

A BROADER CONCEPT OF CAPLAN'S SYNDROME RELATED TO RHEUMATOID FACTORS

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The rheumatoid pneumoconiosis syndrome was originally described as a characteristic chest radiographic appearance in coal-workers associated with clinical rheumatoid arthritis (Caplan, 1953). This association was later confirmed as real and not fortuitous by Miall, Caplan, Cochrane, Kilpatrick, and Oldham (1953) using an unselected population. The original communication defined the radiographic picture as one showing multiple, well-defined round opacities 0.5 to 5 cm. in diameter distributed throughout the lung field. We will call this the classical appearance. It was noted that cavitation and calcification of the opacities was frequent. There was a tendency for the opacities to appear suddenly before, coincident with, or after the onset of arthritis. Reference was also made to the fact that only a few round opacities may be present, and in many instances the lesions become confluent and may be indistinguishable radiographically from progressive massive fibrosis. It was suggested that more cases would be recognized if it were realized that there is often a mixed radiographic picture of round opacities and opacities indistinguishable from progressive massive fibrosis and tuberculosis.

Subsequent observations on more than 550 cases of the syndrome have confirmed in the main the original radiographic description and in particular emphasized the high incidence of cavitation as a characteristic feature. Additional experience among coal-workers has suggested an association of clinical rheumatoid arthritis with discrete nodular opacities 0.3 to 1 cm. in diameter, i.e., somewhat smaller than was originally found, and classifiable under the International Classification of Radiographs of Pneumoconiosis (I.L.O., 1959) as categories 1, 2, or 3 nodular simple pneumoconiosis. Furthermore, even in the absence of clinical arthritis, the sensitized sheep cell agglutination test (S.S.C.A.T.) in these cases, and in others with a mixed nodular and progressive massive fibrosis picture, was found to be positive

in a fairly high proportion of cases. Such cases were therefore considered likely to be associated with rheumatoid disease. It was decided to investigate the presence of clinical rheumatoid arthritis and of positive rheumatoid factor tests in coal-workers with a variety of pneumoconiotic appearances to determine whether there was a significantly higher incidence of arthritis and/or positive tests associated with distinguishable radiographic appearances and, in particular, whether there was an association between positive tests and these appearances in the absence of arthritis.

METHODS

SELECTION OF SUBJECTS.—The subjects were 269 coal-workers attending the Cardiff Pneumoconiosis Medical Panel and the Pneumoconiosis Research Unit of the Medical Research Council. Of 193 miners and ex-miners from the Pneumoconiosis Medical Panel, 168 were selected on the basis of chest radiographic appearances characteristic or suggestive of the rheumatoid pneumoconiosis syndrome, whether or not clinical rheumatoid arthritis was present. Twenty-five coal-workers with no pneumoconiosis, simple pneumoconiosis, or progressive massive fibrosis were included as controls. Seventy-six miners attending 14 outpatient clinic sessions at the Pneumoconiosis Research Unit of the Medical Research Council were included without selection as a further control group. Details of the mean age and dust exposure at the coal face in the various radiographic categories of pneumoconiosis are shown in Table I.

CLASSIFICATION OF RHEUMATOID ARTHRITIS.—The first six criteria of a committee of the American Rheumatism Association (1959) were used for the classification of rheumatoid arthritis into 'definite,' 'probable,' and 'possible.' The results of the rheumatoid factor tests were not taken into account in the classification as this would have biased our inquiry.

CLASSIFICATION OF CHEST RADIOGRAPHS.—The chest radiographs of all 269 subjects were classified by one observer (A.C.) without knowledge of the clinical history. When possible, the international classifica-

TABLE I
AGE AND DUST EXPOSURE IN THE VARIOUS RADIOLOGICAL CATEGORIES OF PNEUMOCONIOSIS

	Rheumatoid Syndrome Not Suspected			Rheumatoid Syndrome Probable or Suspected		
	No Pneumoconiosis	Simple Excluding Nodular	Progressive Massive Fibrosis	Classical	Nodular	Mixed Nodular and Irregular Opacities
Number	11	28	62	56	74	38
Mean age (yr.)	56.7	54.2	52.0	52.9	53.6	50.1
Mean years worked at coal face	25.4	19.5	21.7	18.6	18.7	17.1

tion (I.L.O., 1959) was followed, the exceptions which would not fit into the classification being some of the suspected and all the classical cases of the rheumatoid syndrome. The chest radiographs were divided into two main groups, those in which the rheumatoid syndrome was not suspected, and those in which it was probable or suspected.

The rheumatoid syndrome was not suspected when there was (a) no pneumoconiosis; (b) simple pneumoconiosis excluding the nodular type; or (c) progressive massive fibrosis.

The rheumatoid syndrome was probable or suspected when (a) the classical rheumatoid appearance of multiple well-defined round opacities larger than 1 cm. in diameter with or without cavitation (Fig. 1) was seen; or (b) nodular discrete 0.3 to 1.0 cm. round opacities varying from a few confined to the upper zones (Fig. 2a) to 'snowstorm' appearances (Fig. 2b); or (c) mixed nodular and irregular opacities: a few rounded and/or irregular opacities on a background of no pneumoconiosis or category 1 simple pneumoconiosis, particularly when there was or had been evidence of cavitation (Fig. 3).

RHEUMATOID FACTOR TESTS.—Sheep cell agglutination and latex fixation tests were used in this investigation because there is considerable evidence that the factor which agglutinates sensitized cells is not identical with the factor which agglutinates inert particles coated with gamma globulin (Heller, Jacobson, Kolodny, and Kammerer, 1954; Lospalluto and Ziff, 1959).

The sensitized sheep cell agglutination test (S.S.C.A.T.) of Greenbury (1957) was performed on serum specimens from all 269 subjects. Perspex agglutination trays were used. Sheep serum diluent was not used. All sera were absorbed for two hours

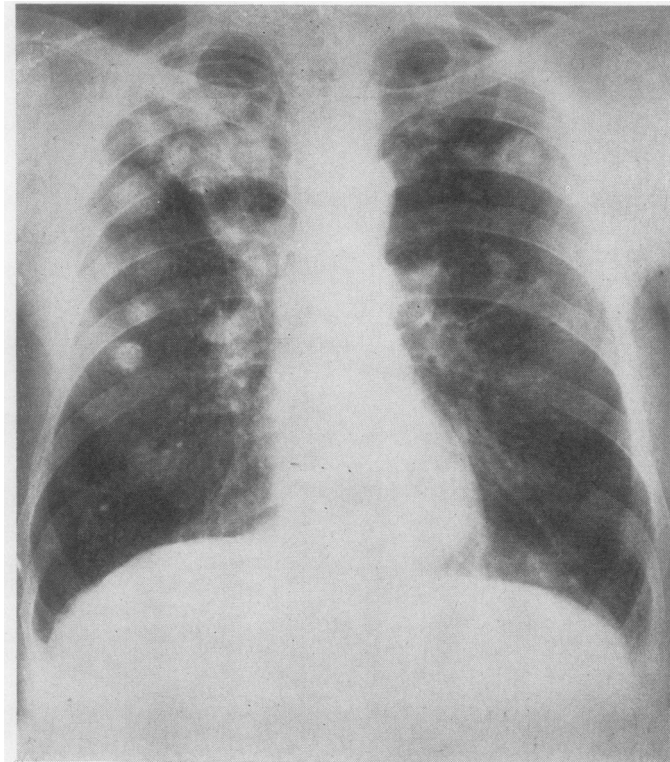


FIG. 1. Classical rheumatoid pneumoconiosis.

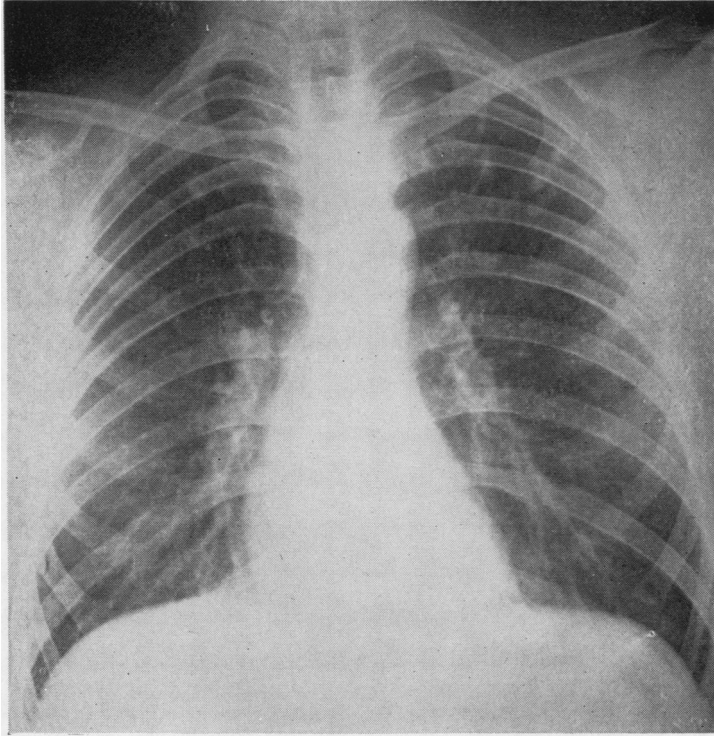


FIG. 2A. *Rheumatoid pneumoconiosis showing very sparse small discrete nodules.*

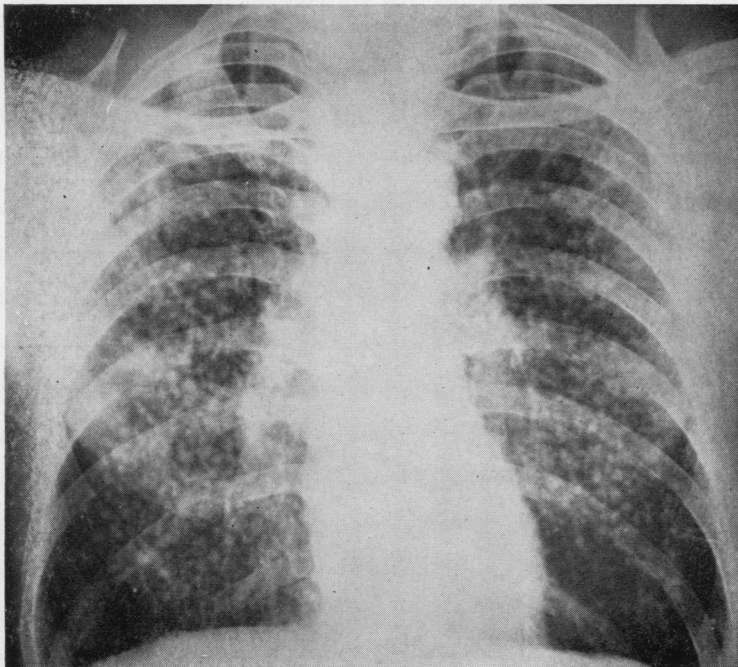


FIG. 2B. *Rheumatoid pneumoconiosis showing numerous small discrete nodules.*

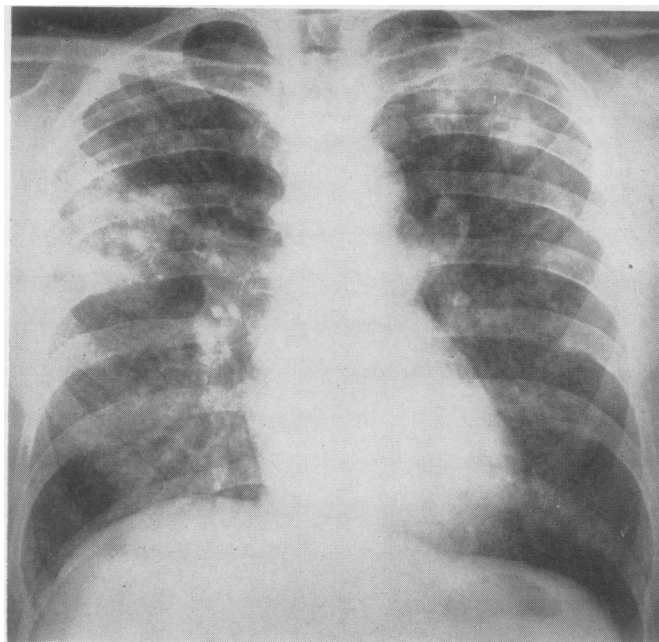


FIG. 3. *Rheumatoid pneumoconiosis showing a mixture of small nodules and irregular opacities.*

at 37° C. with washed unsensitized sheep cells. Occasionally absorption was incomplete. A differential titre (Rose, Ragan, Pearce, and Lipman, 1948) was then calculated. Agglutination at an initial serum dilution of 1 in 32 or greater was considered positive.

A latex fixation test using bovine gamma globulin as the reactant (Payne, 1961) was performed on 241 sera. Agglutination at an initial serum dilution of 1 in 80 or greater was considered positive.

A slide latex fixation test using human gamma globulin as the reactant, the RA test (Hyland), was performed on 232 of these specimens at a single initial serum dilution of 1 in 20.

The readings of the S.S.C.A.T. were made by J. L. W. and of the two latex tests by R. B. P. without knowledge of the clinical or radiographic observations.

RESULTS

PREVALENCE OF RHEUMATOID ARTHRITIS IN CHEST RADIOGRAPH GROUPS.—The prevalence of clinical manifestations of rheumatoid disease in each chest radiograph group is shown in Table II. About two-thirds of the subjects with a classical radiographic appearance and about one-third of those with 'nodular' and 'mixed' pictures had definite rheumatoid arthritis. The prevalence of arthritis was significantly greater in the classical

group than in the other two groups ($P < 0.01$) and was significantly greater in the latter two groups than in a combination of the three radiographic groups in which rheumatoid pneumoconiosis was not suspected ($P < 0.001$).

TABLE II
PREVALENCE OF CLINICAL RHEUMATOID DISEASE IN THE VARIOUS RADIOLOGICAL CATEGORIES OF PNEUMOCONIOSIS

	Rheumatoid Syndrome Not Suspected			Rheumatoid Syndrome Probable or Suspected		
	No Pneumoconiosis	Simple Excluding Nodular	Progressive Massive Fibrosis	Classical	Nodular	Mixed Nodular and Irregular Opacities
Definite rheumatoid arthritis	2 (18.2%)	1 (3.6%)	6 (9.7%)	36 (64.3%)	23 (31.1%)	13 (34.2%)
Probable and possible rheumatoid arthritis	0	4 (14.3%)	3 (4.8%)	1 (1.8%)	6 (8.1%)	3 (7.9%)
Olecranon nodules only	0	0	0	2 (3.6%)	1 (1.4%)	1 (2.6%)
No arthritis	9 (81.8%)	23 (82.1%)	53 (85.5%)	17 (30.4%)	44 (59.4%)	21 (55.3%)
Total	11 (100%)	28 (100%)	62 (100%)	56 (100%)	74 (100%)	38 (100%)

RHEUMATOID FACTOR TESTS IN THE CLINICAL AND RADIOGRAPHIC GROUPS.—The following results were obtained.

Definite Rheumatoid Arthritis.—Eighty-one of all the subjects had definite rheumatoid arthritis; 71 of these (87.7%) has a positive sensitized sheep cell agglutination test. Seventy-one of the 81 were tested by the bovine globulin latex method and 63 (88.7%) were positive. Fifty-nine out of the 67 tested (88.1%) had a positive RA test. There was a high proportion of positive rheumatoid factor tests in subjects with rheumatoid arthritis irrespective of the chest radiographic appearance (Table III).

TABLE III
DEFINITE RHEUMATOID ARTHRITIS
RHEUMATOID FACTOR TESTS RELATED TO CHEST RADIOGRAPH APPEARANCES

	Rheumatoid Syndrome Not Suspected			Rheumatoid Syndrome Probable or Suspected		
	No Pneumoconiosis	Simple Excluding Nodular	Progressive Massive Fibrosis	Classical	Nodular	Mixed Nodular and Irregular Opacities
Sensitized sheep cell agglutination test	1/2 (50.0%)	1/1 (100%)	5/6 (83.3%)	32/36 (88.9%)	19/23 (82.6%)	13/13 (100%)
Bovine globulin latex test	0/1 (0.0%)		4/4 (100%)	31/34 (91.2%)	16/19 (84.2%)	12/13 (92.3%)
RA test (Hyland)	0/1		4/4	29/32 (90.6%)	15/19 (78.9%)	11/11 (100%)

Probable and Possible Rheumatoid Arthritis.—Nine out of the 17 subjects (53%) with probable and possible rheumatoid arthritis had a positive S.S.C.A.T., six out of 15 (40.8%) had a positive bovine globulin latex test, and five out of 15 (33.3%) had a positive RA test. The significance of differences between the proportion of positive tests in the chest radiograph groups could not be determined because of small numbers (Table IV).

Olecranon Nodules without Arthritis.—Four subjects had olecranon nodules and no arthritis. One had a nodular appearance in the chest radiograph, one a mixture of nodular and irregular

TABLE IV
PROBABLE AND POSSIBLE RHEUMATOID ARTHRITIS

	Rheumatoid Syndrome Not Suspected			Rheumatoid Syndrome Probable or Suspected		
	No Pneumoconiosis	Simple Excluding Nodular	Progressive Massive Fibrosis	Classical	Nodular	Mixed Nodular and Irregular Opacities
Sensitized sheep cell agglutination test		2/4 (50.0%)	0/3 (0.0%)	1/1 (100%)	4/6 (66.7%)	2/3 (66.7%)
Bovine globulin latex test		1/4 (25.0%)	1/3 (33.3%)	1/1 (100%)	1/5 (20.0%)	2/2 (100%)
RA test (Hyland)		2/4 (50.0%)	0/3 (0.0%)	1/1 (100%)	1/1 (0.0%)	2/2 (100%)

opacities, and two a classical rheumatoid radiographic appearance. All four had positive sheep cell and latex tests.

Arthritis Absent.—Positive rheumatoid factor tests were found in a large proportion of the subjects without clinical arthritis but with classical chest radiographic appearances. The positive results varied from 61.5% to 70.6%, depending on the test used (Table V).

TABLE V
NO ARTHRITIS
Rheumatoid Syndrome Not Suspected Rheumatoid Syndrome Probable or Suspected

	Rheumatoid Syndrome Not Suspected			Rheumatoid Syndrome Probable or Suspected		
	No Pneumoconiosis	Simple Excluding Nodular	Progressive Massive Fibrosis	Classical	Nodular	Mixed Nodular and Irregular Opacities
Sensitized sheep cell agglutination test	0/9 (0.0%)	1/23 (4.3%)	7/53 (13.2%)	12/17 (70.6%)	21/44 (47.7%)	9/21 (42.9%)
Bovine globulin latex test	0/9 (0.0%)	0/23 (0.0%)	6/48 (12.5%)	64/3% (64.3%)	9/14 (26.3%)	10/38 (31.6%)
RA test (Hyland)	0/9 (0.0%)	0/23 (0.0%)	6/46 (13.0%)	8/13 (61.5%)	11/36 (30.6%)	7/19 (36.8%)

The S.S.C.A.T. was positive in 42.9% of the non-arthritic subjects with a mixed picture and in 47.7% of those with nodular opacities. The bovine globulin latex test was positive in 31.6% of those with a mixed picture who were tested by this method and in 26.3% of those with nodular opacities, while the RA test was positive in 36.8% and 30.6% respectively of those tested in the two groups. About 13% of the miners without arthritis with progressive massive fibrosis had a positive S.S.C.A.T. and positive latex tests. Of those with simple pneumoconiosis, 4.3% had a positive S.S.C.A.T. while none had a positive latex test. There were no positive rheumatoid factor tests in those with no radiological evidence of pneumoconiosis.

The proportion of positive S.S.C.A.T.s and latex tests was significantly higher in non-arthritic subjects with classical chest radiographic appearances and in subjects with nodular or mixed opacities than in a combination of all the non-arthritic subjects in whom the rheumatoid pneumoconiosis was not suspected ($P < 0.001$). The S.S.C.A. and the RA tests in those with nodular and mixed appearances taken together were more often positive than in those with progressive massive fibrosis ($P < 0.001$ for the S.S.C.A.T.; $P < 0.05$ for the RA test), but the difference between these radiological groups for the bovine globulin latex test did not reach significance ($0.10 > P > 0.05$).

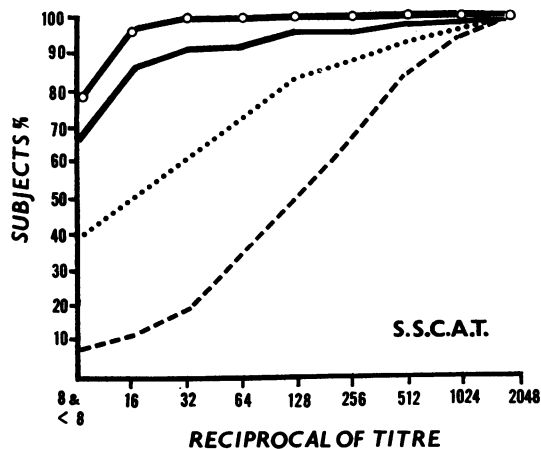


FIG. 4. Distribution of S.S.C.A.T. titres showing the percentage of subjects with the indicated titre or a lower titre.

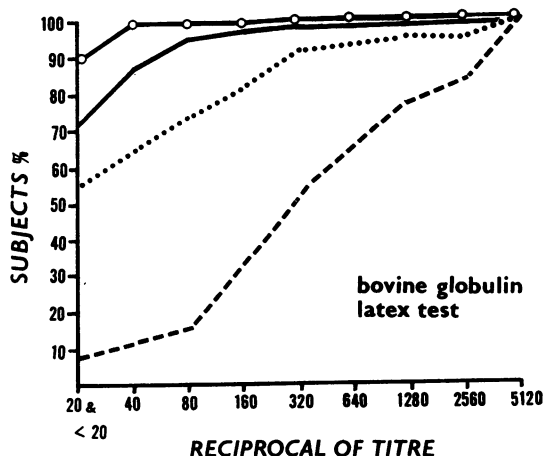


FIG. 5. Distribution of bovine globulin latex test titres showing the percentage of subjects with the indicated titre or a lower titre.

o—o—o Simple pneumoconiosis and no pneumoconiosis; no arthritis. — progressive massive fibrosis; no arthritis. . . . rheumatoid pneumoconiosis syndrome suspected radiologically; no arthritis. - - - - rheumatoid pneumoconiosis syndrome suspected radiologically; definite rheumatoid arthritis.

Distribution of Titres.—The distribution of titres in the S.S.C.A.T. and the bovine globulin latex test in miners with classical, nodular, and mixed radiographic appearances with and without arthritis and with other forms of pneumoconiosis without arthritis is shown in Figs. 4 and 5.

Difference between Tests.—Table VI shows that the results of the S.S.C.A.T. and the bovine globulin latex test agreed in from 84.4% to 96.9% of subjects with rheumatoid arthritis and nodular, mixed, or classical radiographic appearances and in subjects with no arthritis in whom the rheumatoid syndrome was not suspected. The tests agreed in only 46 out of 71 (64.8%) subjects without arthritis who had nodular, mixed, or

classical radiographic appearances. The difference, which is statistically significant ($P < 0.01$), was largely due to the number of subjects with a positive S.S.C.A.T. and a negative bovine globulin latex test in the latter groups. The median titre in the subjects with a positive S.S.C.A.T. only was 1 in 64 compared with 1 in 256 in the subjects with both tests positive in these groups. A similar relatively low level of agreement in these groups was found when the S.S.C.A.T. and the RA test were compared. There was from 89.1% to 100% agreement between the bovine globulin latex test and the RA test in all groups.

Pleural Effusion.—There was a history of the aspiration of a pleural effusion in eight subjects,

TABLE VI
COMPARISON OF RHEUMATOID FACTOR TESTS RELATED TO CHEST RADIOGRAPHIC APPEARANCES

	Arthritis Absent				Definite Rheumatoid Arthritis Present	
	Simple Pneumoconiosis + No Pneumoconiosis	Progressive Massive Fibrosis	Classical	Nodular and Mixed	Classical	Nodular and Mixed
1 S.S.C.A.T. + Latex +	0/32 (0.0%)	4/48 (8.3%)	8/14 (57.1%)	12/57 (21.1%)	30/34 (88.2%)	26/32 (81.3%)
2 S.S.C.A.T. - Latex -	31/32 (96.9%)	39/48 (81.3%)	1/14 (7.1%)	25/57 (43.9%)	2/34 (5.9%)	1/32 (3.1%)
3 S.S.C.A.T. + Latex -	1/32 (3.1%)	3/48 (6.2%)	4/14 (28.6%)	16/57 (28.1%)	1/34 (2.9%)	3/32 (9.4%)
4 S.S.C.A.T. - Latex +	0/32 (0.0%)	2/48 (4.2%)	1/14 (7.1%)	4/57 (7.0%)	1/34 (2.9%)	2/32 (6.3%)
Agreement (1+2)	31/32 (96.9%)	43/48 (89.6%)	9/14 (64.3%)	37/57 (64.9%)	32/34 (94.1%)	27/32 (84.4%)
5 Latex + RA test +	0/32 (0.0%)	5/46 (10.9%)	8/13 (61.6%)	14/55 (25.4%)	29/32 (90.6%)	26/30 (86.6%)
6 Latex - RA test -	32/32 (100.0%)	39/46 (84.8%)	5/13 (38.4%)	35/55 (63.6%)	3/32 (9.4%)	3/30 (10.0%)
7 Latex + RA test -	0/32 (0.0%)	1/46 (2.2%)	0/13 (0.0%)	2/55 (3.6%)	0/32 (0.0%)	1/30 (3.3%)
8 Latex - RA test +	0/32 (0.0%)	1/46 (2.2%)	0/13 (0.0%)	4/55 (7.3%)	0/32 (0.0%)	0/30 (0.0%)
Agreement (5+6)	32/32 (100.0%)	44/46 (95.6%)	13/13 (100.0%)	49/55 (89.1%)	32/32 (100.0%)	29/30 (96.6%)

of whom three had a classical rheumatoid picture with definite rheumatoid arthritis, four had a classical picture without arthritis, and one had progressive massive fibrosis without arthritis. All except the one subject with progressive massive fibrosis had positive rheumatoid factor tests.

DISCUSSION

This investigation has again confirmed the high prevalence of rheumatoid arthritis in miners with the classical chest radiographic appearance described by Caplan (1953). It has also shown that certain less characteristic appearances were associated with a prevalence of clinical arthritis higher than that found in other forms of coal-workers' pneumoconiosis, but lower than that associated with the classical radiographic appearance of the rheumatoid syndrome.

The expected high proportion of positive rheumatoid factor tests, about 88%, was found in the presence of definite rheumatoid arthritis (Greenbury, 1960) irrespective of the chest radiographic appearance. It is interesting that when the rheumatoid syndrome was considered probable or was suspected from chest radiographs and there was no arthritis, there was a positive S.S.C.A.T. in 70.6% of those with classical appearances, 47.7% of those with nodular simple pneumoconiosis, and 42.9% of those with a mixture of nodular and irregular opacities.

The characteristic pathology of rheumatoid pneumoconiosis has been described by Gough, Rivers, and Seal (1955). It has been found that the pulmonary lesions in miners with classical chest radiographs but with no arthritis are indistinguishable from the lesions found in miners with the complete syndrome (Gough, 1959). However, it is likely that some of our non-arthritic subjects with nodular and mixed radiological appearances and negative rheumatoid factor tests had opacities that were not rheumatoid in origin, for an unpublished correlation of radiographic appearances and post-mortem findings (Caplan and Gough, 1962) has shown that while many cases show the characteristic pathology of rheumatoid pneumoconiosis, others have silicosis, infective nodules, progressive massive fibrosis, and, rarely, tuberculosis. Caplan and Gough have also found that the aftermath of coalescence, cavitation, and fibrosis of the nodules of rheumatoid pneumoconiosis can result in massive lesions radiographically indistinguishable from progressive massive fibrosis. It is possible that this accounts for the 13% positive tests in the progressive massive fibrosis group, although a real association between rheumatoid

factors and progressive massive fibrosis cannot be excluded. Ball (1955) found that the incidence of positive S.S.C.A.T.s was higher in arthritic subjects with progressive massive fibrosis than in arthritic subjects with simple pneumoconiosis or a normal chest radiograph and suggested, as one possible explanation, that progressive massive fibrosis may itself be associated in a proportion of cases with positive tests in the absence of arthritis. The recognition of the less characteristic small nodular picture, particularly in the absence of clinical arthritis, as being of possible rheumatoid origin is not only of academic interest. Failure to consider rheumatoid pneumoconiosis as a possible diagnosis may lead to an unnecessary diagnostic thoracotomy. This investigation has also shown that pleural effusion is not uncommonly associated with the classical radiographic appearances and may occur in the absence of clinical arthritis. In all these cases tuberculosis was strongly suspected but in none was it proven.

The two latex tests, which showed good agreement with each other, were less often positive than the S.S.C.A.T. in non-arthritic miners with rheumatoid radiographic appearances but not in the other groups. This finding supports the view that there are at least two rheumatoid factors with different specificities.

The results of some rheumatoid factor tests (two sensitized cell tests and two latex fixation tests) in coal-workers have been published by Dickmans (1960). Positive tests were found in from one third to one half of his subjects without arthritis in whom the chest radiographic appearances suggested the rheumatoid syndrome. However, positive tests were found in a relatively high proportion of subjects with neither arthritis nor pneumoconiosis.

Serum specimens from 10 of Dickmans's non-arthritic subjects with classical radiographic appearances were examined by Schroeder, Franklin, and McEwen (1962). They found a positive euglobulin S.S.C.A.T. in all 10, but the latex fixation test of Singer and Plotz (1956) was positive in only six, agreeing with our finding that these two kinds of test tend to give different results in this group of subjects.

Claeys (1954), Ishinishi and Miyazaki (1958), and other workers found that the serum of miners with classical silicosis agglutinated suspensions of quartz coated with protein. This reaction appears to be similar to latex fixation. However, latex fixation tests may become positive in a variety of non-rheumatoid diseases while the S.S.C.A.T. remains negative (Fudenberg and Kunkel, 1961).

We have been unable to find any reference to sheep cell tests in silicosis or evidence that the prevalence of rheumatoid arthritis is increased in this disease. It seems unlikely that the small amount of silica in coal dust accounts for the positive rheumatoid factor tests we have found in non-arthritic miners with distinguishable chest radiographic appearances. Miall (1955) found no increase in the prevalence of rheumatoid arthritis among miners and ex-miners in a defined population and concluded that exposure to dust was of no aetiological importance in the disease.

Ball and Lawrence (1961) found that only 19.4% of subjects with positive sheep cell tests from two British population samples had definite rheumatoid arthritis. They also found that two out of seven non-arthritic subjects with positive tests seen five years earlier had developed rheumatoid arthritis in the interval. Both Caplan (1953) and Miall *et al.* (1953) pointed out that the chest radiographic changes of the rheumatoid syndrome may precede the arthritis by a number of years. It is therefore possible that non-arthritic miners with these radiographic changes and a positive S.S.C.A.T. represent the non-arthritic members of the general population with positive tests, and that they can be identified because they develop nodular lesions in the lungs in the presence of coal dust. A follow-up of this group should be of interest, particularly to find out whether there is any difference in the frequency or rapidity of development of clinical rheumatoid arthritis in those with positive sheep cell and latex tests, those with positive sheep cell tests only, and those with negative tests. The subjects in this investigation were selected from miners attending the Cardiff Pneumoconiosis Medical Panel and the Pneumoconiosis Research Unit. We are co-operating with the Epidemiological Research Unit of the Medical Research Council in investigating the possibility of using a random sample of a mining population to see if our finding can be confirmed in a less selected population.

SUMMARY

Clinical observation over the last few years suggested that some widening of the definition of the pulmonary radiographic side of the rheumatoid pneumoconiosis syndrome was needed. Clinical and radiological investigations in a group of coal-miners showed that there was an increased

prevalence of rheumatoid arthritis both in miners with small nodular discrete radiographic opacities, normally defined as nodular simple pneumoconiosis, and in miners with a mixture of nodular and irregular opacities, normally included in the category of progressive massive fibrosis.

In addition, independent immunological studies showed that miners with these radiographic appearances or the classical chest radiographic changes of the rheumatoid pneumoconiosis syndrome, who had no history, signs, or symptoms of rheumatoid arthritis, had a high proportion of positive rheumatoid factor tests.

We are grateful to Professor Jethro Gough, Professor A. L. Cochrane, and Dr. W. E. Miall for valuable criticism and advice. Facilities for the examination of subjects at the Pneumoconiosis Research Unit of the Medical Research Council were kindly provided by the Director, Dr. J. C. Gilson, and we are indebted to the Chief Medical Officer of the Ministry of Pensions and National Insurance for permission to publish the results of the examination of subjects at the Cardiff Pneumoconiosis Medical Panel. We are grateful to Mr. M. Letton and Mr. G. S. Smart for technical assistance. The photographs of the chest radiographs were taken by the late Mr. H. M. Travers.

REFERENCES

- American Rheumatism Association (1959). *Ann. rheum. Dis.*, **18**, 49.
 Ball, J. (1955). *Ibid.*, **14**, 159.
 — and Lawrence, J. S. (1961). *Ibid.*, **20**, 235.
 Caplan, A. (1953). *Thorax*, **8**, 29.
 — and Gough, J. (1962). Personal communication.
 Claeys, C. (1954). *Rev. méd. min.*, **7**, Nos. 26–27, p. 22.
 Dickmans, H. (1960). *Med. Welt*, **1**, 1276.
 Fudenberg, H. H., and Kunkel, H. G. (1961). *J. exp. Med.*, **114**, 257.
 Gough, J. (1959). In *Modern Trends in Pathology*, ed. D. H. Collins, p. 280. Butterworth, London.
 — Rivers, D., and Seal, R. M. E. (1955). *Thorax*, **10**, 9.
 Greenbury, C. L. (1957). Broadsheet No. 18 (New Series) of the Association of Clinical Pathologists.
 — (1960). *J. clin. Path.*, **13**, 325.
 Heller, G., Jacobson, A. S., Kolodny, M. H., and Kammerer, W. H. (1954). *J. Immunol.*, **72**, 66.
 International Labour Office (1959). *Occup. Safety Hlth*, **9**, 63.
 Ishinishi, S., and Miyazaki, T. (1958). *Compte Rendu des Journées Françaises de Pathologie Minière*, p. 319. Charbonnages de France, Paris.
 Lospalluto, J., and Ziff, M. (1959). *J. exp. Med.*, **110**, 169.
 Miall, W. E. (1955). *Ann. rheum. Dis.*, **14**, 150.
 — Caplan, A., Cochrane, A. L., Kilpatrick, G. S., and Oldham, P. D. (1953). *Brit. med. J.*, **2**, 1231.
 Payne, R. B. (1961). *J. clin. Path.*, **14**, 309.
 Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 1.
 Schroeder, W., Franklin, E. C., and McEwen, C. (1962). *Arthr. and Rheum.*, **5**, 10.
 Singer, J. M., and Plotz, C. M. (1956). *Amer. J. Med.*, **21**, 888.