit from a thyroid carcinoma and 1 with a probable pleuro-pericardial cyst.

Fractured ribs were observed on the films of 4 per cent of men and 5 per cent of women in the rheumatoid group. The figures in the D.J.D. group were 1.6 per cent and 2.5 per cent respectively. Four of the 5 men and 12 of the 16 women with fractures in the rheumatoid group had received steroid therapy.

There was an increased incidence of cardiomegaly with age in both groups (Figure 21). Although cardiomegaly was more common in the D.J.D. group there was no significant difference in any decade from the corresponding figures in those with rheumatoid arthritis.

Fig.20 *X-ray evidence of tuberculosis*

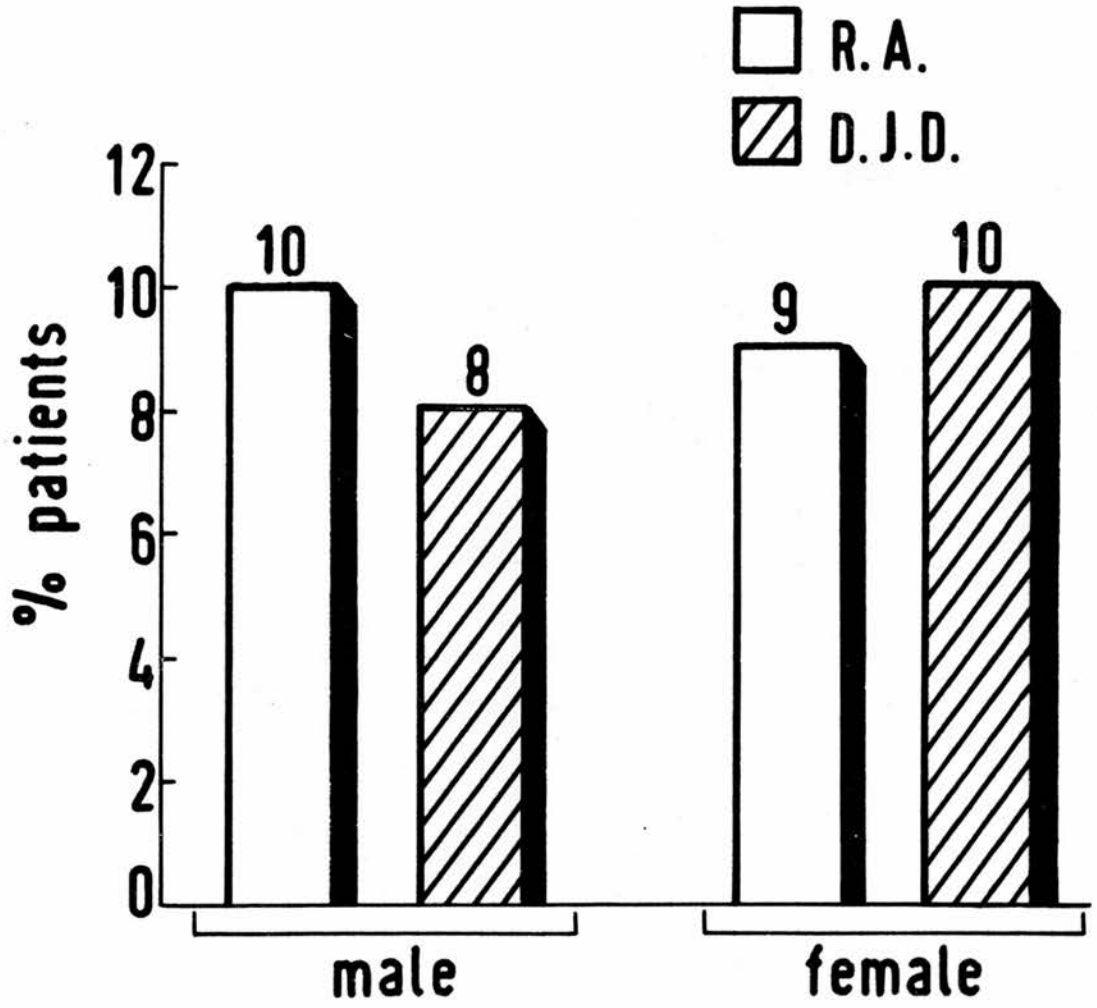
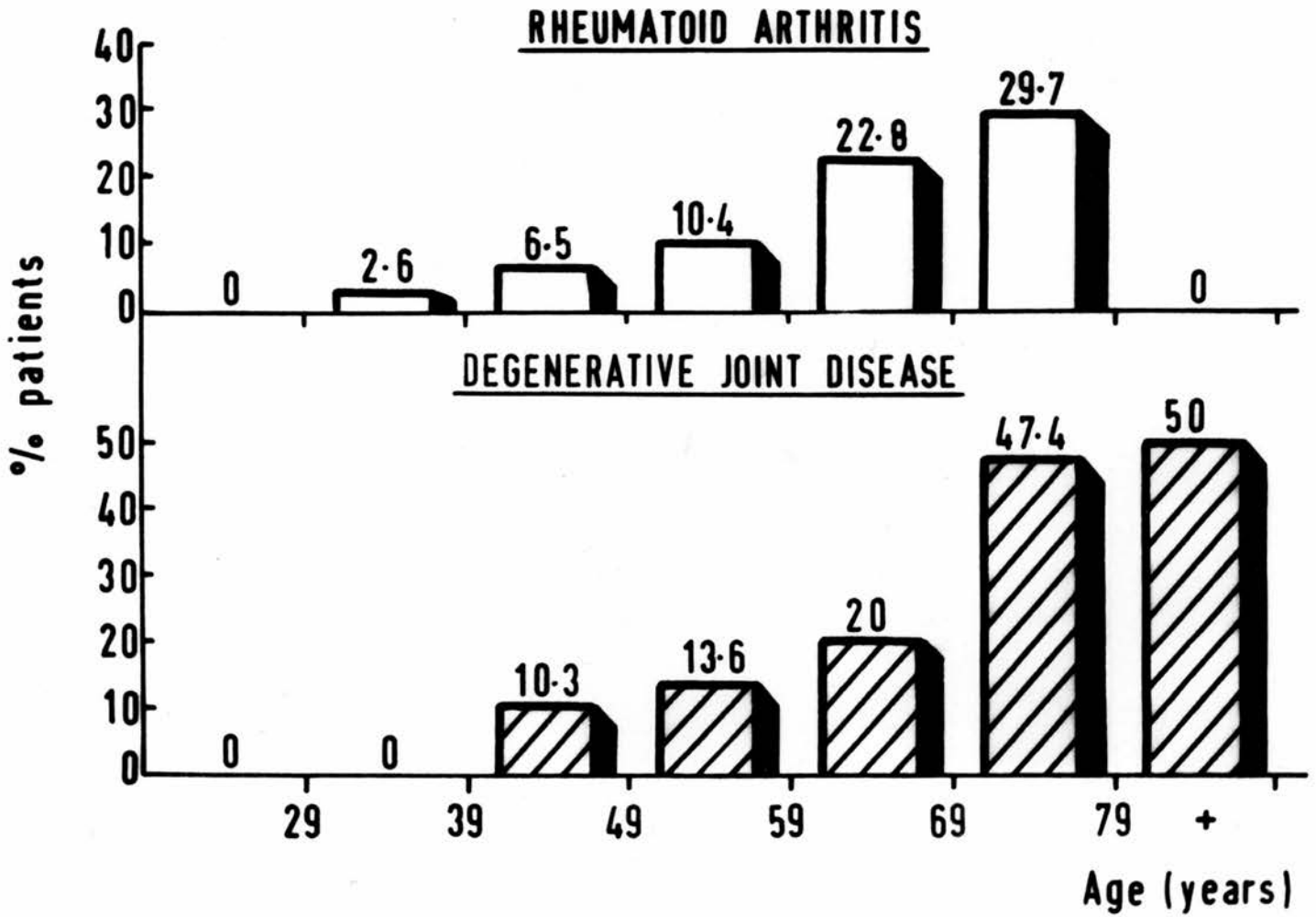


Fig. 21 *Incidence of cardiomegaly in each decade*



V. DISCUSSION

V. DISCUSSION

The rheumatoid series studied appears to have been representative of the disease as encountered in hospital practise. The female to male ratio was 2.7:1, which corresponds closely with that found by Sclater (1943) in patients admitted to hospital with rheumatoid arthritis, and is similar to the series of Short et al. (1957). In the D.J.D. group there were four times more women than men, which is not representative of the prevalence of the disease in the community (Sharp, 1964). However, after the age of 55 more women have multiple joint involvement and this, together with the increased incidence of obesity, may account partly for the excess of women who were seen (Kellgren and Lawrence, 1958). As a control group from the respiratory point of view the sex distribution in the D.J.D. group was acceptable.

Duthie (1964) stated that the age of onset of rheumatoid arthritis was between 25 and 54 years in 70 per cent of cases; the figure in this series was 71 per cent. Forty five per cent of this series had had arthritis for more than 10 years at the time of review. This can be compared with the figure of 13 per cent found by Short et al. (1957). The relatively high percentage with long-standing disease is reflected in the functional grading, in which 16 per cent were in grade 4 and 2 per cent in grade 5.

The reported incidence of subcutaneous nodules in rheumatoid arthritis has varied. Short et al. (1957) found them in 11.6 per cent of their cases at initial review, rising to 21.3 per cent during follow up. Thompson (1965) gave a figure of 30 per cent. The incidence in this series in men was unexpectedly high and in women slightly more than usual. This was probably due to the stringent criteria used for diagnosis and the substantial proportion with long-standing disease.

Splenomegaly was present rather less often than in the series of Short et al. (1957), 3.6 per cent compared with 6 per cent.

The percentage with a positive S.C.A.T. (a titre of 1:32 or greater) was as expected in a hospital rheumatoid population (Wilson et al. 1960). L.E. cells were present in six per cent of these in whom the examination was done, but there was no other evidence of systemic lupus erythematosus. Although it is appreciated that the significance of L.E. cells in such cases is controversial, it was decided not to exclude these patients in whom the diagnosis by all other criteria was rheumatoid arthritis.

Pleural lesions

This investigation has demonstrated a significantly higher incidence of pleural effusions in the rheumatoid population than in the D.J.D. group. Locke (1963) had found a greater frequency of pleural effusion in rheumatoid patients compared with a control series, but his cases were highly selected, all having been in-patients who were referred for radiographic examination. The present result is at variance with the findings of Aronoff et al. (1955) and of Stack and Grant (1965). However, Aronoff et al. (1955) x-rayed their patients only when clinically indicated and used as a control group patients referred to hospital for chest radiography. Stack and Grant (1965) reviewed the chest radiographs of rheumatoid patients taken at their first attendance at a rheumatic clinic and therefore they would only detect cases who had a pleural effusion at that time. In the present study account has been taken of pleural effusions occurring at any time during the natural history of the rheumatoid arthritis and cases covering a wide spectrum of the disease were included in the review. Moreover, in none of the previous controlled investigations has a comparison been made with patients in whom there is

no known association with respiratory disease.

Some of the patients in whom the pleural effusion was accepted as due to the rheumatoid process had supportive evidence for the diagnosis on investigation. In those in whom this was lacking the diagnosis was only accepted when there was no evidence of an alternative cause after careful evaluation and follow up. There was considerable variation in the size of the effusions encountered in this series; they were bilateral in 20 per cent and of the remainder they occurred more frequently on the right side. All these features were in close accord with the information derived from the analysis of the literature. On the other hand, 29 per cent of the cases previously described had been asymptomatic, whereas all but 2 of the patients in this series had symptoms attributable to pleurisy or the presence of an effusion. The relationship between the occurrence of the effusion and the onset of the arthritis in the present series and in the cases previously described was remarkably similar, and the proportion of the two groups in which the pleurisy was accompanied by an exacerbation of arthritis was essentially the same. Intra-pulmonary disease of rheumatoid origin was found in 20 per cent of the author's series compared with 22 per cent of the cases described in the literature.

One of the aims of this investigation was to assess the value of positive diagnostic criteria in rheumatoid pleural effusions, because without them early definitive diagnosis is impossible. The differential cell count in the pleural fluid was very variable and therefore of no value in this respect. Carr and Mayne (1962) emphasised the diagnostic value of a very low glucose level in rheumatoid pleural effusions, when they found a level of 15 mgms. per 100 mls. or less in 10 of 11 specimens from 9 patients. However, a level of 40 mgms. or less was found in only 3 of the 8 patients in this series in whom the investigation was done. Moreover, of 3 other patients with levels of 65 mgms.

per 100 mls. or more, subsequent histological examination of the pleura was undertaken at autopsy in 2, and after decortication and resection of an intra-pulmonary lesion in 1. No evidence of an alternative cause for the pleural effusion was found in any of them. There is no obvious reason why the pleural glucose level is very low in some patients and normal in others. There was no correlation with the histological findings in the pleura as revealed by biopsy, which were non-specific in two of those with low levels and in the third, one pathologist regarded the changes as non-specific and the other as consistent with rheumatoid pleuritis. Serial readings in three patients did not suggest that the low glucose levels were dependent on the duration of the effusions.

Rodnan et al. (1962) showed that occasionally the S.C.A.T. was positive in the joint fluid and negative in the blood. The S.C.A.T. was done on the pleural fluid from eight patients. In three with a negative S.C.A.T. in the blood the test was also negative in the pleural fluid. However, in three others with a positive S.C.A.T. in the blood a higher titre was present in the pleural fluid. It is possible that such a finding might be of diagnostic value, but clearly more cases require to be studied, including a group of rheumatoid patients with effusions due to other causes.

Although rheumatoid granulation tissue had been obtained by means of needle biopsy of the pleura, in general most authors have commented on the fact that the changes found by this technique have been non-specific, and therefore of no positive help in diagnosis (Ward, 1961; Carr and Mayne, 1962; Mattingly, 1964). The independent observations of two pathologists on twelve specimens from this series are, therefore, of interest. They agreed that in five of them the histological changes were either related to or likely to be related to the rheumatoid process.

On the other hand in the series of 8 specimens which acted as controls only 1 pathologist regarded 1 of them as rheumatoid in nature. Synovial tissue only occasionally contains histological changes similar to those of a subcutaneous nodule (Cruickshank, 1957) and usually the pathologist can only say that the appearances are compatible with rheumatoid arthritis. The same is likely to apply to the pleural lesions. For this reason, and in view of the misinterpretation of one specimen in this study, the results must be viewed with caution and appropriate steps taken to exclude tuberculosis. Particularly in view of the age group usually affected carcinoma must also be eliminated. With these limitations pleural biopsy was of value in 42 per cent of this series, which compares well with results obtained in other diseases in which the technique is accepted as a useful diagnostic procedure.

Although systemic lupus erythematosus must always be considered in the differential diagnosis and indeed prolonged observation may be required to settle the issue, certain features are considered to be of value in the diagnosis of rheumatoid pleural effusion. In the presence of rheumatoid arthritis bilateral pleural effusions are likely to be rheumatoid in nature, unless there is clinical evidence of an alternative cause. A pleural effusion at the onset of arthritis or accompanied by an exacerbation is also likely to be rheumatoid in origin. The presence of intra-pulmonary lesions related to the rheumatoid process is a strongly suggestive feature. Although the glucose level may be very low in some cases, it is often normal. It is possible that a higher titre of the S.C.A.T. in the pleural fluid than in the blood is also a helpful feature, but this requires further evaluation. Pleural biopsy yielded information of positive value more frequently in this series than has been suggested by previous investigators.

In this series resolution of the effusions occurred within 3 months in 13 of the 19 cases compared with 7 of 13 described by Carr and Mayne (1962). The effusions were unduly persistent in four of the patients, as has been the experience of others. Hitherto, little stress has been laid on possible complications of rheumatoid effusions, apart from residual pleural thickening which has usually been minimal. However, in two of the author's cases major pleural complications ensued and these were the only examples in the series in which lesions regarded as intra-pulmonary rheumatoid nodules were present. In one case pleural thickening was so extensive that decortication was required to relieve dyspnoea. In the second there was an empyema which persisted for five years to death and there were reasonable grounds at autopsy for believing that the initial pleural pathology was rheumatoid in nature. It is well known that pyarthrosis may complicate rheumatoid arthritis (Kellgren et al., 1958) and this case demonstrates that the clinician needs to be alert to the possibility of empyema, particularly in unduly persistent pleural effusions.

This series has added little to the scanty information in the literature on the treatment of rheumatoid pleural effusion. The one patient who received intra-pleural corticosteroids did not benefit. In the two patients who received oral corticosteroids the pleural effusions resolved quite rapidly, but it is uncertain whether this was the result of treatment.

The incidence of rheumatoid pleural effusion in this investigation was 3.3 per cent of the total and 7.9 per cent of the men, compared with 5 per cent and 16 per cent respectively in the study of Horler and Thompson (1959). The higher incidence in their series may well have been due to the fact that they did not review an unselected rheumatoid population. The reason for the striking male predominance in this and

previously reported series of cases remains obscure. Investigation of smoking habits, occupation and other respiratory illnesses did not suggest that any of them were responsible. Although the age of onset of the arthritis conformed closely with that in the rheumatoid population, the effusions usually developed in the latter decades. Among the women the range was 53-64 years (mean 58.5) and amongst the men the range was 33-69 years (mean 51.9). Thus the analysis of the literature and the information from this series is in keeping with the widely held impression that rheumatoid pleural effusion is more likely to occur in middle-aged men.

Subcutaneous nodules were more common in those with pleural effusion than in the rheumatoid population, particularly in men. In addition, the only three examples of pericarditis in men, encountered in the whole series, occurred in patients with pleural effusion. This finding suggests that there is a correlation between involvement of the pleura and pericardium in rheumatoid arthritis in men. Although two of the patients with pleural effusions had L.E. cells in the peripheral blood, these were absent from the patients with pericarditis. The levels of the haemoglobin and B.S.R. corresponded closely with those in the rheumatoid population. There was, therefore, no evidence to support the suggestion from the analysis of the literature that anaemia was more common in those with pleural effusion, nor was the tentative conclusion of a high incidence of systemic lesions in women upheld. More of the patients with pleural effusion had a decreased serum albumin than in the rheumatoid population. Subsequent analysis revealed that there was also a correlation between a low serum albumin and the presence of subcutaneous nodules in the rheumatoid population and it is possible that this association may be the explanation. In view of the male predominance in the cases of rheumatoid pleural

effusion it is of interest to note the greater frequency of a history of pleurisy in men with rheumatoid arthritis compared with the D.J.D. group, and the temporal relationship to the arthritis.

The incidence of pleural thickening was also significantly higher in the rheumatoid group, again particularly in men. This is in keeping with previous pathological observations, but not with radiographic studies done by others (Aronoff et al., 1955; Stack and Grant, 1965). It will be recalled, however, that the findings of Aronoff et al. (1955) were similar in that twice as many in the rheumatoid group had pleural thickening as in their control group. Stack and Grant (1965) dealt exclusively with new patients and, therefore, their series was not strictly comparable with this one.

Removal from consideration of those patients in both groups who had a possible cause for pleural thickening other than a history of pleurisy, revealed that about half of the D.J.D. group and a similar proportion of the females in the rheumatoid group remained unexplained. Of the male rheumatoid patients, however, many more were left without a possible cause. These unexplained examples of pleural thickening were no doubt due to pleurisy of varying aetiologies, but the excess in men suggests that some of them were related to rheumatoid pleuritis. On the other hand, the presence of pleural thickening without one of the conditions previously listed as a possible cause does not permit the conclusion that it is related to the rheumatoid process.

Interstitial lung disease

This investigation revealed definite radiographic evidence of interstitial lung disease in 1.6 per cent of the patients with rheumatoid arthritis, an incidence very similar to that of Patterson et al. (1965) and of Thompson (1965). There were no examples in the D.J.D. group.

The difference was not statistically significant. Nevertheless, the study has produced further support for the view that interstitial lung disease may be an integral feature of the rheumatoid process and indeed it is difficult to believe that the consistent detection of these cases in different rheumatoid populations, albeit rarely, is without significance. Moreover, as indicated by the analysis of the cases already recorded in the literature rheumatoid granulomata have been found in the lungs in ten per cent. If statistical confirmation of the association is required an even larger study than the present one would be required.

Locke (1963) thought that interstitial lung disease was much more frequent than the above figures suggest, and indeed he concluded from his controlled study that it was the commonest respiratory complication of rheumatoid arthritis. He diagnosed the condition from the chest radiograph and included as one diagnostic criterion an exaggeration of the normal peripheral vascular pattern of the lungs. The incidence he found was considerably in excess of any other series, namely twenty eight per cent. He did not, however, present full clinical and physiological data on all the cases he mentioned.

Even allowing for the fact that Locke's cases were highly selected, has findings cannot be ignored and accordingly in this series particular attention was paid to the lung markings in the hope of detecting cases which might otherwise have been overlooked. As has been shown, prominent lung markings were not present more frequently in rheumatoid patients and in most of them who were investigated with lung function tests evidence of an alternative cause was present. However, a doubtful increase in lung markings, for which admittedly the observer error was high, was commoner in the rheumatoid patients. It is possible that as more rheumatoid patients were likely to be thin the peripheral lung markings appeared more prominent. Nevertheless, of the patients with

either a definite or doubtful increase in lung markings in whom pulmonary function tests were performed six had an unequivocal reduction in the carbon monoxide uptake as an isolated finding. Although the present author is reluctant to make a firm diagnosis of interstitial lung disease on the basis of an abnormality in a single laboratory test combined with what must be regarded as an equivocal radiographic change, it seems likely, as Locke has suggested, that the condition is commoner than is generally supposed, perhaps in a mild form.

A notable feature of the analysis of the literature and of this series is the male predominance in cases of interstitial lung disease, despite the fact that rheumatoid arthritis is more common in women. Moreover, idiopathic interstitial lung disease is also commoner in women (Stack et al., 1965). There is no obvious cause for this difference and, although it is reasonable to evaluate environmental factors, there is no convincing evidence that they are responsible. Analysis of occupational factors and other lung disease, such as chronic bronchitis, did not reveal any difference from the rheumatoid population in this study. Although relatively more of the men had smoked heavily for more than twenty years, the number is too small from which to draw conclusions.

All the patients with interstitial lung disease in this series were in the sixth or seventh decades at the time of review. It was possible to make a reasonable deduction as to the age of onset of the lung disease in nine patients. The range was 49 - 63 years (mean 56 years). This was rather higher than in the cases previously reported in the literature. Livingstone et al. (1964) found an age range of 20 - 78 years (mean 50.5 years) in a series with the idiopathic type and Stack et al. (1965) in a similar series found the age range to be 12 to 77 years. In the rheumatoid group both in this series and in

the cases described in the literature patients have on the whole been in the older age groups. In the present series the radiographic appearances and clinical signs were in no way distinct from those which occur in the idiopathic type. Pleural thickening, possibly of rheumatoid origin, was present in one man. The mean duration of the lung disease was 4.7 years, and in general the course seemed less rapidly progressive than usually encountered in the idiopathic type. No examples of synchronous exacerbations of the disease in the joints and in the lungs (Brannan et al., 1964) were encountered, perhaps because of the chronicity of the cases detected in the review. Two patients have since died, one from unrelated causes and the other from pneumonia. Of the remainder only one was sufficiently disabled by dyspnoea to warrant the use of corticosteroid therapy. This clinical assessment was reflected in the lung function tests, which showed less impairment than in a series of cases with idiopathic interstitial lung disease.

There is, then, a predominance of men affected by rheumatoid interstitial lung disease and some suggestion that the age of onset tends to be later than in the idiopathic type. It is likely that the cases encountered in this series were representative of rheumatoid interstitial lung disease, but those without arthritis, who were studied, were not an unselected sample. Although the comparison drawn between them must be interpreted with caution the difference in the degree of impairment of respiratory function is of interest. It was shown in the review of the literature that dyspnoea was less common in those with rheumatoid arthritis and arthritic disability was suggested as a possible cause for this. However, Scadding (1960) thought that on the whole the acuteness of interstitial lung disease and the rate at which it progressed tended to vary inversely with age and Stack et al. (1965) drew attention

to the fact that a more benign type may exist in older subjects. The results of this study suggest that more cases with rheumatoid than idiopathic interstitial lung disease may be in this group, and therefore the prognosis in some of them may be better than is generally supposed.

Careful attention has been paid to the arthritis in those with interstitial lung disease by comparing the data obtained from the collective analysis of the literature and from the patients in the series with the rheumatoid population. As far as extent of arthritis and radiographic severity were concerned. there was no difference. The age of onset of the arthritis in those in the series with interstitial lung disease was greater than in the rheumatoid population. Analysis of the literature had suggested a greater frequency of subcutaneous nodules in men but not in women. However, this series and that of Patterson et al. (1965) strongly suggests that there is an association between interstitial lung disease and subcutaneous nodules in both sexes. There was no suggestion either from the literature or from this series of a greater frequency of systemic lesions of rheumatoid arthritis. The increased incidence of anaemia, suggested by Stack and Grant (1965) and by the analysis of previously reported cases, was not present in the current series. This cannot be explained by less active disease, since the B.S.R. tended to be higher in the present author's cases than in the rheumatoid population.

A correlation between serum rheumatoid factor and interstitial lung disease in rheumatoid subjects was demonstrated in the review of the literature and upheld by the findings of this series. However, by no means all of the patients had high titres of rheumatoid factor and the author is reluctant to accept the hypothesis advanced by Tomasi et al. (1962) for the pathogenesis of the lung disease for this reason. Never-

theless, it would be unwise to dismiss it before the cause of rheumatoid interstitial lung disease is established. Chloroquine is known to reverse positive serological reactions in a proportion of cases (Popert and Meijers, 1961), and anti-malarial therapy was employed in two patients with interstitial lung disease and rheumatoid arthritis and in one with the idiopathic type who had a positive test for the rheumatoid factor. Serial lung function tests were only available in two of these patients, since the third died from a cause unrelated to the lung disease before they could be repeated. In one of the remaining patients there was evidence of slight improvement at 3 months, although there had been slight deterioration 6 weeks later. In the second patient there was marginal objective improvement only, and clearly the considerable symptomatic benefit reported was largely a placebo effect. It is not possible to reach a firm conclusion from these studies, since dramatic benefit would not be anticipated. It is, however, suggested that this therapeutic approach merits further exploration before it is dismissed, particularly since administration of corticosteroids is not only without benefit in many cases but may be harmful (Stack and Grant, 1965). Corticosteroids were only employed as treatment for rheumatoid interstitial lung disease on one occasion in this series. It probably decreased the rate of progression of the disease, which clinically appeared to be rapid.

The pathological examinations performed yielded evidence of interstitial lung disease without specific rheumatoid features. However, as previously emphasised, these would not necessarily be anticipated as they are only present in ten per cent of cases. There was no evidence of carcinoma in the patient who died and no radiographic suggestion of this in the remainder. An example of this possible complication of interstitial lung disease proven at autopsy, was recently encountered

by the author in a female patient of 75 years who had never been a smoker.

Pulmonary infections

One of the most striking results of this investigation was the significantly higher incidence of bronchiectasis in the rheumatoid patients compared with those with D.J.D. The true incidence of bronchiectasis in the community is not known, but from the figures of Clark (1963) and of Perry and King (1940) it can be deduced approximately. Clark (1963) found a rate of 1.06 per 10,000 children per annum up to the age of 10 years inthe North-eastern Hospital Region of Scotland, and Perry and King (1940) found the age of onset to be up to 10 years of age in 42 per cent, between 11 and 20 years in 27 per cent, between 21 and 40 years in 24 per cent and over 40 years in 7 per cent. Clark (1963) thought that his figure included virtually all cases of bronchiectasis in the region and assuming that the incidence is similar elsewhere it becomes 0.25 per cent in the community. Wynn-Williams (1953) at a chest clinic serving 150,000 people found an incidence of 0.14 per cent. Although the figure of 0.25 per cent cannot be claimed to be strictly accurate it does provide some idea of the prevalance and conforms closely with that found in the D.J.D. group. There can be no doubt that the incidence in the rheumatoid group was unexpectedly high.

However, before concluding that there is a genuine association between the two diseases alternative explanations require exploration. For example, patients with bronchiectasis might have been kept under observation because of the presence of the two diseases, but this is clearly not the cause of the greater frequency of bronchiectasis since the incidence in newly referred patients was almost identical with that in the whole series. Aronoff *et al.* (1955) offered as a possible reason for a similar

finding that more patients with two diseases than with one were likely to be referred to hospital. Although this is probably true regarding admissions to a general hospital, it seems doubtful that it applies to a specialist rheumatic out-patient clinic. However, it cannot be denied that general practitioners might more readily refer a rheumatoid patient with bronchiectasis because of the potential risks of corticosteroid therapy. There was no evidence that this applied in the present review. It is also possible that more cases with bronchiectasis would be referred to a rheumatic clinic if the pulmonary infection had a deleterious effect on the arthritis, but comparison between those with and without bronchiectasis did not confirm that this was so. Aronoff et al. (1955) also suggested that an increased susceptibility to infection might account for the higher prevalence of bronchiectasis which they had observed. However, in this series symptoms of bronchiectasis preceded those of arthritis in the majority of cases by many years. Agammaglobulinaemia was also considered by the present author as a possible explanation for the association but this was not present in any of the patients in whom serum proteins were estimated.

In view of the above findings the greater prevalence of men with chronic bronchitis in the rheumatoid group, than in the D.J.D. group is of interest. However, before drawing conclusions from this it is necessary to consider more carefully the incidence in the D.J.D. group. It was initially intended to include only those with the "complex" syndrome (Reid et al., 1964), but since dyspnoea was obviously difficult to assess this was not possible. As an alternative, the criteria utilised for diagnosis included productive cough in more prolonged episodes than that utilised in the diagnosis of simple chronic bronchitis, where the period is three months. The expected prevalence in this series would,

therefore, be less than that for simple chronic bronchitis and probably more than that for the complex syndrome. Most of the patients were resident in a city, some in towns and a few in rural areas. Ten per cent were less than 40 years old, and 19 per cent were non-smokers. Taking all these factors into consideration and comparing the prevalence with that found in the report of the College of General Practitioners (1961) it is possible that the incidence of chronic bronchitis as defined in this study in the D.J.D. group is an underestimate of that in the population.

However, the men in the rheumatoid group had an unequivocally greater prevalence of the disease than in the D.J.D. group. More men with rheumatoid arthritis than those with D.J.D. were smokers, and as expected, there was a correlation between smoking and chronic bronchitis. It was possible that more men smoked because they developed rheumatoid arthritis, but this proved not to be the case since all but two had started to smoke before theydeveloped arthritis. In most cases symptoms of chronic bronchitis antedated those of arthritis.

The higher frequency of a history of pneumonia in the rheumatoid group was not unexpected, but, most of the attacks, particularly in men, had occurred before the onset of the arthritis, a finding in keeping with that of Short et al. (1957). However, the greater frequency of chronic lung disease may well be the explanation as of the rheumatoid men with a history of pneumonia 18 (49%) of 37 had either chronic bronchitis or bronchiectasis.

This investigation, therefore, has provided strong support for an association between bronchiectasis and rheumatoid arthritis, and suggestive evidence of a greater prevalence of chronic bronchitis in men with the disease. Moreover, in both bronchiectasis and chronic bronchitis symptoms of the lung diseases antedated those of arthritis

in the majority of cases. The implications of these findings require discussion.

It is possible that the rheumatoid diathesis prior to the onset of arthritis is associated with an increased susceptibility to infections. Lewis-Faning (1950) reported the results of a controlled investigation into illnesses prior to the onset of rheumatoid arthritis. Compared with the control group the rheumatoid patients more frequently gave a history of tonsillitis and during the three months prior to the onset of arthritis more had had coryza. However, these were the only infections which were more common in the rheumatoid group and little importance was attached to them by the author.

In this study a history of infections other than those of the lung was no more frequent in the rheumatoid group than in the D.J.D. group with the exception of herpes zoster but the relationship of the latter to the onset of arthritis and the administration of corticosteroids was not specifically noted. There is, therefore, little evidence to suggest that rheumatoid patients, prior to the onset of arthritis, are unduly susceptible to infections.

The association could also be explained if subjects with bronchiectasis or men with chronic bronchitis were more likely to develop rheumatoid arthritis and it is interesting to speculate how this might occur. There is considerable interest at the present time in the possibility that rheumatoid arthritis may be caused by micro-organisms. Duthie (1963) reported that a growth of an unidentified organism had been obtained on several occasions from cultures of rheumatoid synovial membrane and he suggested that this organism might represent a living intracellular agent. Subsequently mycoplasma were isolated from cases of rheumatoid arthritis (Bartholomew and Himes, 1964). Certain strains of mycoplasma

produce a polyarthritis in rats and mice with some similarity to rheumatoid arthritis (Findlay et al., 1940). It responds to treatment with organic gold salts (Sabin and Warren, 1940). There is, therefore, some circumstantial evidence to support the possibility that such an organism might cause rheumatoid arthritis. Although, there is, as yet, no known association between mycoplasma and chronic lung diseases Taylor-Robinson (1966) is shortly to investigate this possibility and feels that the suggested link may be more than wild speculation. The findings of the present study, therefore, are of particular interest.

Apart from providing a source of a directly invasive micro-organism chronic pulmonary infection could have an aetiological role by an alternative mechanism. A source of chronic infection was, of course, at one time thought to be an important cause of rheumatoid arthritis, but this theory was subsequently discarded because of lack of evidence. Davidson et al. (1949) did not find a higher incidence of foci of infection in the ear, nose or throat of patients with rheumatoid arthritis compared with a control group. In another study focal sepsis was found to be more common in rheumatoid subjects than in controls at examination (Lewis-Faning, 1950), but it was not clear whether the sepsis had preceded the arthritis or followed it. More recently auto-immune mechanisms have been considered to be closely associated with the underlying pathology of rheumatoid arthritis, but it is uncertain whether they are directly responsible for the genesis of the disease. It has been postulated that infection might be the event which initiates abnormal immune mechanisms (Vaughan and Orbison, 1959; Christians, 1964). At the Second Nuffield Conference on Rheumatism Hill (1964) included this mechanism when discussing possible aetiologies, and Kellgren (1964) thought that the available data suggested that rheumatoid arthritis might result from an immunological abnormality which could be enhanced

by chronic infection and other forms of antigenic stimulation. Rotstein and Good (1961) from their study of patients with agammaglobulinaemia, in which they found one-third to be suffering from connective tissue disorders and in which resistance to infection is low, believe that infection may have an important role in pathogenesis. More recently, Hamerman (1966) has postulated that components of bacterial cell walls or capsules might be the inciting agent in rheumatoid arthritis. He suggested that in predisposed individuals connective tissue cells took up these components and incorporated them into their proteinpolysaccharides, which, now altered, resulted in local cellular damage through immunological mechanisms. There has, therefore, in recent years been a renewal of interest in the possibility that micro-organisms, either, directly or indirectly, might have an important aetiological role in rheumatoid arthritis.

There are inevitable limitations in any comparitive study involving patients attending a hospital and, therefore, it cannot be claimed that a relationship between chronic pulmonary infection and rheumatoid arthritis has been unequivocally established. However, from the evidence presented it appears to the author that this possibility requires further evaluation, preferably on an epidemiological basis. If such an association is confirmed with the temporal relationships encountered in this investigation it would provide a firm lead for further research into the aetiology of rheumatoid arthritis.

VI. SUMMARY

SUMMARY

The literature on the pleuro-pulmonary lesions of rheumatoid arthritis has been reviewed and the evidence for and against each manifestation described has been presented. For comparitive purposes the cases previously recorded have been analysed by the same methods as employed in the author's investigation.

516 patients with definite or classical rheumatoid arthritis have been studied clinically, radiographically and serologically in order to evaluate the pleuro-pulmonary manifestations more fully and to assess the significance of respiratory infections. 301 patients with degenerative joint disease were simultaneously investigated to serve as a control group.

Pleural effusion, radiographic evidence of pleural thickening and a history of pleurisy were more common in the rheumatoid group, particularly in men. Evaluation of patients with pleural effusion revealed an association with subcutaneous nodules and with pericarditis in men, but otherwise there were no distinguishing features from the remaining rheumatoid patients. Methods for establishing an early definitive diagnosis of rheumatoid pleuritis have been assessed. Very low glucose levels in the pleural fluid were less useful than previously suggested but pleural biopsy proved valuable in 42 per cent. Investigation of the titres of rheumatoid factor in the blood and pleural fluid was undertaken.

Radiographic evidence of interstitial lung disease was present in 1.6 per cent of the rheumatoid group, but not encountered in the control group. There was a correlation between subcutaneous nodules, a very high B.S.R., the presence of the serum rheumatoid factor, and serum protein abnormalities in those with interstitial lung disease, otherwise there were not distinguishing rheumatoid features. A clinical and physiological

comparison between interstitial lung disease in patients with and without rheumatoid arthritis revealed less impairment of respiratory function in the rheumatoid group. Rheumatoid interstitial lung disease seems in general to have a better prognosis. Application of lung function tests to patients with radiographic changes of doubtful significance produced evidence suggesting that interstitial lung disease in rheumatoid arthritis is more common than generally supposed.

Intra-pulmonary rheumatoid nodules were very rare. In two cases serious pleural complications ensued.

The incidence of radiographic evidence of tuberculosis and of opacities due to old or recent inflammatory lesions were the same in both groups. Fractured ribs were slightly more common in the rheumatoid group but the difference was not significant.

Bronchiectasis was significantly more frequent in the rheumatoid group and in the majority of cases symptoms from the lung disease antedated those of arthritis by many years. In men chronic bronchitis was more common in the rheumatoid group and in most cases the onset preceded the arthritis. A history of pneumonia prior to the onset of arthritis was more frequent in the male rheumatoid population. The reasons for these associations have been explored and a role in the aetiology of rheumatoid arthritis postulated.

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IX. APPENDICES

APPENDIX 1.

Date: RESPIRATORY DISEASE IN RHEUMATOID ARTHRITIS

Name:	No.	1	2	3	4	5	6	Age	7	8	Sex M / F	11 / 12

Age of onset 9

1-15	0
16-25	1
26-35	2
36-45	3
46-55	4
56-65	5
66-75	6
76+	7

Diagnosis

d.j.d.	8
r.a.	9

Smoking 10

non-smoker	0
stopped	1
cigs. 1-10	2
11-20	3
21+	4
Pipe smoking	5
durn. 0-10 yrs.	6
11-20 yrs.	7
21+ yrs.	8

Industrial

associated	9
not associated	11
(specify)	

Hb.(g./100ml.) 11

< 9	0
9-10.4	1
10.5-12.6	2
12.7+	3

Whites (thousands)

0-3	4
3-5	5
5-10	6
10-15	7
15+	8

Duration 12

0-11 months	0
1-2 years	1
3-5 "	2
6-10 "	3
11-20 "	4
20+ "	5

Function

1	6
2	7
3	8
4	9
5	11

Treatment 13

steroids none	0
-6/12	1
6/12+	2
1-10mg.	3
10mg.+	4
ACTH	5
gold	6
antimalarial	7
phenylbutazone	8

Extent arthritis

mild	9
moderate	11
severe	12

B.S.R. mm.1st.hr. 14

0-20	0
21-40	1
41-60	2
61+	3

D.A.T. titre

not done	4
0-16	5
32-64	6
128-256	7
512+	8

Previous resp. history 15

chron. bronchitis	0
tuberculosis	1
bronchiectasis	2
pneumonia	3
haemoptysis	4
pleural pain	5
other (specify)	6

Present resp. symptoms

cough	7
sputum	8
haemoptysis	9
dyspnoea	11
pleural pain	12

Nodules 16

present	0
absent	1

Systemic

ocular	2
neuropathy	3
myopathy	4
amyloid	5
splenomegaly	6
arteritis	7
cardiac	8
other (specify)	9

L.E. cells 17

not done	0
absent	1
scanty	2
numerous	3

Proteins 18

not done	0
normal albumin	1
low albumin	2
normal globulin	3
high globulin	4
abn. electroph.	5
normal electroph.	6
n.d. electroph.	7

Urine

abnormal	8
normal	9

Previous illness	19	20	21	22	Previous illness	23	24	25	26
Previous illness	27	28	29	30	Previous illness	31	32	33	34

(This is the lower half of the first page - the preceding page and this one were combined on a foolscap page).

X-RAY 35

Hands r.a.	normal	0
	doubtful	1
	mild	2
	moderate	3
	severe	4
Feet r.a.	normal	5
	doubtful	6
	mild	7
	moderate	8
	severe	9

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d.j.d.	normal	0
	doubtful	1
	mild	2
	moderate	3
	severe	4
Pleura	normal	5
	shadow	6
	costo-phrenic	7
	effusion	8
	unilateral	9
	bilateral	11

37

Chest

vascular markings	+	
	absent	0
	doubtful	1
	present	2
interstitial	absent	3
	doubtful	4
	present	5
nodules		6
other poss. rheumatoid (specify)		7
emphysema		8
old tuberculosis		9
diaphragm abnormality		11
other non-rheumatoid (specify)		12

38

Relation to arthritis (temporal)

chronic bronchitis		
	not known	0
	before	1
	after	2
bronchiectasis		
	before	3
	after	4
pneumonia		
	before	5
	after	6
pleurisy		
	before, > 5 yrs.	7
	before, < 5 yrs.	8
	synchronous	9
	after	11
	exacerbation	12

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Miscellaneous

dyspnoea	mod. exertion	0
	mild exertion	1
	at rest	2
pleural effusion any time		3
old tb. absent		4

bronchiectasis

x-ray	possible	5
	definite (bronchography)	6
	definite (clinical and straight x-ray)	7
cause for effusion/costo-phrenic other than r.a.		8
cardiac enlargement (x-ray)		9

APPENDIX 2.

Case L.H.

Sex = female.

Occupation = housewife.

Diagnosis = Rheumatoid arthritis. Left pleural effusion.

In May 1962, when 53 years old, she developed left sided pleuritic pain followed ten days later by pain and swelling in several joints. She was admitted to hospital where examination revealed signs of a symmetrical polyarthritis of rheumatoid type and of a left pleural effusion. The relevant investigations were as follows:-

Haemoglobin = 9.8 g. per 100 mls.

White cell count = 7,800 per c.mm. Normal differential count.

B.S.R. = 55 mm./1hr.

S.C.A.T. positive 1:1024.

Serum proteins = 6.9 g. per 100 mls. Albumin = 3.8 g., Globulin = 3.1 g.

Electrophoresis = Marked increase in alpha 2 globulin, slight increase in gamma globulin, slight decrease in albumin.

No L.E. cells seen in peripheral blood.

Chest x-ray showed a left pleural effusion (Figure 22a).

X-ray of hands = no definite rheumatoid change.

Bronchoscopy (by the author) showed a normal bronchial tree.

Pleural aspiration revealed clear straw coloured fluid, which contained no pus cells, secondary organisms, tubercle bacilli or malignant cells.

Punch biopsy of parietal pleura was reported as consistent with rheumatoid pleuritis.

Treatment and progress

She received a five day course of cortico-trophin as well as symptomatic treatment for her arthritis in the form of physiotherapy and

salicylates. She was discharged home and was reviewed three months after initial admission. The chest x-ray at that time is shown in Figure 22b. A small, left pleural opacity was present. The arthritis was well controlled by salicylates. Although she continued to have intermittent joint pain she was otherwise well until October, 1964, when she had a further attack of left sided pleuritic pain. Figure 22c shows the chest x-ray at this stage, the left pleural opacity persisting. The fluid was again aspirated and contained no glucose, the S.C.A.T. was negative in the pleural fluid and at this stage also negative in the blood. There have been no respiratory symptoms since. Figure 22d shows the chest x-ray 3 years after the onset of her illness when only slight left pleural thickening persists.

Figure 22a.

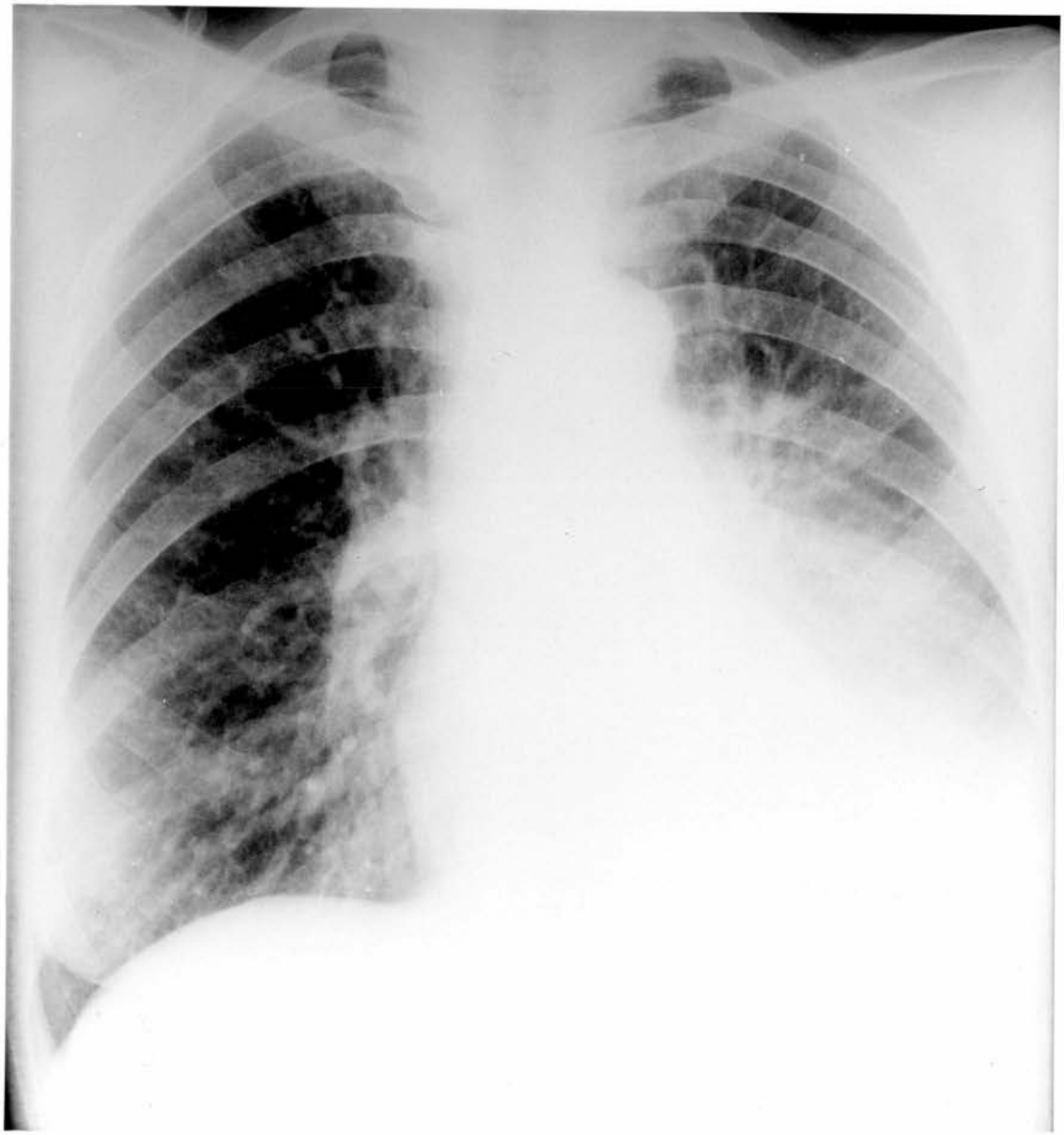


Figure 22b.

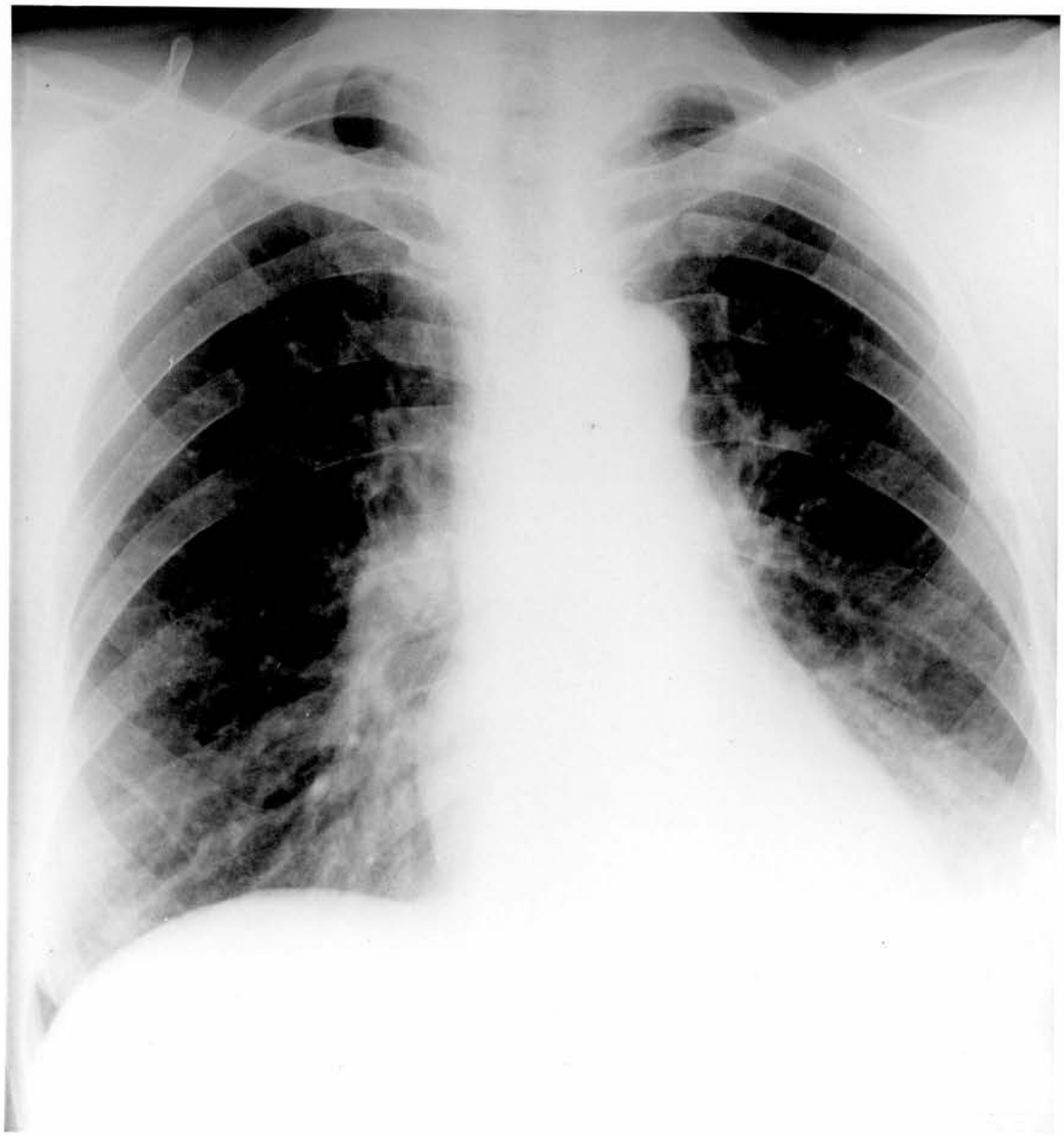


Figure 22c.

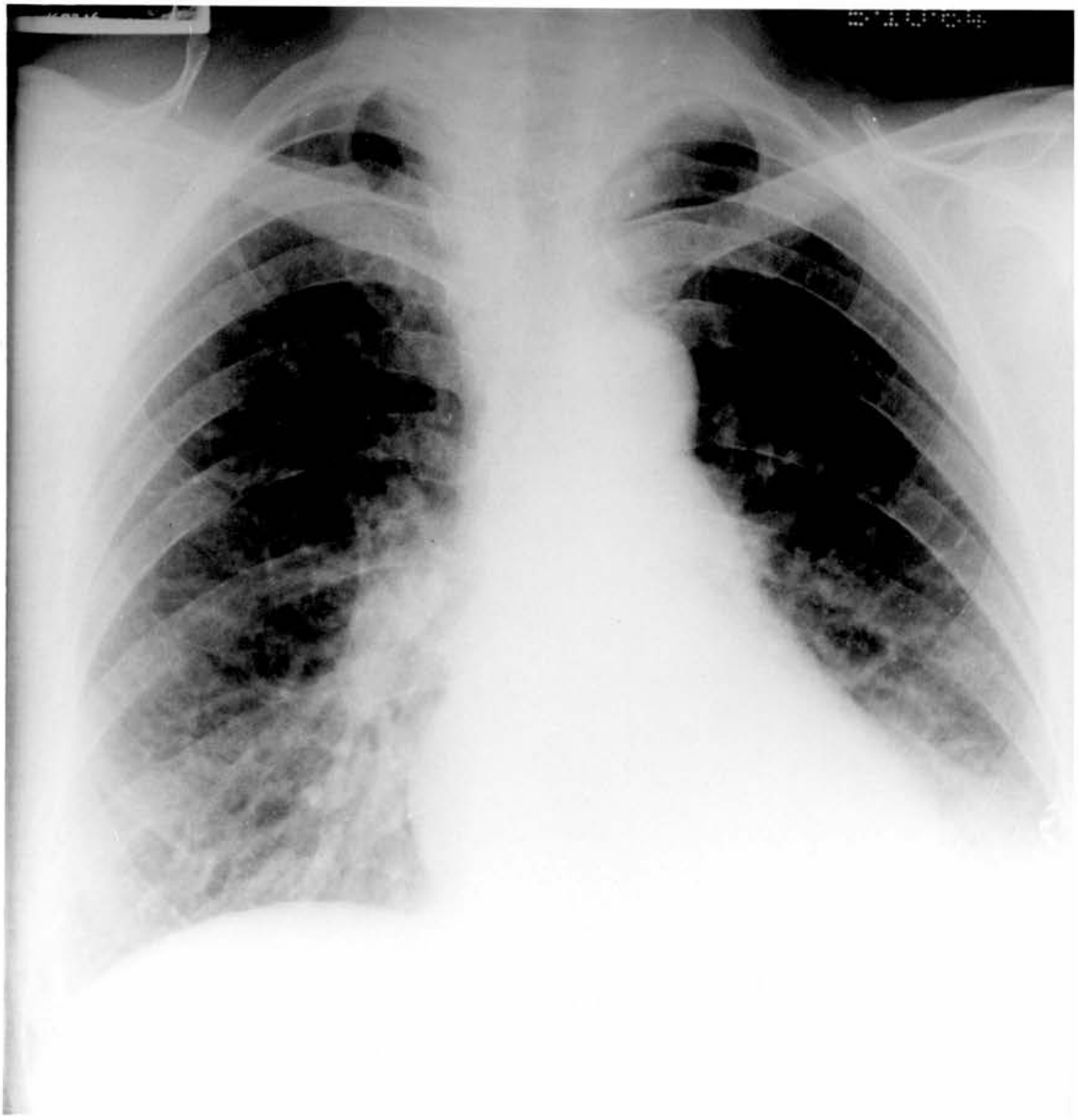
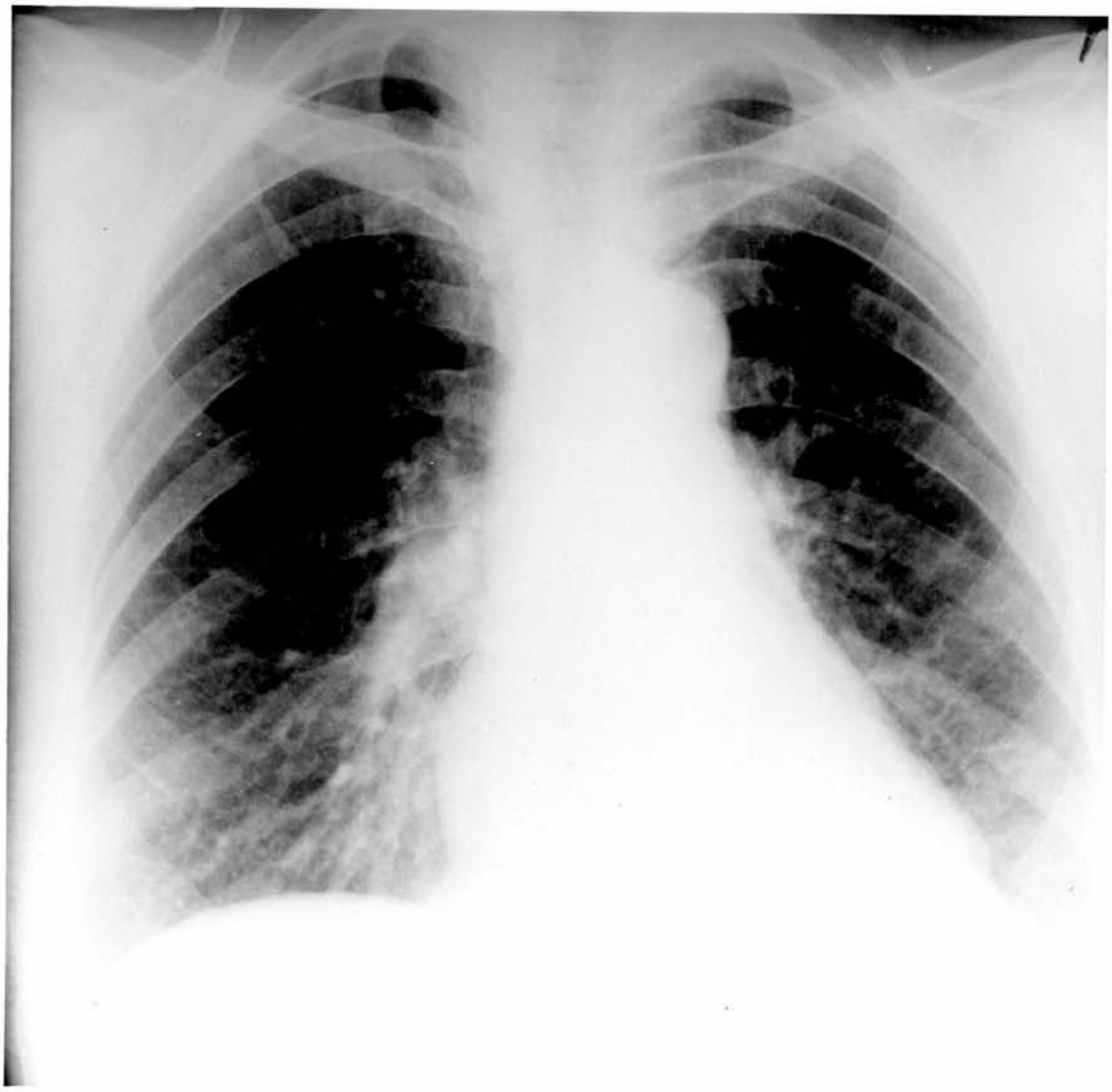


Figure 22d.



APPENDIX 3.

Case: D.H.

Sex = male

Age = 32 years.

Occupation = Tailor's cutter.

Diagnosis = Rheumatoid arthritis. Right pleural effusion.

Onset of rheumatoid arthritis in 1951 involving the hands, shoulders, knees and feet. In 1955 he had sub-sternal pain aggravated by breathing but was not investigated for this. Shortly afterwards corticosteroid therapy was started and was continued until April, 1956. His arthritis remained in a satisfactory remission thereafter and he was discharged from out-patient supervision in 1958. He was referred again in 1961 with a recurrence of articular symptoms which were treated with hydroxychloroquine and salicylates. In June, 1963 he developed right sided pleuritic pain and was referred to the chest clinic where his x-ray was normal. In September, 1963 right sided pleuritic pain recurred accompanied by fever, and he was admitted to hospital for further investigation. Examination revealed signs of a right pleural effusion and of a symmetrical polyarthritis of rheumatoid type. The relavant investigations were as follows:-

Haemoglobin = 17.2 g. per 100 mls.

White cell count = 4,700 per c.mm.

B.S.R. = 78 mm./1hr.

S.C.A.T. positive 1:512.

Serum proteins = 5.9 g. per 100 mls. Albumin = 3.5 g., Globulin = 2.4 g.

Electrophoresis = No definite abnormality.

No L.E. cells seen in peripheral blood.

Chest x-ray showed a right pleural effusion (Figure 23a). Mild erosive changes were present in the hands and feet. Pleural aspiration revealed

clear straw coloured fluid containing a mixture of cells. No tubercle bacilli were isolated.

Pleural biopsy was regarded as containing rheumatoid granulation tissue.

Treatment and progress

He was treated initially with salicylates and his next chest film after one month is shown in Figure 23b. Corticosteroid therapy was then started and Figures 23c and 23d show further films 1 month and 5 months later. Gradual clearing occurred and the final film was normal.

During 1964 he developed anterior chest pain, sharp in character and aggravated by breathing. When seen at the out-patient clinic no pericardial friction rub was audible but the electrocardiogram was consistent with pericarditis. There has been no recurrence of chest pain or other respiratory symptoms during further follow up and his arthritis is in a satisfactory remission.

Figure 23a.

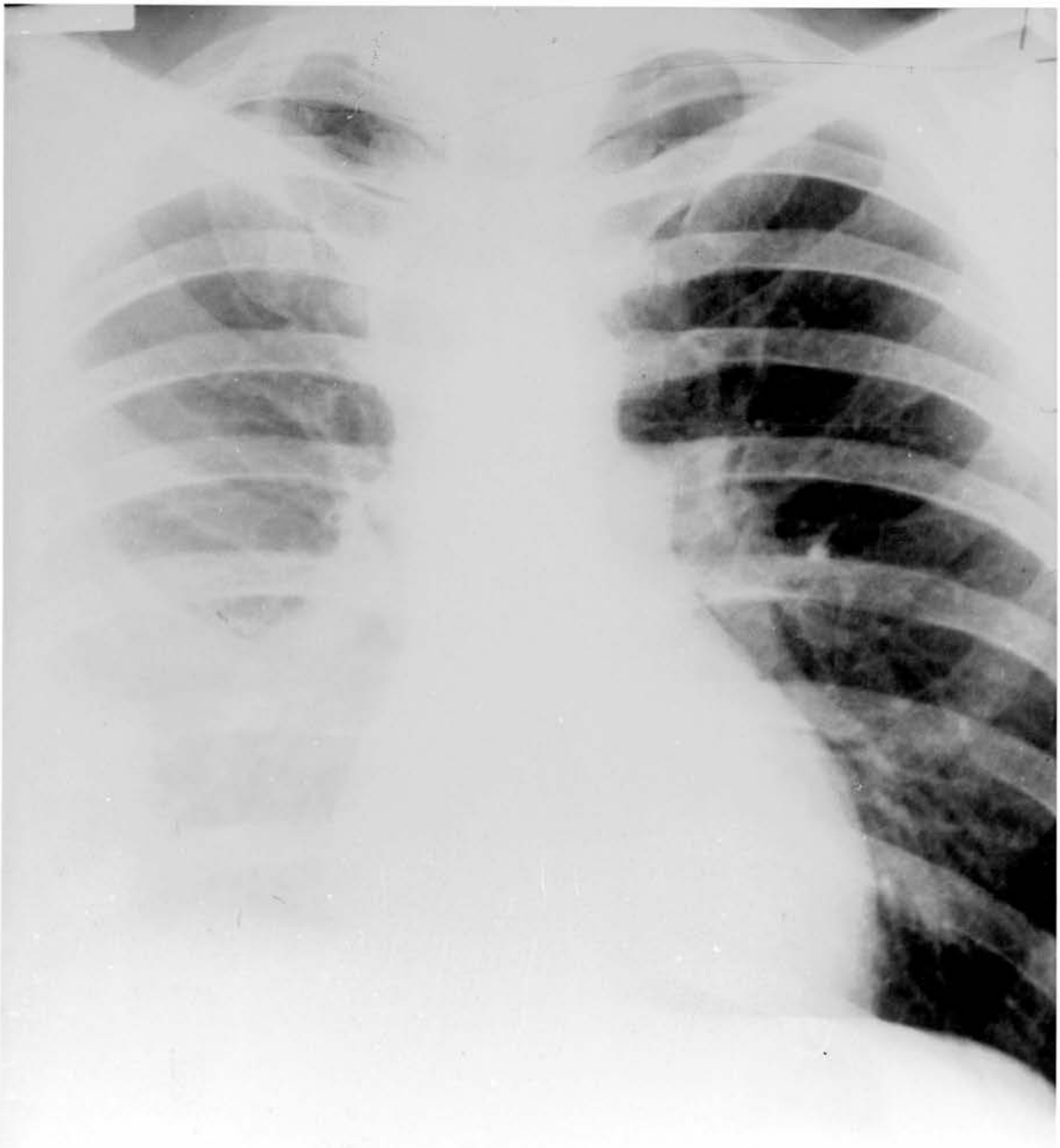


Figure 23b.

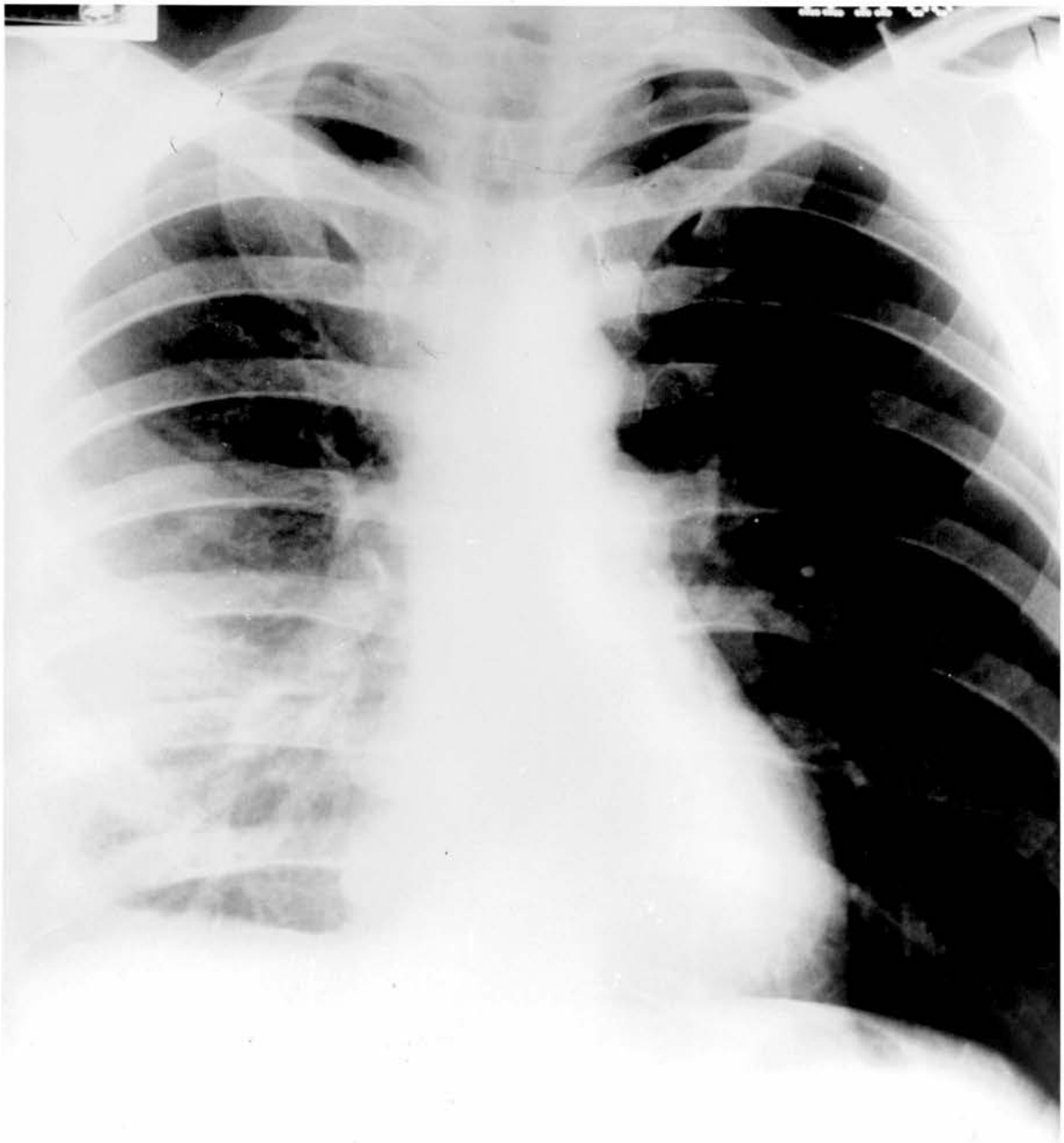


Figure 23e.

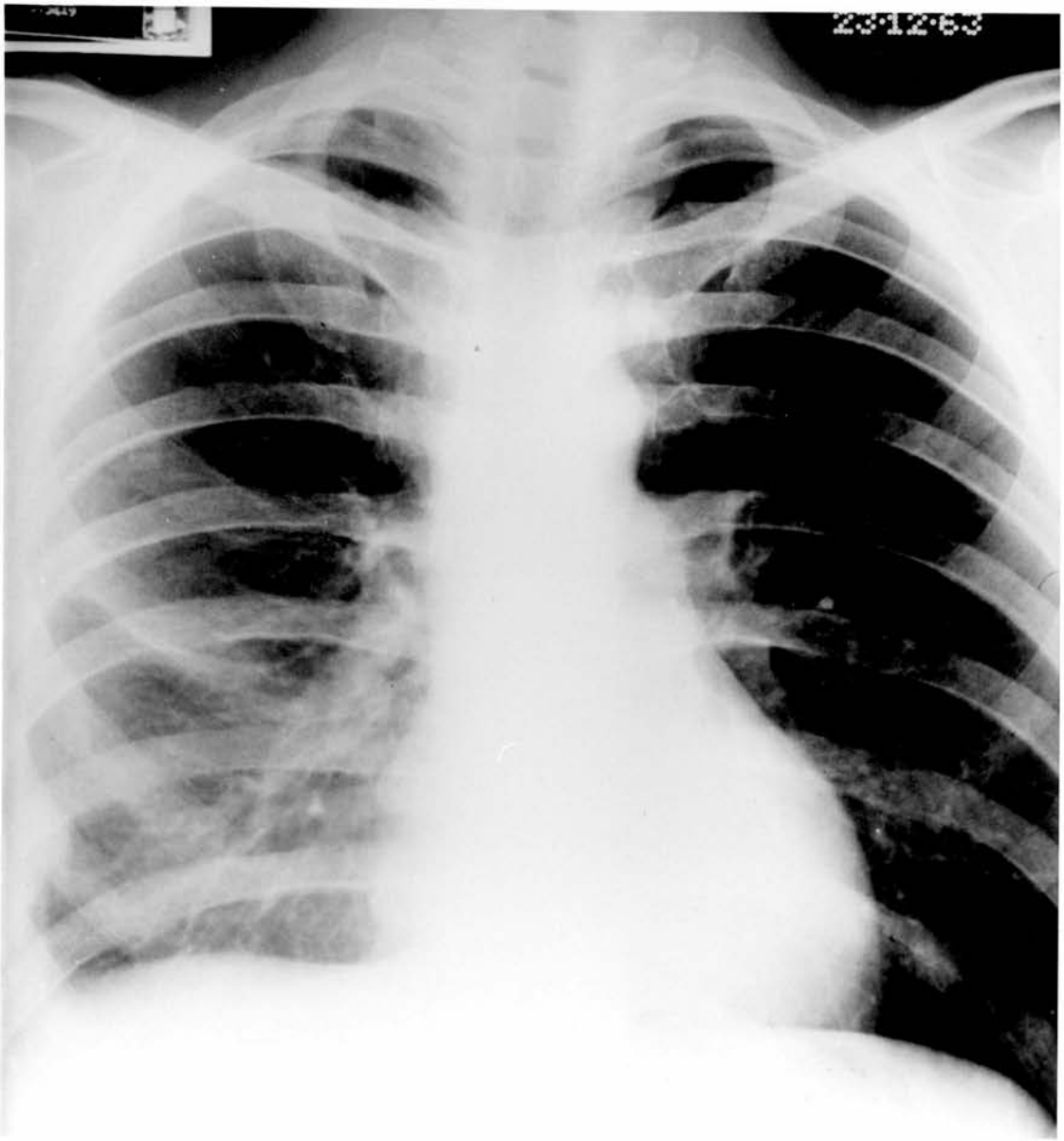
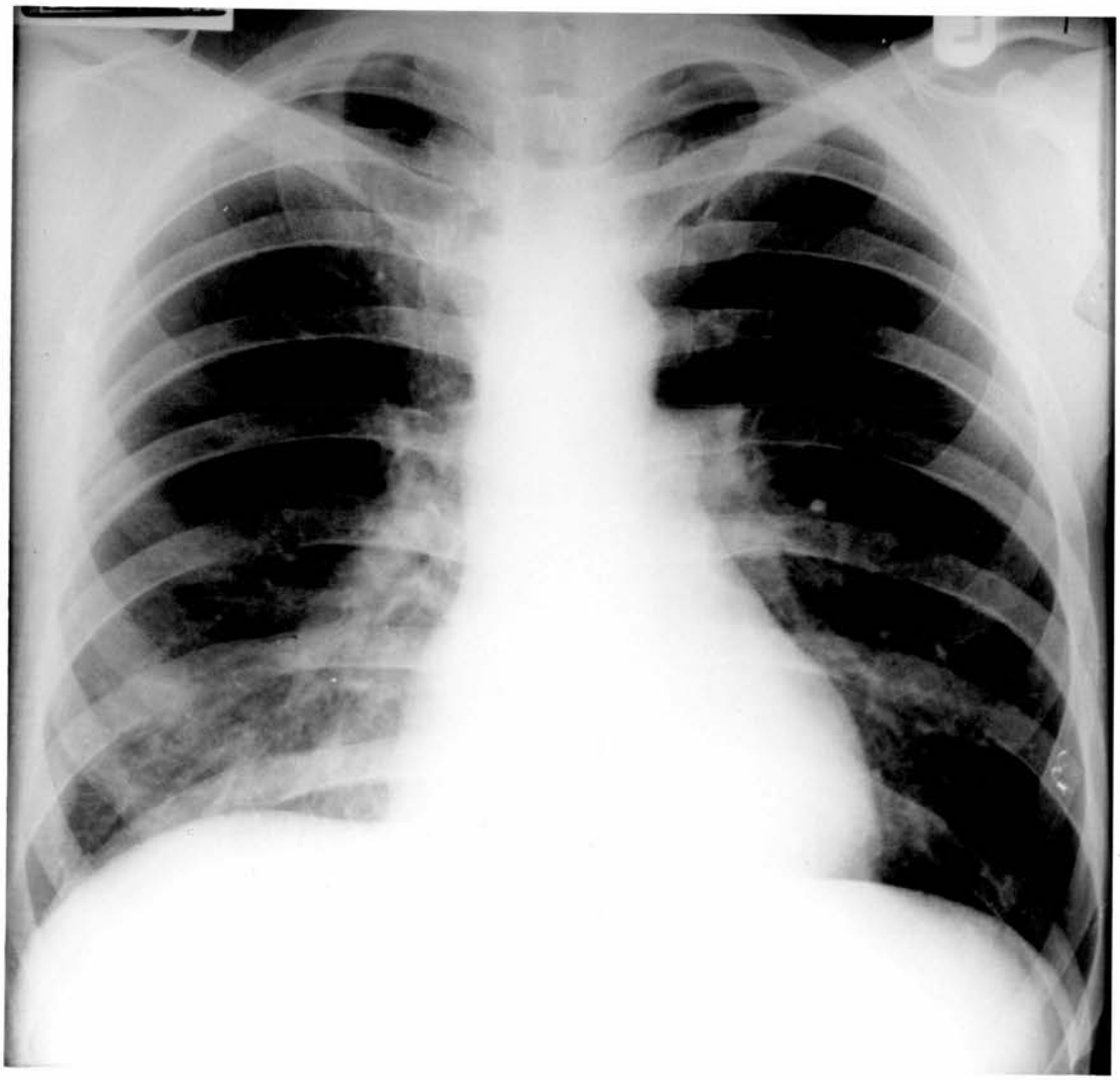

23·12·63

Figure 23d.



APPENDIX 4.

Case histories of two patients with interstitial lung disease

Case T.J.

Sex = male

Age = 62 years.

Occupation = Retired accountant.

Diagnosis = Rheumatoid arthritis. Interstitial lung disease.

This man had a mass miniature chest x-ray in 1958 which was normal. A similar film taken in 1963, was consistent with interstitial lung disease. He was seen elsewhere and no action was taken as he had no respiratory symptoms. In 1964 he developed pain and swelling in both knees and ankles followed by pain in the hands and wrists and marked morning stiffness. In October, 1964 effort dyspnoea and cough began. He was referred to Dr. Maxwell Telling at the General Infirmary at Leeds for further investigation and subsequently to Dr. V. Wright because of his arthritis.

Examination revealed that he was obviously easily dyspnoeic and had marked finger clubbing. There was swelling and tenderness of some of the metacarpo-phalangeal joints, proximal interphalangeal joints, both wrists, and the right ankle. Subcutaneous nodules were present at the right elbow. Crepitations were audible over both mid and lower zones. There were no other abnormal findings.

Investigations

Haemoglobin = 13.3 g. per 100 mls.

White cell count = 9,200 per c.mm. Normal differential.

B.S.R. = 73 mm./1hr.

S.C.A.T. positive 1:128.

Serum proteins = 6.8 g. per 100 mls. Albumin = 3.4 g., Globulin = 3.4 g.
Electrophoresis = Diffuse increase in alpha 1, alpha 2, beta and gamma globulins.
No L.E. cells seen in peripheral blood.
Chest x-ray (Figure 13) showed widespread mottling in both lung fields.
X-ray of hands showed doubtful early changes of rheumatoid arthritis.
Lung function tests: vital capacity = 2.98 litres, residual volume = 0.84 litres, F.E.V.$_1$ = 2.39 litres (80% of vital capacity). Carbon monoxide uptake = 14.5 ml/min/mm.Hg. (61% of predicted normal).
Lung biopsy (Figure 15a) showed diffuse interstitial fibrosis with obliteration and gross distortion of alveolar spaces.

Treatment and progress

Corticosteroid therapy was started in the form of Prednisolone 30 mgms. per day which was slowly reduced to 20 mgms. per day and finally 15 mgms. per day. He was re-admitted two months after treatment was started with a respiratory infection which responded to Penicillin. Serial tests of lung function showed an initial fall in carbon monoxide uptake and a subsequent slight rise but no change in vital capacity.

Case M.B.

Sex = female
Age = 64 years.
Occupation = housewife.
Diagnosis = Rheumatoid arthritis. Interstitial lung disease.
Onset of rheumatoid arthritis in 1958.

Corticosteroid therapy was started in 1959 and has been maintained ever since. Gold was administered from August, 1964 - April, 1965. Subcutaneous nodules were recorded in 1959. Her chest x-ray taken when reviewed in the series is shown in Figure 24. At this stage she admitted to a cough

for five years but had not noticed dyspnoea. Her activities had been restricted by arthritis and an exercise test revealed dyspnoea on moderate exertion.

On examination there was no cyanosis or finger clubbing. Crepitations were audible over both mid and lower zones anteriorly and posteriorly. Apart from arthritic changes there were no other abnormalities.

Investigations

Haemoglobin = 12.7 g. per 100 mls.

White cells = normal

B.S.R. = 80 mm./1hr.

S.C.A.T. negative.

Serum proteins = 6.1 g. per 100 mls. Albumin = 3.8 g., Globulin = 2.3 g.

Electrophoresis within normal limits.

No L.E. cells seen in peripheral blood.

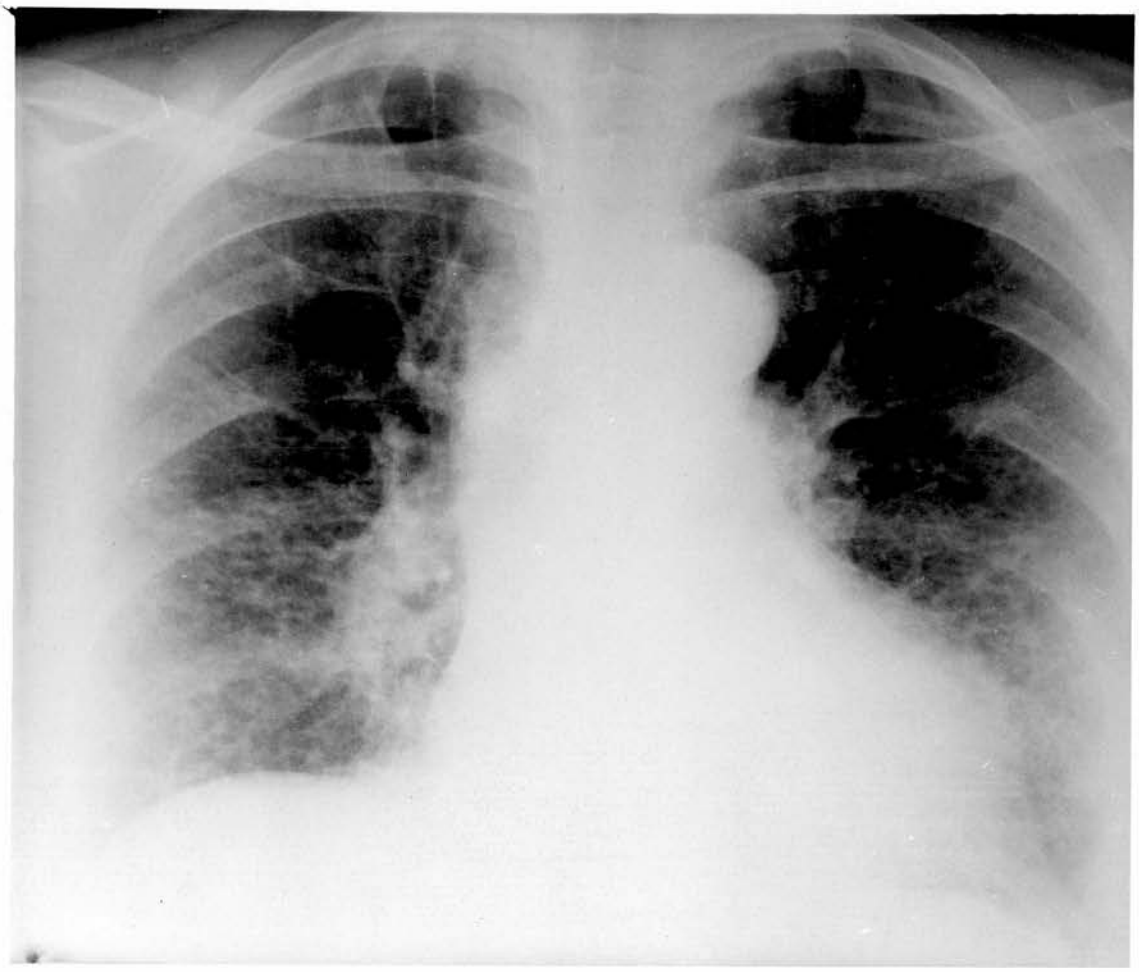
X-ray of hands and feet showed severe erosive changes. Scrutiny of a previous chest x-ray taken six years before review revealed suggestive changes of interstitial lung disease.

Lung function tests: vital capacity = 2.04 litres, residual volume = 0.94 litres, F.E.V.$_1$ = 1.85 litres (91% of vital capacity), carbon monoxide uptake = 10.1 ml/mm.Hg/min (42% of predicted normal).

Treatment and progress

A clinical diagnosis of interstitial lung disease was made. She subsequently received a course of hydroxy-chloroquine without sustained objective improvement. When last seen in February, 1966 her arthritis was more troublesome but she had no dyspnoea.

Figure 24.



APPENDIX 5.

Lung function tests in 18 patients with definite increase in lung markings

Initials	Sex	V.C.	T.L.C.	F.E.V.$_1$	R.V.	M.V.	PCO_2	Carbon monoxide uptake, ml/min/mm.Hg.
A.S.	F	2.14(80)	4.28(91)	1.28(60)	2.14(105)	8.5	39	25.4 (101)
W.S.	M	3.06(111)	4.76(83)	2.01(66)	1.7 (57)	17.4	40	16.7 (69)
G. de B.	M	3.96(84)	5.6 (77)	3.14(96)	1.75(68)	10.9	-	34.4 (127)
M.D.	M	1.68(52)	3.92(73)	.84(50)	2.24(103)	-	42	19.3 (85)
E.D.	F	2.92(89)	3.96(77)	2.07(71)	1.04(57)	6.6	40	15.6 (52)
M.C.	F	2.76(101)	6.32(139)	1.18(43)	3.56(195)	10.0	41	30.1 (128)
A.C.	M	2.87(122)	4.2(89)	1.68(64)	1.32(56)	7.3	40	15.4 (77)
C.S.	M	4.68(123)	5.9(86)	2.89(62)	1.23(40)	10.4	38	16.1 (64)
C.T.	M	2.43(83)	4.15(71)	1.44(59)	1.74(60)	8.2	44	11.7 (62)
E.W.	F	2.36(88)	3.65(79)	1.68(71)	1.29(67)	7.9	38	12.8 (57)
J.L.	M	2.72(81)	5.84(101)	1.56(57)	3.12(130)	7.1	42	28.7 (113)
L.R.	F	2.95(110)	3.51(79)	2.47(84)	.58(33)	9.3	33	15.6 (73)
S.T.	F	3.74(113)	5.44(105)	2.88(77)	1.7 (91)	12.5	-	25 (98)
H.D.	M	4.38(97)	5.82(82)	3.33(76)	1.44(56)	12.0	-	27.5 (101)
J.P.	M	3.2 (94)	5.25(84)	1.96(61)	2.05(72)	8.5	38	21.9 (86)
E.T.	F	2.76(99)	4.08(87)	2.3 (83)	1.33(71)	8.5	36	15.6 (59)
B.W.	F	2.62(112)	3.59(84)	1.97(75)	.97(50)	11.8	35	16.8 (83)
L.S.	F	2.04(83)	3.57(83)	1.69(83)	1.54(84)	8.2	43	15.4 (59)

V.C. = vital capacity in litres; T.L.C. = total lung capacity in litres; R.V. = residual volume in litres. Percentage of predicted normal in parenthesis.
F.E.V.$_1$ = forced expiratory volume in 1 second. Figures in parenthesis = percentage of V.C.
M.V. = minute volume in litres.
PCO_2 = arterial carbon dioxide tension.

APPENDIX 6.

Lung function tests in 15 patients with a doubtful increase in lung markings

Initials	Sex	V.C.	T.L.C.	R.V.	F.E.V.,	M.V.	PCO_2	Carbon monoxide uptake in ml/min/mm.Hg.
A.T.	M	3.72(94)	5.37(87)	1.66(75)	2.92(78)	10.2	43	19.2 (75)
J.H.	M	4.5 (106)	6.56(91)	2.06(69)	3.21(71)	12.0	40	23.8 (89)
G.C.	M	4.5 (103)	5.86(99)	1.38(86)	3.34(74)	11.2	42	26.3 (90)
J.D.	M	3.68(80)	6.31(86)	2.64(95)	1.9 (52)	11.0	38	17.4 (57)
A.G.	F	2.72(126)	3.57(84)	1.18(59)	1.94(71)	4.7	37	17.2 (74)
N.J.	F	2.71(101)	4.43(97)	1.72(91)	1.86(69)	7.0	40	24.9 (101)
H.U.	M	4.04(105)	7.05(110)	3.01(118)	3.15(78)	17.2	38	22.8 (94)
N.W.	F	3.8 (128)	5.55(114)	1.75(93)	3.0 (79)	14.5	36	21.6 (86)
F.S.	M	3.48(81)	4.78(70)	1.3 (51)	2.82(81)	8.2	39	19.3 (65)
E.B.	M	3.64(99)	6.37(95)	2.64(86)	2.03(56)	12.3	-	31.9 (132)
R.H.	M	3.2 (81)	5.35(79)	2.16(76)	2.36(74)	18.5	38	36.8 (136)
J.H.	M	5.04(115)	7.25(106)	2.23(91)	2.77(55)	13.8	41	34 (113)
J.P.	M	4.21(102)	5.53(77)	1.32(43)	3.39)81)	11.5	36	24.4 (90)
E.B.	F	2.46(101)	3.49(81)	1.04(55)	1.86(76)	6.5	36	16.5 (66)
M.B.	F	3.58(116)	5.22(108)	1.64(94)	3.0 (84)	7.0	34	20.2 (86)

V.C. = vital capacity in litres; T.L.C. = total lung capacity in litres; R.V. = residual volume in litres. Percentage of predicted normal in parenthesis.
F.E.V., = forced expiratory volume in 1 second. Figures in parenthesis = percentage of V.C.
M.V. = minute volume in litres.
PCO_2 = arterial carbon dioxide tension.

APPENDIX 7.

Lung function tests in miscellaneous group

Initials	Sex	V.C.	T.L.C.	R.V.	F.E.V.$_1$	M.V.	PCO_2	Carbon monoxide uptake in ml/min/mm.Hg.
A.C.	M	4.66(99)	5.66(93)	1.0 (73)	3.77(81)	9.5	-	25.7 (95)
B.C.	F	3.4 (117)	4.55(93)	1.6 (80)	2.5 (74)	9.8	-	31 (121)
J.F.	M	4.4 (103)	5.36(76)	.96(35)	2.57(60)	12.9	39	22.6 (79)
G.W.	M	2.63(76)	4.16(64)	1.53(51)	1.35(51)	10.3	33	22 (95)
J.W.	M	2.42(62)	5.6 (83)	3.18(111)	.92(38)	7.6	46	23.5 (93)
G.W.	M	3.3 (82)	6.21(100)	2.91(135)	2.48(75)	6.9	41	24.5 (91)

V.C. = vital capacity in litres; T.L.C. = total lung capacity in litres; R.V. = residual volume in litres. Percentage of predicted normal in parenthesis.
F.E.V.$_1$ = forced expiratory volume in 1 second. Figures in parenthesis = percentage of V.C.
M.V. = minute volume in litres.
PCO_2 = arterial carbon dioxide tension.

APPENDIX 8.

Case R.S.

Sex = male

Occupation = Motor driver

Diagnosis = Rheumatoid arthritis. Empyema. Intra-pulmonary rheumatoid nodules.

Onset of rheumatoid arthritis in 1956.

Admitted to the General Infirmary at Leeds under the care of the late Mr. Digby Chamberlain in 1957 for removal of an empyema of the gall bladder. He had an aspiration pneumonia in the right lower lobe during this admission but a subsequent chest x-ray and diaphragmatic screening were normal. Corticosteroid therapy was started later that year. In May, 1958 he complained of left sided pleuritic pain for a short period. In 1959 he was referred for a barium meal because of dyspepsia when a left pleural effusion was detected. He was not investigated at that time. Following further attendance at the out-patient clinic in 1962 he was admitted for further investigation.

On examination there were advanced arthritic changes in the hands, wrists, elbows, shoulders, knees, ankles and feet. Subcutaneous nodules were present. There were signs of a left pleural effusion.

Investigations

Haemoglobin = 14.1 g. per 100 mls.

White cell count = 8,900/c.mm. Polymorphs 89%.

B.S.R. = 31 mm./1hr.

S.C.A.T. positive 1:256.

Serum proteins = 7.0 g. per 100 mls. Albumin = 3.8, Globulin = 3.2.

Electrophoresis = an increase in alpha 2 and beta globulins.

No L.E. cells seen in peripheral blood.

X-ray of hands and feet showed severe erosive changes. Pleural aspiration revealed a purulent exudate. No secondary organisms or tubercle bacilli were isolated. Pleural biopsy showed chronic inflammatory changes only.

Treatment and progress

He was referred to Mr. D. A. Watson, thoracic surgeon, who felt that in view of the advanced arthritic disability he should be treated with aspiration and antibiotics.

He was followed up at the clinic remaining were disabled by arthritis and developing symptoms from erosive changes in the cervical spine with subluxation. He was eventually admitted to the Royal Bath Hospital, Harrogate and died there in October, 1964.

Autopsy was performed by Dr. M. Hamilton. There was a loculated empyema in the left pleural space and bilateral pleural adhesions. A nodule 3.0 cms. in diameter was present in the right lower lobe, the centre of which was necrotic. Sections of the pleura in the region of the empyema showed a deposit of acellular cosinophilic material on the pleural surface. At the margin of this material there was a zone of pyknotic cells overlying a fibrous zone containing chronic inflammatory cells, including plasma cells. In some areas there was a suggestion of palisading of fibroblasts.

Sections from the intra-pulmonary lesion are shown in Figures 25a and b. Figure 25a shows epithelioid cells with a conspicuous tendency to palisade associated with a central defect and Figure 25b shows a large area of necrobiosis with underlying fields of epithelioid cells. Specially stained sections revealed no acid fast organisms or fungi. Other findings were a fibrinous pericarditis and focal necrosis and atrophy of skeletal muscle. He had died from uraemia due to renal papillary necrosis.

The intra-pulmonary lesion was considered to be a rheumatoid nodule and the pathologist thought it likely that the left pleural lesion was primarily rheumatoid in origin becoming secondarily infected.

Figure 26a shows the chest radiograph some months after cholecystectomy. Figure 26b is of a film taken in 1959 which showed a moderate left pleural effusion and a pleural reaction on the right. Figure 26c is of the film taken when he was investigated in 1962 when a rounded opacity had appeared at the right base. Figure 26d was review film in 1964.

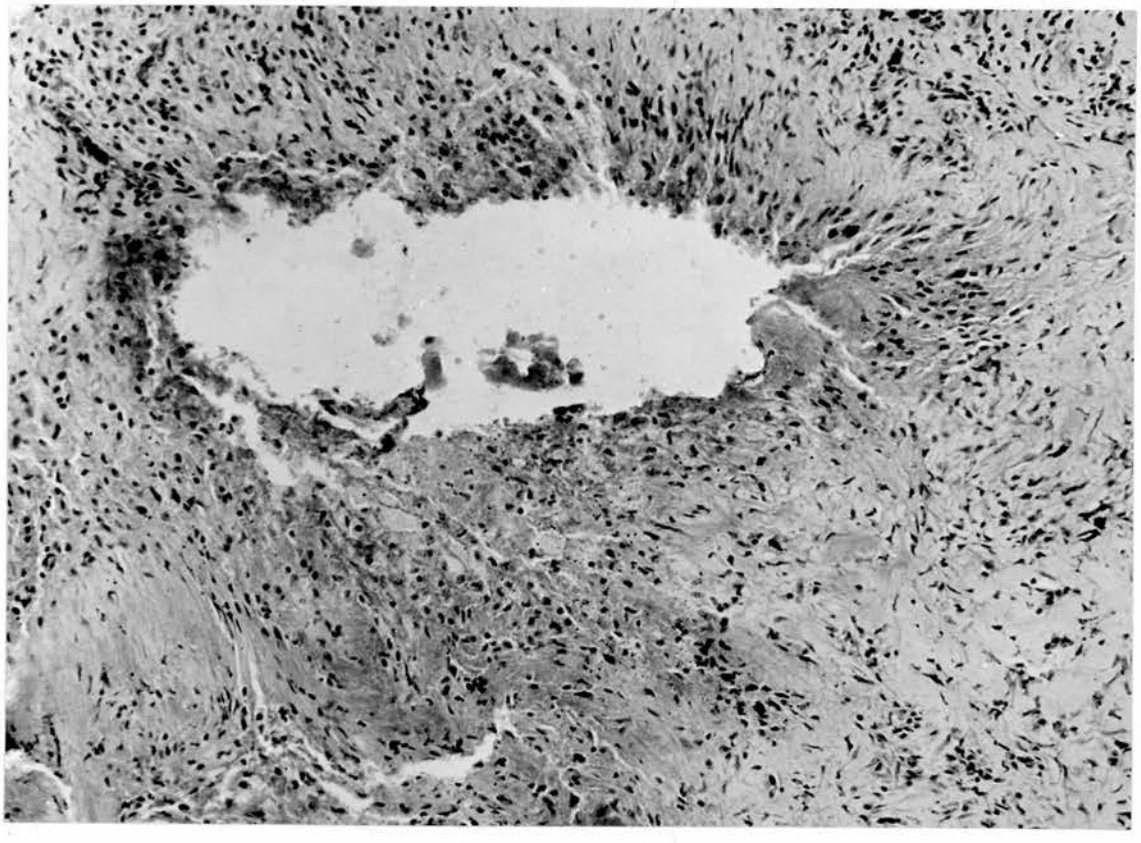


Figure 25a.

Autopsy section from lesion in right lower lobe. H. and E. × 170.

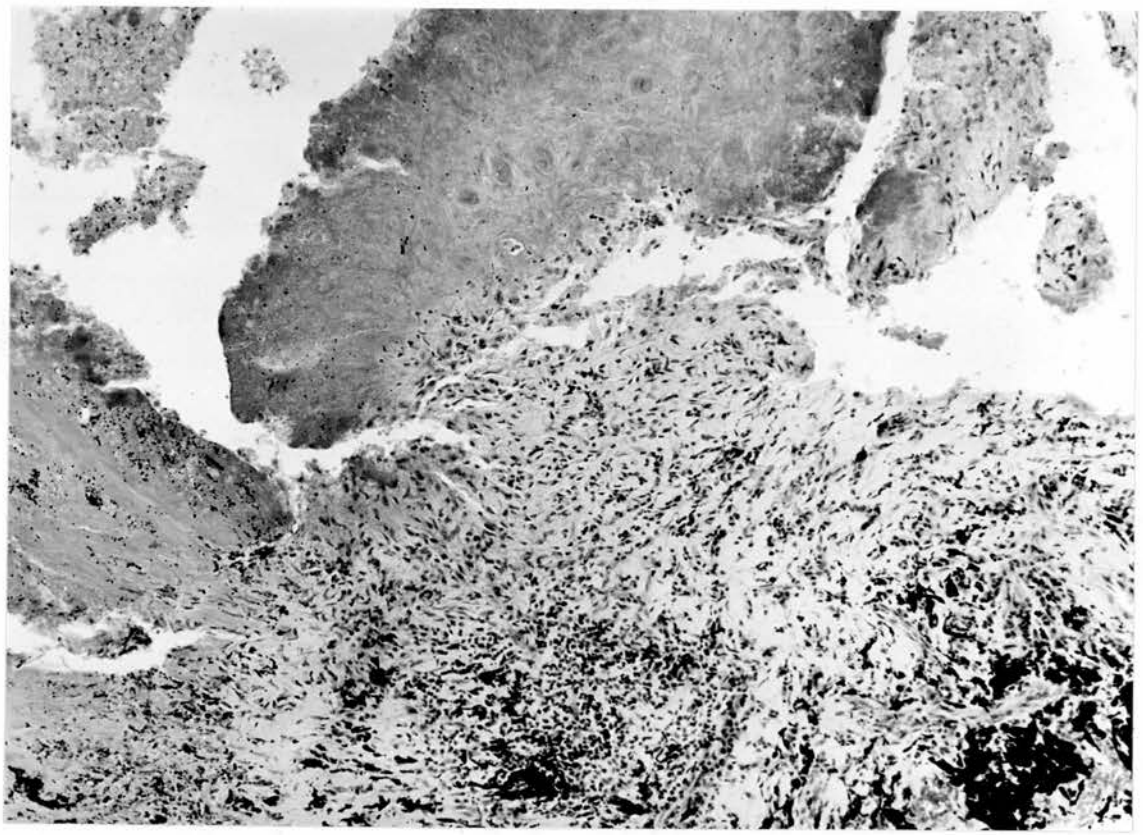


Figure 25b.

Autopsy section from lesion in right lower lobe. H. and E. x 170.

Figure 26a.

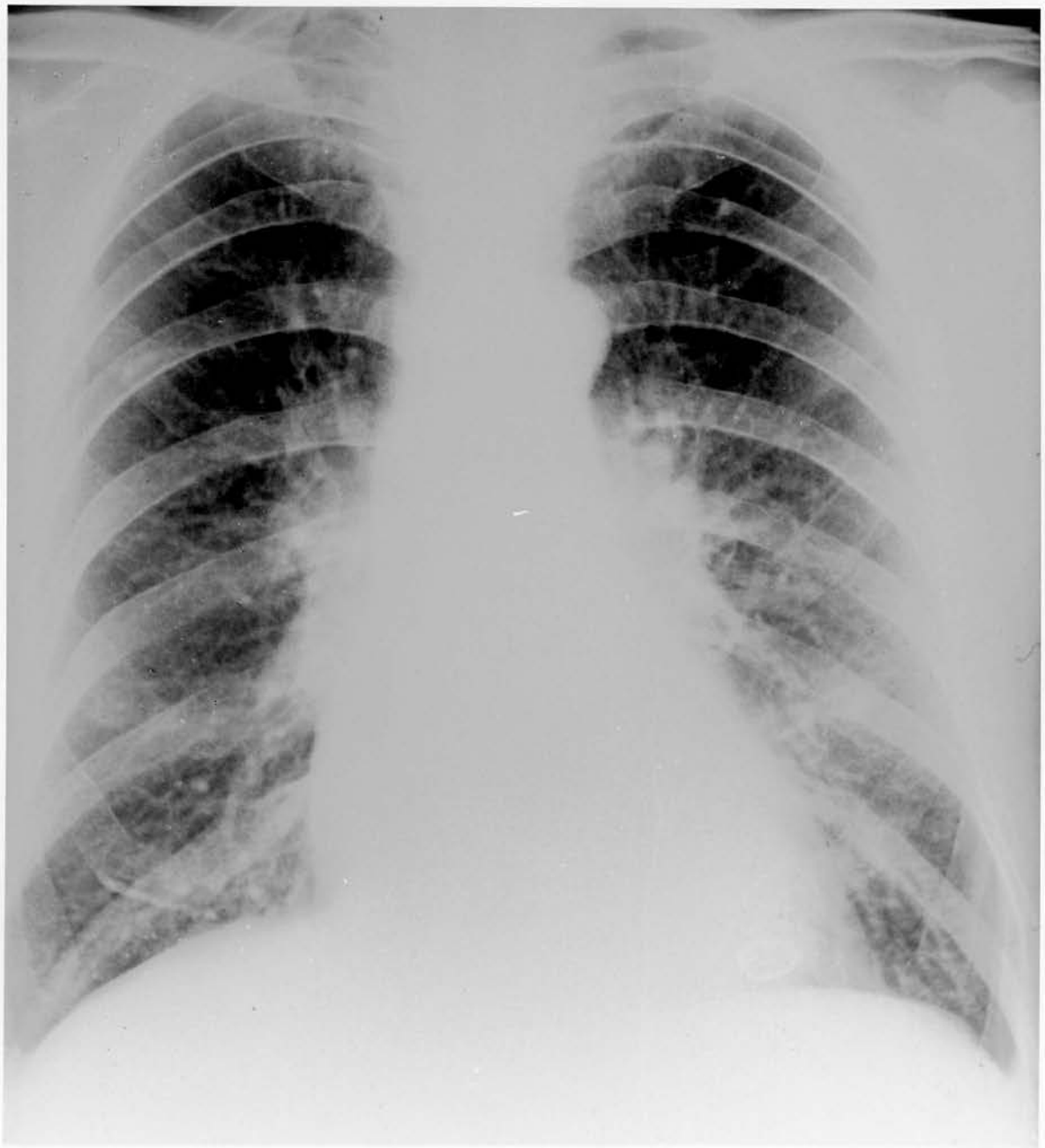


Figure 26b.

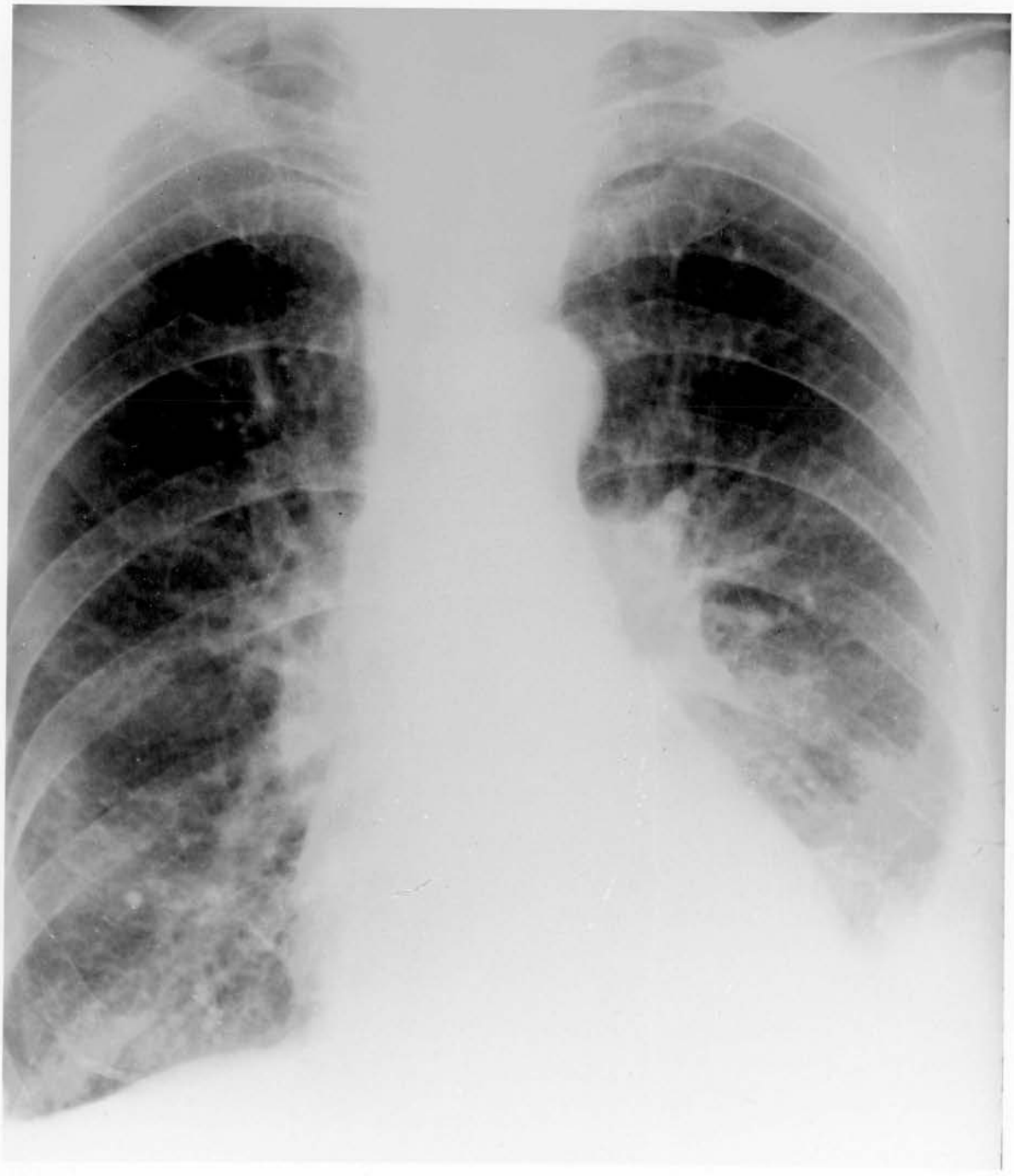


Figure 26e.

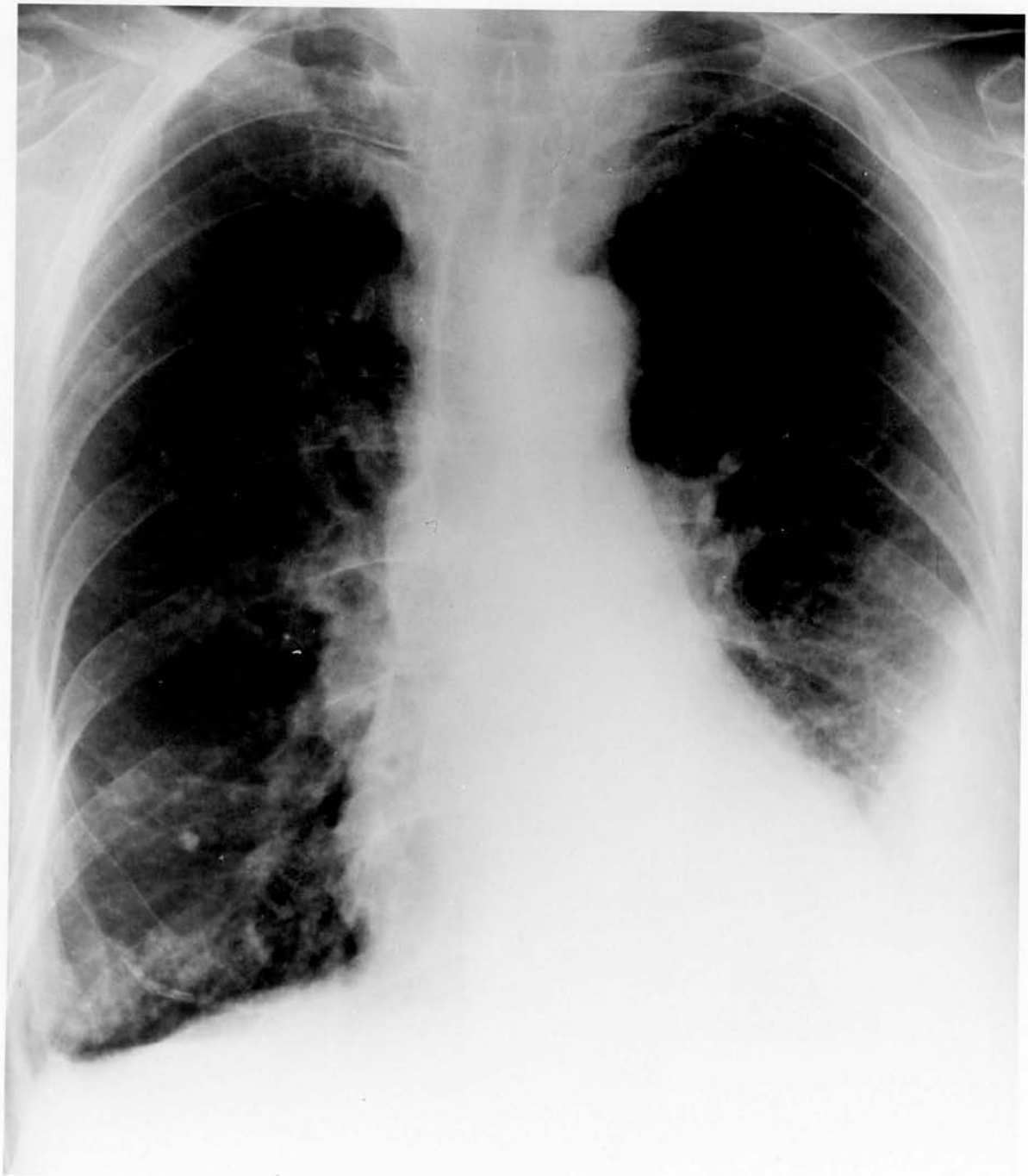
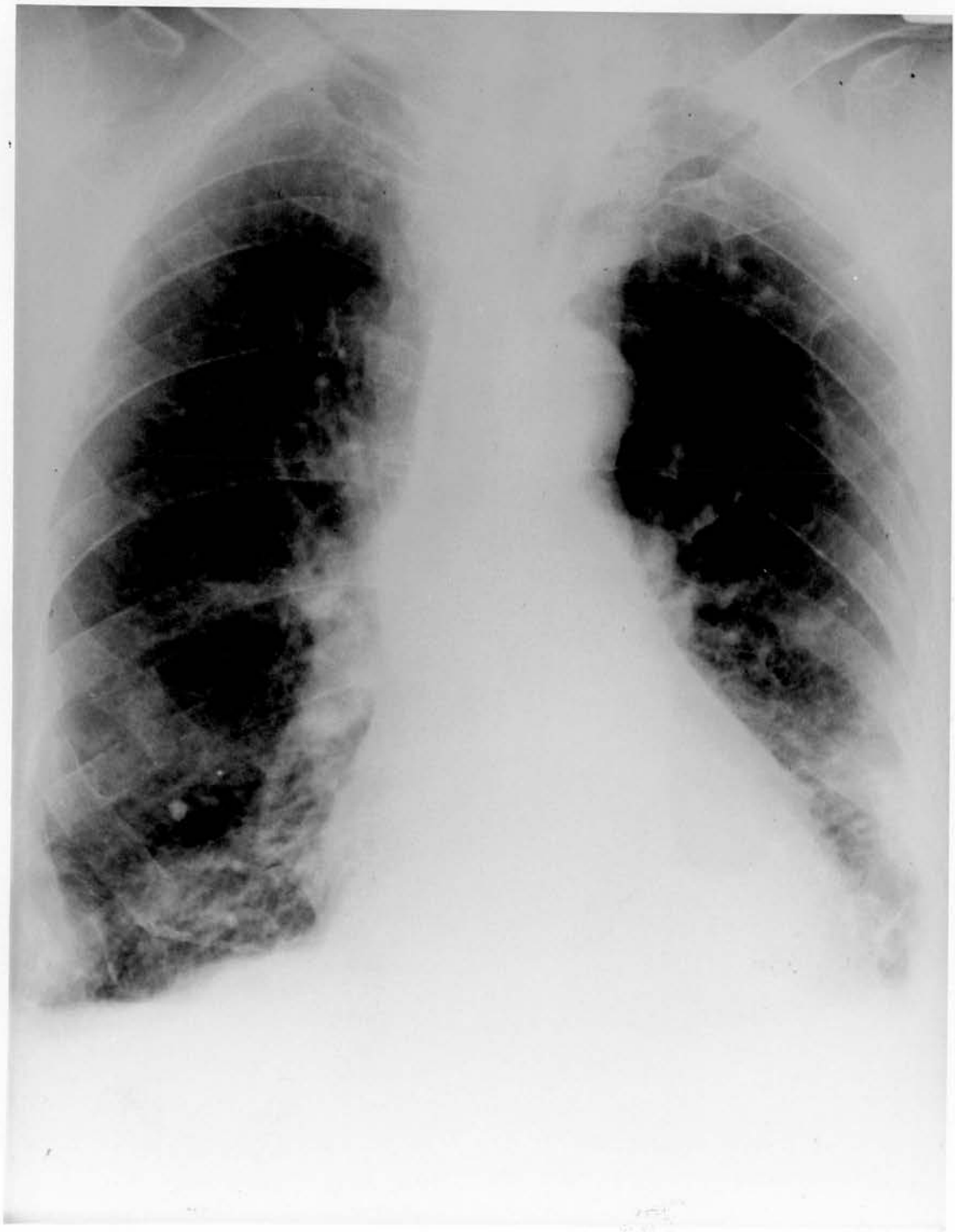


Figure 26d.



APPENDIX 9.

Case H.C.

Sex = male

Diagnosis = Rheumatoid arthritis. Intra-pulmonary rheumatoid nodules.

At the age of 29 this man, a taxi driver who had previously been a motor engineer, developed pain and swelling in the hands and feet as well as pain in both shoulders. Shortly afterwards he had a chest x-ray with a view to emigration to Australia and because this was abnormal he was referred to Dr. Maxwell Telling at the General Infirmary at Leeds for further investigation.

Clinical examination revealed swelling of the small joints of both hands but no other relevant finding. The chest x-ray, Figure 27a, showed a rounded opacity just above the left costo-phrenic angle which on tomography contained a small central cavity. There were further excavated nodular shadows in the right mid zone. The haemoglobin was normal; B.S.R. = 27 mm./1hr. Twelve specimens of sputum and 3 of gastric washings were negative for tubercle bacilli. No fungi were isolated from the sputum. L.E. cells were not present in the peripheral blood. X-rays of the hands and feet showed probable early rheumatoid changes.

Until he finally did emigrate to Australia in 1963 he remained under periodic supervision as an out-patient. In 1961 he developed a productive cough and had haemoptysis but this was only temporary. Until 1963 the only treatment he required for his arthritis was analgesics but at this stage he received a course of gold with benefit. After his initial admission his sedimentation rate fell to normal and remained so apart from one reading in 1958 of 27 mm./1hr. Specimens of sputum were examined for tubercle bacilli at intervals but all of these were negative and further examination for L.E. cells in the peripheral blood was also negative. The S.C.A.T. in 1961 was positive in a titre of 1:64.

At the same time x-raysof his hands were repeated which showed well marked erosive changes in some of the metacarpo-phalangeal joints and proximal interphalangeal joints. Serial chest x-rays were of interest. A film in 1956 showed that the right upper cavitated lesion was much less obvious. In 1957 there was some ill defined opacity in the right mid zone and the lesion at the left base was much less obvious. In 1958 there was little change (Figure 27b). In 1959 there was a larger dense shadow in the right mid-zone and the appearances of a cavitated lesion below this. In 1960 the mid-zone lesion also appeared to have cavitated (Figure 27c). There was little change in the film of 1961 and the final film available, taken in 1962, still showed the cavitated lesion in the right mid-zone but the other abnormalities were much less conspicuous (Figure 27d).

Despite the absence of pathological confirmation the diagnosis in this case was considered to be rheumatoid arthritis with intra-pulmonary nodules.

Figure 27a.

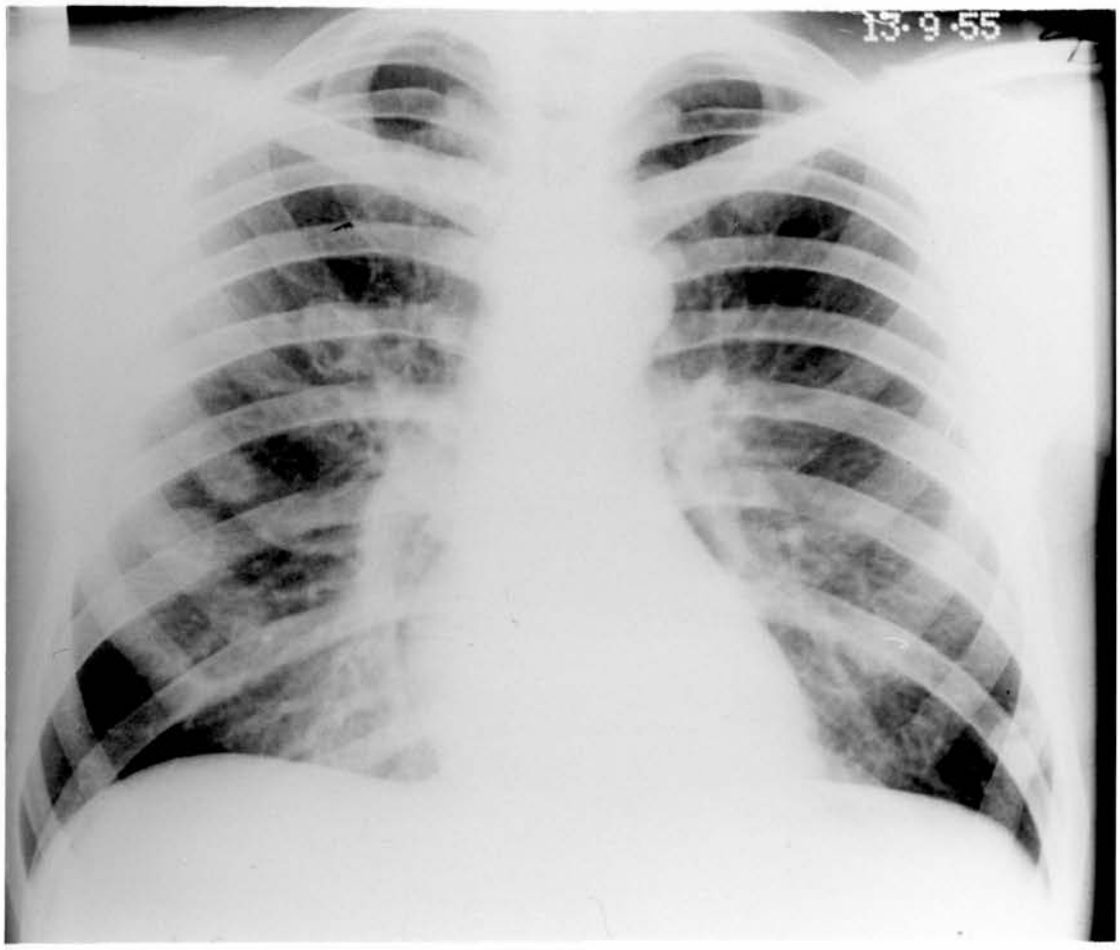

13.9.55

Figure 27b.

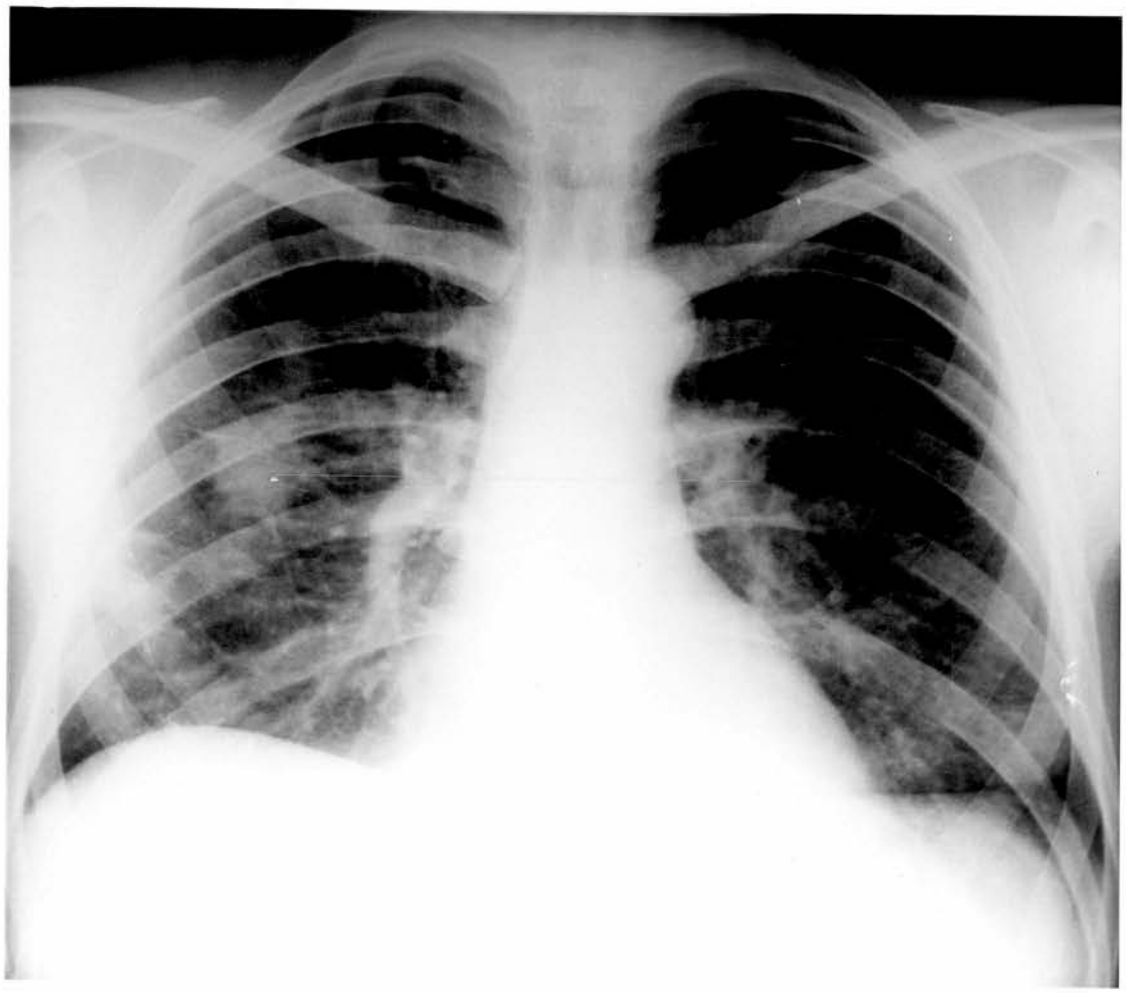


Figure 27c.

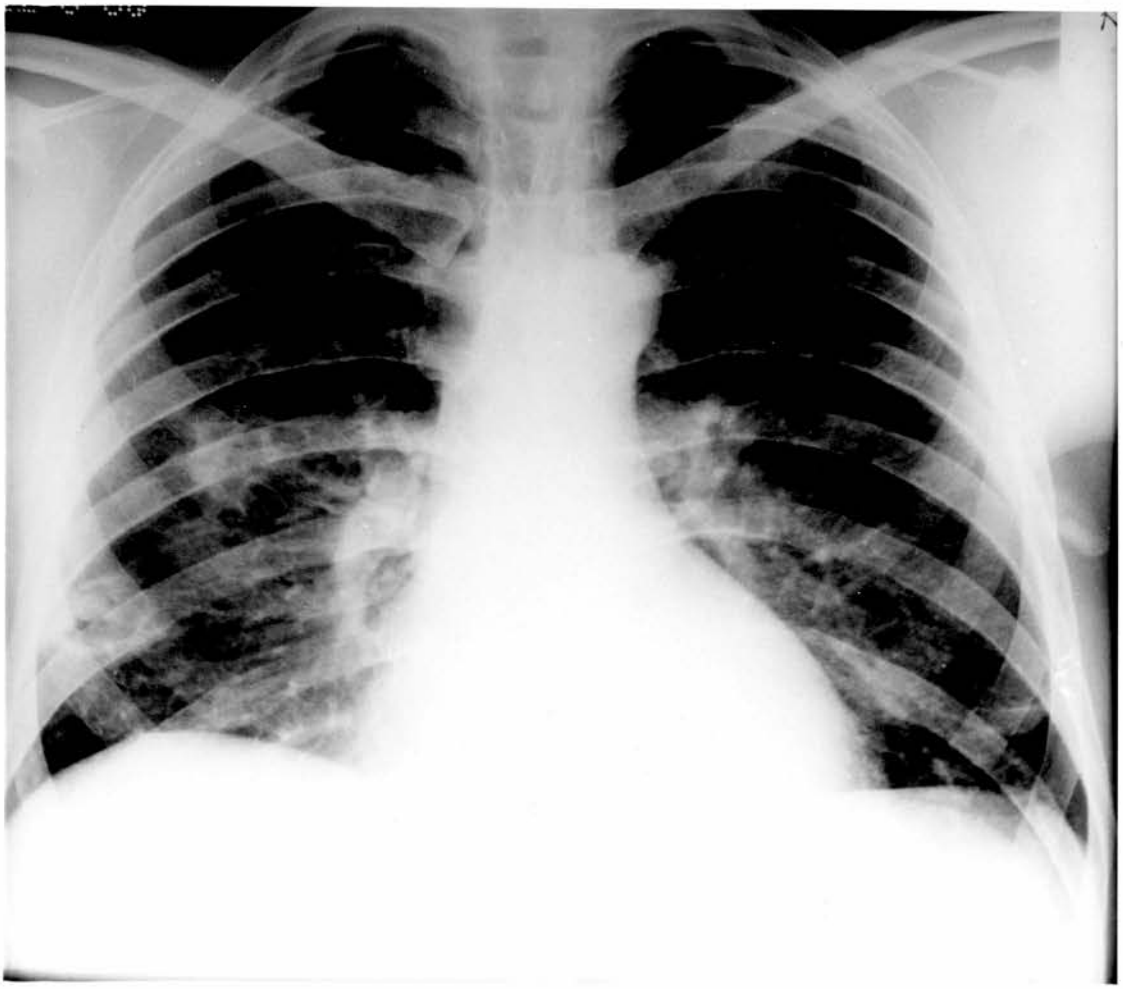
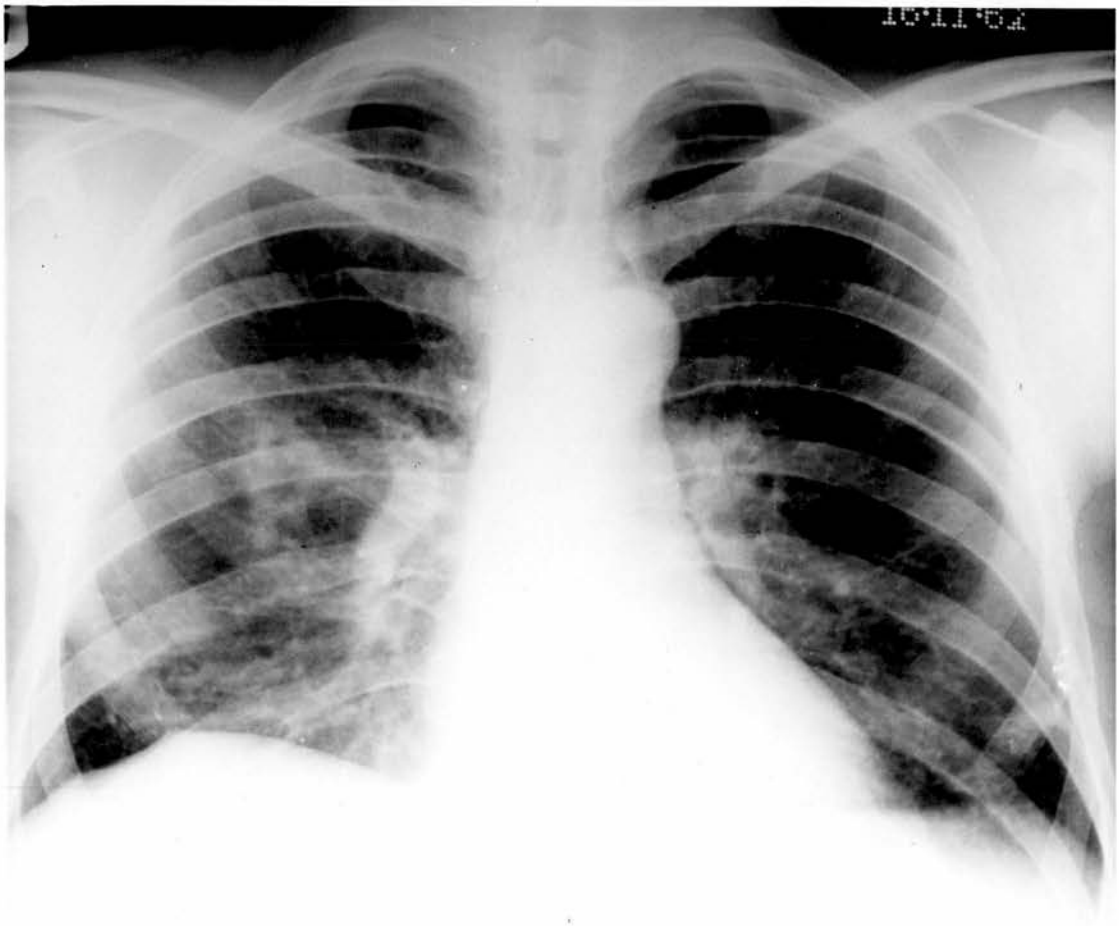


Figure 27d.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