FACTORS INFLUENCING THE RADIOLOGICAL ATTACK RATE OF PROGRESSIVE MASSIVE FIBROSIS

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Progressive massive fibrosis (P.M.F.) is the more serious form of coal-workers' pneumoconiosis. It causes serious disability (Gilson and Hugh-Jones, 1955; Gilson and Carpenter, 1956), probably causes excessive mortality (Carpenter and Cochrane, 1956), and has a surprisingly high prevalence among miners and ex-miners in South Wales (Cochrane *et al.*, 1952). The disease is slowly progressive and its natural history is little affected by treatment (Miall *et al.*, 1954; Gilson and Kilpatrick, 1955). A knowledge of the factors influencing the aetiology of the disease is therefore of the greatest importance to speed prevention.

Detailed pathological and bacteriological investigations over a period of years have thrown great light on the structure and nature of the lesion as well as demonstrating a close relationship with tuberculosis (Gough, 1947; Fletcher, 1948; Fletcher and Gough, 1950; James, 1954). It has not, however, been possible to decide whether tuberculosis is acting as a primary aetiological agent or as a secondary invader of diseased tissue. Many experiments on animals have also been carried out (Cummins, 1940; Attygalle *et al.*, 1954; King, 1956). Their results show that the presence of coal dust modifies the animal's response to tuberculosis, but the relevance of these results to an understanding of the human reaction remains doubtful.

This paper is concerned with the epidemiological approach to the problem of the factors influencing the attack rate—that is, rate of appearance—of P.M.F. It consists of (1) a brief description of a pilot experiment, (2) a description of the first results of a planned "forward" experiment to test the hypothesis that P.M.F. is caused by exogenous tuberculous infection of lungs which already have definite radiological signs of simple pneumoconiosis, and (3) a discussion of the importance of some other factors influencing the attack rate of P.M.F.

Previous Work

The "two-disease" hypothesis (Gough, 1947; Fletcher, 1948) suggesting that P.M.F. is a different disease from simple pneumoconiosis is not completely accepted outside this country, so there has been relatively little published about the attack rate of P.M.F. If the two-disease hypothesis is not accepted, an attack of P.M.F. would be regarded as a progression of pneumoconiosis.

The first indirect discussion of this important index is in Fletcher's Goulstonian Lectures (Fletcher, 1948), where reference is made to a critical stage of simple pneumoconiosis below which there was no risk of developing P.M.F. His estimate was based on a review of all the Hart and Aslett (1942) cases that had been followed up, to see at what stage the "A" shadows, the earliest stage of P.M.F., tended to develop. He suggested that the attack rate of P.M.F. varied with the category of simple pneumoconiosis and that it was negligible below a certain critical stage which corresponded to our present category 3, and concluded that men might be promised safety from P.M.F. if they were advised to leave a dusty environment at a stage slightly earlier than that at which they qualified for certification.

Further evidence on this point was brought forward by Davies *et al.* (1949). Their results suggested that the attack rate of P.M.F., once the "critical" stage of simple pneumoconiosis was reached, was independent of further dust exposure and that this rarely occurred below the level of category 3, simple pneumoconiosis. They actually found a higher rate of attack among those miners who had no further dust exposure between the x-ray examinations. They suggested that this might be due to the lower economic status of the group, of whom many had been unemployed during this period. The actual figure they found for the attack rate was 20% in 7.7 years, or approximately 25 per 1,000 per year (recalculated from their data).

Mann (1951) carried the analysis a little further by studying the appearance of tuberculosis and P.M.F. in 1,514 pairs of radiographs. His analysis showed that the attack rate of tuberculosis and P.M.F. varied with the category of simple pneumoconiosis in the initial x-ray films.

The Pilot Experiment

To investigate, *inter alia*, the technical difficulties of measuring the actual attack rate of P.M.F. and various factors which might be influencing it, the defined underground population of a Welsh colliery (C), which had been x-rayed by the Pneumoconiosis Research Unit in 1947, was x-rayed again in 1949, 2½ years after the original survey, and the attempt was made to measure several other characteristics, environmental and personal, of the population at risk. The results have been, in part, published previously (Cochrane *et al.*, 1951). Although the population was small, some important information was obtained.

The extent of the follow-up achieved is shown in Table I. The measurement of the attack rate of P.M.F. and tuber-

TABLE I.—Extent of Follow-up of Underground Population of a Colliery in Valley A X-rayed in 1947 and 1949

No. X-rayed in 1947	Died	% of	Un-traced	% of	Re-X-rayed in 1949	% of	No. with Tub. or P.M.F. in 1947	% of	No. without Tub. or P.M.F. in 1947	% of
(1)	(2)	(1)	(3)	(1)	(4)	(1)	(5)	(4)	(6)	(4)
499	8	1.6	7	1.4	484	97.0	23	4.8	461	95.2

culosis appeared to be easier and more reproducible than, say, the progression of simple pneumoconiosis. The total number of attacks was, however, too small for detailed analysis. It was, however, found to be impossible to differentiate between tuberculosis and P.M.F. in these early lesions. It was therefore found more satisfactory to combine the two from the point of view of statistical analysis.

The relationship of this combined attack rate of tuberculosis and P.M.F. to the category of simple pneumoconiosis in the first x-ray examination is shown in Table II. This

TABLE II.—*Attack Rate of Pulmonary Tuberculosis and P.M.F. in a Colliery in Valley A X-rayed in 1947 and in 1949*

X-ray Category in 1947	No.	No. Attacked, Tuberculosis or P.M.F.	Annual Attack Rate
0	170	0	0%
1	124	0	0%
2	95	6	2.5%
3	72	4	2.2%
Total	461	10	0.9%

suggested that the "critical level" of Fletcher (1948) and Davies *et al.* (1949) was too high, because "A" shadows, the earliest stage of P.M.F., could clearly appear on a background of category 2 simple pneumoconiosis. Their appearance on a background of category 1 simple pneumoconiosis at a lower rate was, of course, not excluded by this survey. No significant relationship was found between the attack rate and any other of the environmental and personal characteristics measured, but there were two suggestive trends with anthropometry (Rees and Eysenck, 1945) and with overcrowding.

The results of this pilot experiment were encouraging practically, though not very enlightening theoretically. The "tuberculosis modified by dust" hypothesis still appeared to be the simplest hypothesis which covered the facts, so it was agreed to plan a forward experiment to investigate this.

The Plan

The object of the plan was to try out the hypothesis that the attack rate of P.M.F. among miners was related to the tuberculous infectivity of the area in which they lived. As it was impossible to find two mining areas in this country with widely different tuberculosis mortality rates amongst the females, it was decided to attempt to reduce the tuberculous infectivity in one mining area and compare the attack rate of P.M.F. in that area with another in which no such effort was made. It was agreed that this would only test the possibility that the attack rate of P.M.F. was associated with exogenous infection and that the possibility of endogenous infection being important would not be covered by the experiment.

Two Welsh mining valleys, valley A and valley B, were therefore selected. In both there were four collieries, working the same rank of coal, containing approximately the same number of miners, with similar high certification rates for pneumoconiosis. The economic and social conditions were similar in the two valleys, though it seemed possible that in valley B they were slightly better. This was confirmed by the results of the tuberculin-testing of the schoolchildren in the two valleys (Jarman, 1953).

In order to reduce the tuberculous infectivity in valley A, it was proposed (1) to attempt to take radiographs of as high a proportion of the population over the age of 5 as possible, (2) by duplicate readings and wide use of sputum examination to find as high a proportion of all the infectious cases as possible, (3) to arrange for immediate hospitalization and treatment of these patients, and (4) to arrange for supervision by a health visitor of all those infectious patients who might leave hospital before their sputum converted.

At the same time it was proposed to measure the Mantoux reactions in schoolchildren in both valleys on two separate

occasions, 2½ years apart, so that the changes in prevalence of positive reactors would give us a measure of the infectivity of the two areas during the period between the surveys.

The measurement of the attack rate of P.M.F. in the two valleys would be obtained by x-raying again 2½ years later all the miners x-rayed in the two valleys on the first occasion. As the prevalence of infectious tuberculosis is low among working miners (Cochrane *et al.*, 1952) it was not thought probable that the x-raying of the miners in valley B would affect the infectivity of the area to any large extent.

Two points require further discussion. The use of our fellow human beings as controls always has an unpleasant sound and always demands a detailed justification. In this case we feel it was entirely justified. It would have been technically impossible to have given, at that time, more than one small area in Wales the detailed attention that valley A received, and the fact that it could not be given to all is no reason for not giving it to one. On the other hand, the chest service in valley B was probably above the average for Wales, and the routine x-raying of the miners by ourselves and the mining entrants by the National Coal Board there tended to improve it to some extent. In addition, valley B received its fair share of mass radiography in the intersurvey period. The details of the controlled experiment were known to the medical authorities and practitioners in the area and to the more senior members of the National Coal Board and the National Union of Mineworkers. The other point concerns the use of B.C.G. We did not feel that the evidence in favour of the efficacy of B.C.G. was sufficient to make it essential that B.C.G. should be given in both valleys, and as we, on the other hand, were very keen to attempt to make accurate measurements of the Mantoux positivity rates, we decided not to give it in either valley. Exceptions were made in the case of children under 5 who were exposed to infection in their homes and of other children exposed to infection on whose behalf a special request was made by their parents. The number of the latter was small and did not interfere with the statistical analysis of the Mantoux testing.

The plan obtained general scientific approval from the Medical Research Council's Industrial Pulmonary Diseases Committee, a local advisory committee was formed in South Wales on which all interested bodies were represented, and from this a small executive committee on whose shoulders the main burden of the work fell. The work was throughout a co-operative venture between the chest service of the Welsh Regional Hospital Board and the Pneumoconiosis Research Unit. The hospitalization of the patients in valley A was made possible by the rapid transformation of an old hospital for infectious diseases into a tuberculosis hospital.

Methods

The methods used during the two x-ray surveys (2.6 years apart) in valley A have already been described (Cochrane *et al.*, 1952, 1955), and similar methods were used in valley B to radiograph the miners. The only change introduced for the comparison between the two valleys was that all films which the Pneumoconiosis Research Unit observers had read as showing pneumoconiosis of category 2 or more were re-read by Dr. Springett in order to avoid any suspicion of a bias. Dr. Springett had not seen any of the films before, and the pairs of films from the two valleys were arranged in random order and the dates and numbers on the films concealed. His readings divided the pairs of films into two groups—those showing the appearance of a localized shadow (which might be tuberculosis or P.M.F.) and those which showed no such change.

Results

The results fall into three main groups: (1) The evidence that we reduced the infectivity of valley A below that of valley B in the intersurvey period. (2) The comparison of the attack rate of tuberculosis and P.M.F. amongst the

miners in the two valleys. (3) The use of these data to investigate other factors which might influence the attack rate of P.M.F.

Evidence About Reduced Tuberculous Infectivity in Valley A Compared with that in Valley B

We planned, as stated, to rely on the changes in Mantoux positivity rates to give us an objective measure of the tuberculous infectivity of the two valleys in the intersurvey period. The results of the tuberculin-testing at the time of the first survey, reported by Jarman (1953), showed that the infectivity of valley B was significantly lower than that in valley A. The dice were therefore weighted against us. Fig. 1 shows a comparison between the Mantoux tests in valley A at the time of the two surveys. The difference is visually striking and statistically significant (Jarman, 1955). Fig. 2 shows the comparable results from valley B, where we see some suggestion of a decline. The difference in this case is, however, insignificant, and the decline in percentages in valley A is significantly greater than in valley B. It there-

FIG. 1.—Results of tuberculin-testing in valley A in 1950-1 and 1953.

FIG. 2.—Results of tuberculin-testing in valley B in 1951 and 1954.

fore seems reasonable to conclude that in the period between the two surveys the tuberculous infectivity in valley A was lower than in valley B.

Comparison of Attack Rate of Tuberculosis and P.M.F. Amongst Miners in the two Valleys

In Table III the fate of the two populations of miners who were working at the time of the first survey is shown.

The attack rate of tuberculosis and P.M.F. on these two populations is shown in Table IV. It is clear that the attack rate is somewhat lower in valley A than in valley B, in spite of the fact that the Mantoux results suggested that valley B had a somewhat lower infectivity than valley A before the survey started. Owing, however, to differences in the distribution of the categories of pneumoconiosis in the two valleys, we must examine these results in greater detail.

In Table IV the attempt has also been made to differentiate between tuberculosis and P.M.F. by dividing the population at risk into those who had categories 0 and 1 simple pneumoconiosis in their x-ray films and those who had categories 2 and 3—the conventional Pneumoconiosis Research Unit

TABLE III.—Summary of Follow-up of Miners in the Two Valleys at Time of First Survey

	No. Working at 1st Survey	No. X-rayed at 1st Survey	% of	Between Surveys				No. Remain- ing in Area at 2nd Sur- vey (5)	% of	No. X-rayed at 2nd Survey	% of	% of	No. with P.M.F. or Pul. Tub. at 1st Survey	% of	No. Exclud- ing P.M.F. and Pul. Tub. at 1st Survey (8)	% of
				No. Dead (3)	% of (2)	No. Left Area (4)	% of (2)									
	(1)	(2)	(1)	(3)	(2)	(4)	(2)		(2)	(6)	(5)	(2)	(7)	(6)		(6)
Miners living in valley A	2,792	2,764	99.0	50	1.8	320*	11.6	2,394	86.6	2,318	96.8	83.9	192	8.3	2,126	91.7
Miners living in valley B	2,674	2,652	99.2	35	1.3	130	4.9	2,487	93.8	2,453	98.6	92.5	202	8.2	2,251	91.8

* This includes not only those who left valley A but also those who continued living there but worked outside.

TABLE IV.—Attack Rate of Tuberculosis and P.M.F. among Miners in Valley A and in Valley B, Excluding those who had Tuberculosis or P.M.F. at Time of First Survey in 1950-1, Subdivided According to Category of Simple Pneumoconiosis at Time of First Survey, with a Correction for Those whose X-ray Films showed Progression from Category 0 or 1 to 2 or 3

Age Group	Valley A									Valley B								
	Cat. 0 & 1 (1950-1)			Cat. 2 & 3 (1950-1)			Total Re-X-rayed			Cat. 0 & 1 (1950-1)			Cat. 2 & 3 (1950-1)			Total Re-X-rayed		
	No.	No. At-tacked	% per Year	No.	No. At-tacked	% per Year	No.	No. At-tacked	% per Year	No.	No. At-tacked	% per Year	No.	No. At-tacked	% per Year	No.	No. At-tacked	% per Year
15-24	281	1	1.4	10	—	—	291	1	1.3	307.5*	1	1.3	3.5	—	—	311	1	1.2
25-44	805.5	1	0.5	216.5	7	12.4	1,022	8	3.0	978	4	1.6	195	9	17.8	1,173	13	4.3
45-64	637	—	—	120	2	6.4	757	2	1.0	592	1	0.6	131	4	11.7	723	5	2.7
65+	44	—	—	12	—	—	56	—	—	38	—	—	6	—	—	44	—	—
Total	1,767.5	2	0.4	358.5	9	9.7	2,126	11	2.0	1,915.5	6	1.2	335.5	13	14.9	2,251	19	3.2

* Allowance has been made for those who progressed from category 1 to category 2 between the two surveys, hence the decimal points in some of the figures.

division between clinically significant tuberculosis and P.M.F. The table shows that both the attack rate of tuberculosis and that of P.M.F. were lower in valley A than in valley B. A one-sided test, which is probably justifiable in the circumstances, gives $P < 0.07$. In Table V and Fig. 3 the attack

TABLE V.—Summary of Attack Rates of Tuberculosis and P.M.F. Among Those with Category 2 and 3 at Time of First Survey, Excluding Those who had Pulmonary Tuberculosis or P.M.F. at Time of First Survey, Adjusted to Include Those Whose X-ray Films Showed Progression of Simple Pneumoconiosis from Category 0 or 1 to 2 or 3

Follow-up Survey	Age Group	No. Cat. 2 and 3	No. Attacked	% per year
Pilot survey colliery C 1947-9 (valley A)	15-24	23	2	34.8
	25-44	76	6	31.6
	45-64	60	2	13.3
Valley B 1951-3	15-24	3.5	0	—
	25-44	195	9	17.8
	45-64	131	4	11.7
Valley A 1950-1-1953	15-24	10	0	—
	25-44	216.5	7	12.4
	45-64	120	2	6.4
Ex-miners valley A	15-24	2	0	—
	25-44	68	2	11.3
	45-64	95	2	8.1
	65+	51	1	7.5

Fig. 3.—Annual radiological attack rate of pulmonary tuberculosis and P.M.F. among miners and ex-miners with category 2 or 3 simple pneumoconiosis at the first survey.

rates among those with categories 2 and 3 are compared with the attack rate in the pilot survey at colliery C in valley A. It looks as though between the two surveys there had been a marked drop in the attack rate in valley A which had brought it below the level of that in valley B.

Statistically one can only assess the probability that the difference in attack rate in the two valleys could be a chance finding. No allowance can be made for the fact that the tuberculous infectivity in valley B was originally lower than in valley A. Even so, the analysis shows that such a difference would be expected to occur by chance in only 17% of trials. As the experiment was planned to last 10 years this is at least promising.

In studying the effect of tuberculous infectivity on the attack rate of P.M.F. and tuberculosis, we have so far made

use only of the population of miners. We have, however, another population, that of the ex-miners in valley A, who can be utilized for this investigation. Their derivation is shown in Table VI, and their further breakdown by age and category of pneumoconiosis in Table VII. In order to keep them comparable with the miners, those who worked outside the valley during the intersurvey period have been excluded. The relationship to the attack rates in categories 2 and 3 of the other groups is also shown in Fig 3. The agreement with the attack rate in the miners in valley A is striking and reassuring.

TABLE VII.—Attack Rate of Tuberculosis and P.M.F. Amongst Ex-miners who Lived and Worked in Valley A, Excluding Those who had Tuberculosis or P.M.F. at Time of First Survey in 1950-1, Subdivided According to Category of Simple Pneumoconiosis at Time of First Survey, with a Correction for Those whose X-ray Films Showed Progression from Categories 0 or 1 to 2 or 3

Age Group	Cat. 0 & 1 (1950-1)			Cat. 2 & 3 (1950-1)			Total Re-X-rayed		
	No.	No. Attacked	% Per Yr.	No.	No. Attacked	% Per Yr.	No.	No. Attacked	% Per Yr.
15-24	21	—	—	2	—	—	23	—	—
25-44	158	1	2.4	68	2	11.3	226	3	5.1
45-64	377	—	—	95	2	8.1	472	2	1.6
65+	292	—	—	51	1	7.5	343	1	1.1
Total	848	1	0.5	216	5	8.9	1,064	6	2.2

Other Factors

(a) *Effect of Age.*—Although Fig. 3 suggests that age might influence the attack rate, the effect is statistically insignificant. This point requires further investigation on larger populations, as it is of theoretical and practical importance.

(b) *Effect of Body Type.*—In a previous communication Oldham (1953), using data from the first survey, showed that Rees's body index (Rees and Eysenck, 1945) discriminated between those with tuberculosis and P.M.F. and those without chest abnormalities. Oldham pointed out that it was impossible from prevalence data to state which was cause and which was effect. This can be decided only by a forward experiment such as we have completed. The results are summarized in Table VIII. The average body indices for

TABLE VIII.—Summary of Average Body Indices Among Those at Risk and Those Attacked in Valleys A and B

X-ray Category	Population at Risk at First Survey				Attacks of TB. or P.M.F. Between Surveys		
	No.	No Record of Body Index	Total Body Indices	Means	No.	Total Body Indices	Means
0	3,759	296	355,627	102.7	8	841	105.1
1	804	46	78,038	103.0	1	112	112.0
2	583	26	57,124	102.6	18	1,890	105.0
3	295	5	29,728	102.5	9	946	105.1

Note: Where an attack of P.M.F. occurred concurrently with progression of simple pneumoconiosis, such an attack has been placed with the x-ray reading at the time of the second survey.

those who were attacked are higher, indicating a more asthenic build, than those who were not attacked. It is also the same when those who were attacked are related to the category of their original x-ray examination. The chance that body type does not influence the attack rate is between 10 and 20%.

TABLE VI.—Summary of Follow-up of Ex-miners in Valley A at Time of First Survey

No. Living in Valley	No. X-rayed at 1st Survey	% of	Died	% of	Left Area	% of	Remain- ing at Time of 2nd Survey	% of	No. Re- X-rayed at 2nd Survey	% of	% of	No. Working Outside Valley	% of	No. Working Inside Valley	% of	No. with P.M.F. or Tub. in 1950-1	% of	No. without P.M.F. or Tub. in 1950-1	% of
(1)	(2)	(1)	(3)	(2)	(4)	(2)	(5)	(2)	(6)	(5)	(2)	(7)	(6)	(8)	(6)	(9)	(8)	(10)	(8)
3,431	3,055	89.0	251	8.2	115	3.8	2,689	88.0	2,475	92.0	81.0	996	40.2	1,479	59.8	415	28.1	1,064	71.9

(c) *Occupation*.—Davies *et al.* (1949), in a somewhat selected series, chosen retrospectively, suggested that the attack rate was much the same whether the miner with simple pneumoconiosis left mining or not. This was confirmed by Mann (1951), again using a retrospective selected series. To investigate this we have analysed the miners and ex-miners living in valley A according to whether they worked in mining or outside mining, or whether they did both in the intersurvey period. The results are shown in Table IX. The slightly lower attack rates among those who continued mining might be due to the low prevalence of infectious cases found among working miners (Cochrane *et al.*, 1952). The difficulty of drawing conclusions from

theories. Both the main theories appear in two slightly different forms:

1. The two "silica" theories can be summarized as follows: (a) In cases where P.M.F. appears on a background of simple pneumoconiosis consisting pathologically of "classical" silicotic nodules, it is thought to be due simply to an aggregation of silicotic nodules which is liable to become infected by tuberculosis. (b) In cases where the P.M.F. appears on a background of simple pneumoconiosis, consisting of silicotic nodules modified by the admixture of coal dust or of coal macules, it is thought that it is the silica content of the nodules which is important in causing the change from reticulon to collagen.

2. Both "tuberculosis" theories suggest that simple pneumoconiosis is due to coal dust (the silica content being too small

TABLE IX.—Summary of Attacks of Pulmonary Tuberculosis and P.M.F. in Miners and Ex-miners in Valley A, According to Occupation between Surveys

Age Group	Categories 0 and 1									Categories 2 and 3								
	Mining			Outside Mining			Mining & Outside			Mining			Outside Mining			Mining & Outside		
	No.	No. Attacks	% per Yr.	No.	No. Attacks	% per Yr.	No.	No. Attacks	% per Yr.	No.	No. Attacks	% per Yr.	No.	No. Attacks	% per Yr.	No.	No. Attacks	% per Yr.
15-24	252	1	1.5	21	—	—	29	—	—	10	—	—	1	—	—	12	—	—
24-44	733.5	1	0.5	145	1	2.7	85	—	—	202.5	4	7.6	53	2	14.5	29	3	39.8
45-64	559.5	—	—	374	—	—	81	—	—	109.5	2	7.0	89	2	8.6	16	—	—
65+	23	—	—	296	—	—	17	—	—	9	—	—	51	1	7.5	3	—	—
Total	1,568	2	0.5	836	1	0.5	212	—	—	331	6	7.0	194	5	9.9	49	3	23.5
							2,616	3	0.4							574	14	9.4

Note: Populations in each age/occupation group are adjusted as in Table VI, to allow for those progressing from categories 0 or 1 to 2 or 3.

TABLE X.—Attack Rate of Pulmonary Tuberculosis and P.M.F. in Miners and Ex-miners of Valley A and Miners of Valley B, Analysed by Age and X-ray Category of Simple Pneumoconiosis at Time of First Survey

Age Group	Category 0			Category 1			Category 2			Category 3			All Categories		
	No.	No. of Attacks	% per Yr.	No.	No. of Attacks	% per Yr.	No.	No. of Attacks	% per Yr.	No.	No. of Attacks	% per Yr.	No.	No. of Attacks	% per Yr.
15-24	694	2	1.1	28	—	—	15	—	—	3	—	—	740	2	1.0
25-34	1,045	2	0.7	205	—	—	147	—	—	96	2	8.0	1,493	7	1.8
35-44	910	3	1.3	248	1	1.6	234	3	7.8	141	6	16.4	1,533	18	4.5
45-54	857	1	0.4	247	—	—	169	5	11.4	90	1	4.3	1,363	7	2.0
55-64	622	1	0.6	183	—	—	115	2	6.7	55	—	—	975	3	1.2
65+	297	—	—	87	—	—	52	—	—	19	1	20.2	455	1	0.8
Total	4,425	9	0.8	998	1	0.4	732	18	9.5	404	10	9.5	6,559	38	2.2

Note: This table includes 2 ex-miners who "live only" in valley A (not shown in other tables).

data based on populations which have been self-selected, as opposed to randomly allocated into the critical groups, is clearly demonstrated by the attack rate among those with mixed histories. If such people left mining because they were ill and the illness was associated with the attack, serious bias may have been introduced.

(d) *X-ray Category*.—We have combined the material available from both valleys to investigate the findings of Fletcher (1948), Davies *et al.* (1949), Mann (1951), and Cochrane *et al.* (1951) (Table X). In general, it confirms the idea of a critical level between categories 1 and 2. This, however, uses the conventional definition of P.M.F. which more or less begs the question, although it certainly receives some support from the abrupt rise in attack rate that occurs at that level. Even this, however, might be due to bias on the part of the x-ray readers. The results do, however, tend to confirm the idea that "a little dust is good for you" from the tuberculosis point of view, which one of us put forward as a result of an analysis of mortality and prevalence data (Cochrane, 1954).

Discussion

The various theories about the aetiology of P.M.F. have always suffered from inexact definition, partly due to the widespread use of the word "silicosis" and its equivalents to describe coal-workers' pneumoconiosis, and the unwillingness of others to accept the division into simple and complicated pneumoconiosis. However, a study of the literature, combined with discussion with individuals, suggests that there are two main theories current to-day—the "tuberculosis" and "silica" theories—and two minor ones, which might be called the "other infections" and the "total dust"

to be important) and that P.M.F. is a tuberculous lesion modified by the presence of coal dust. One theory suggests that the tuberculous lesion is present in the lungs before the dust, while the other suggests that the infection, whether endogenous or exogenous, produces P.M.F. by affecting a lung already containing considerable quantities of dust.

3. The third theory is similar to the tuberculosis theory but suggests that other infections in addition to tuberculosis may play a part.

4. The fourth suggests that simple pneumoconiosis is due to the retention of coal dust (as in Nos. 2 and 3), and that P.M.F. is a reaction to an excessive amount of dust in the lungs.

No one in any country believes that the problem of the aetiology is solved, and there is considerable healthy disagreement about the relative probabilities of the various theories in the various countries. All observers would probably agree that, when the simple pneumoconiosis consists pathologically of "classical" silicotic nodules, "P.M.F." as seen radiologically, is probably due to aggregation of the nodules. This type of simple pneumoconiosis is, however, becoming rare amongst European coal-miners, particularly in Great Britain, and few would suggest that the silica theory explains all cases of P.M.F. As a result the second silica theory is considered more probable in France, Belgium, and Germany.

Similarly, most people believe that tuberculosis plays some part in the aetiology of P.M.F., but many fewer believe it to be the only factor (in addition to coal dust). The popularity of this theory is greatest in this country and least in Germany and France, with Belgium in an intermediary position.

In the light of these theories, the various sources of evidence can be reviewed.

Histology.—The different interpretations placed on apparently similar pathological material by the British and German schools should theoretically perhaps prevent one from arguing either way from this particular type of evidence. It does, however, appear possible that pathologists in Germany see a much higher proportion of true silicotics among miners than those in Great Britain, so that we can quote the outstanding work of the Cardiff "School" in favour of the second (tuberculosis modified by dust) hypothesis so far as British coal-miners are concerned (Gough, 1947).

Bacteriology.—The bacteriological findings have recently been reviewed by Thomson and Rivers (1956). Their review shows that their findings are compatible with either late secondary infection with tubercle bacilli or with a tuberculous aetiology of the condition, with the bacilli dying off in many cases.

Radiology.—The x-ray examination of early coalescent shadows shows the extreme difficulty of separating them in a reproducible way into tuberculous and P.M.F. shadows. Alternatively, one can say that there is, radiologically, a complete and continuous spectrum running from typical adult type tuberculosis to typical P.M.F.

Mantoux Testing.—Cases of simple pneumoconiosis which were Mantoux-negative have been described by Hart and Aslett (1942), and we have seen them ourselves. We have never seen a case of P.M.F. which was Mantoux-negative, but the age group concerned makes this finding of limited importance. The one published case of a coal-miner who had P.M.F. and a negative Mantoux test (Friedman, 1955) was shown to be a case of classical silicosis (J. Gough, personal communication, 1955).

Chemistry.—Analyses for coal and free silica have been carried out on a number of lungs of miners who had pneumoconiosis. So far, the numbers involved and the methods of selection used make it dangerous to generalize, but the preliminary results do suggest that cases of P.M.F. contain more coal dust than cases of simple pneumoconiosis.

Epidemiology.—Epidemiological methods have shown (a) that both the appearance and the progression rate of P.M.F. can occur in the absence of further dust exposure, while simple pneumoconiosis does not appear to progress in the absence of further dust exposure; (b) that those attacked by both P.M.F. and tuberculosis are similarly asthenic; (c) that the preliminary findings in this investigation are at least compatible with a tuberculous aetiology of P.M.F.; and (d) that exposure to coal dust profoundly modifies the natural history of tuberculosis.

Animal Work.—Because animals have a very different reaction to both coal dust and tuberculosis from that of man, it is in general improbable that this would be a very useful line of approach; but work has shown that coal dust modifies the animal's reaction to tuberculous infection (Cummins, 1940), and King (1956), using tubercle bacilli resistant to isoniazid, has produced a lesion in animals for which some similarity to P.M.F. is claimed.

Returning now to the hypotheses, we can say that the first silica hypothesis would be attractively simple if the massive fibrosis were surrounded by typical silicotic nodules. This is, however, not our experience. W. R. L. James (personal communication, 1955) found that the same percentage of cases of P.M.F. show a few silicotic nodules in the associated simple pneumoconiosis as do cases of simple pneumoconiosis without P.M.F.

Both silica theories have, in any case, great difficulty in explaining the epidemiological findings, particularly the rate of appearance and progression of P.M.F. being similar in and out of mining. The only way out of the difficulty is to postulate some threshold of silica dosage in the lung above which no increase in silica causes an increased attack rate. However, if this were so, we would expect those with the greatest silica exposure to be more liable to be attacked by P.M.F. An investigation by one of us, however, failed to confirm this (Cochrane, 1954). The appearance of lesions

identical with P.M.F. in industrial workers exposed to dust in which no silica could be found is powerful evidence against the silica hypothesis (Jaffe, 1951; Rüttner *et al.*, 1952).

The tuberculosis theories do explain most of the available facts, but there are two difficulties which prevent its general acceptance: (1) It is superficially surprising that more than half the cases of P.M.F. are negative for tubercle bacilli at necropsy (James, 1954), but it is probable that a similar percentage of known tubercle cases are similarly negative at necropsy. It is, however, more surprising that cases which have been radiologically rapidly progressive up to the time of death should show no sign of tuberculosis at necropsy. In such cases tuberculosis may have been the "trigger" process which started it all off, but it cannot be held responsible for the progression. Such cases are admittedly rare but are clearly important. (2) The increased attack rate of tuberculosis on the background of categories 2 and 3 simple pneumoconiosis is much more easily explained on the silica hypothesis, as silica has been shown, at any rate in animals, to increase the attack rate of tuberculosis (Vorwald and Delahant, 1938). It can, on the other hand, be argued that the presence of so much dust must inevitably reduce tissue resistance.

The third theory is difficult to exclude. All adults suffer from so many upper respiratory infections that it is difficult to prove that they are not related to P.M.F. It is, on the other hand, a matter of frequent observation that men with simple pneumoconiosis may develop pneumonic shadows on their x-rays which later disappear, leaving no trace of P.M.F.

The fourth theory has superficially little to support it, but it may become more important if the preliminary finding that cases of P.M.F. contain more coal dust than cases of simple pneumoconiosis is confirmed.

On the present evidence it seems reasonable to conclude that a certain proportion of P.M.F. cases are tuberculous in origin, although a great deal more information is needed to clear up all the mechanism of the appearance and progression of the lesions from a theoretical point of view.

From a practical point of view the situation is much simpler. It would be correct to wait for more definite information if the action required were expensive and, apart from the prevention of P.M.F., of no other value to the community. For instance, the results might have suggested the use of very expensive masks. The elimination of tuberculosis would, on the other hand, be of the greatest value to the community as a whole and would probably produce, even from the economic point of view, a valuable national saving in return for the money invested. This would, of course, supplement, not replace, the efforts to suppress coal dust which the National Coal Board are already making.

Summary

Of the various hypotheses about the aetiology of progressive massive fibrosis, the only one that can be conveniently investigated epidemiologically is that suggesting that P.M.F. is caused by tuberculous infection in lungs with simple pneumoconiosis. This is being investigated by comparing the rate of appearance of P.M.F. in two areas, in one of which everything possible has been done to reduce tuberculous infectivity.

The two areas have been surveyed again after an interval of 2½ years and the children have again been Mantoux-tested. A significant fall in Mantoux positivity was found in the experimental area but not in the control area. The rate of appearance of P.M.F. was also lower in the experimental area than in the control area, but the difference could have occurred by chance in 17% of such experiments.

The effect of various other factors on the attack rate of P.M.F. was also investigated.

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The third number of the *Bulletin of the International Corresponding Club (Preventive and Social Medicine)* appeared early this year. It is available to non-members (obtainable from the Department of Social and Industrial Medicine, The University, Sheffield, 10, price 5s.). The aim of the Club is to have a corresponding member in as many departments of preventive and social medicine as possible which are actively doing teaching and research. At present there are 42 members from 15 countries. Membership costs 10s. a year, and the bulletin is published twice a year, from Sheffield and Cornell alternately. Among the reports from members is the news from Queen's University, Belfast, that a generous grant from the Nuffield Foundation has made possible an extension of the department's genetic research on populations. Among schemes organized by the Social Medicine Unit at Oxford is a retrospective survey of all children in England, Scotland, and Wales who have recently died either of leukaemia or of malignant disease, work on which began last November. The aim of the survey is to obtain details about the social pathology of the disease and whether its incidence is related to x-ray diagnostic and therapeutic procedures.

MEGALOBlastic ANAEMIA OF INFANCY IN KWASHIORKOR AND OTHER DISEASES

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Megaloblastic anaemia in infancy has been thoroughly reviewed by Zuelzer and Rutzky (1953), who believe that most cases develop as a result of severe infection or malnutrition; a few of their cases occurred in negroes (4 out of 59). Although a similar picture has been described in African infants no large series has been reported. Altmann and Murray (1948) found macrocytosis in only some of their cases, while Wills did not find any true megaloblasts in the bone marrow of the 36 cases of malignant malnutrition (kwashiorkor) recorded by Walt *et al.* (1950). In East Africa, Trowell (1949) had similar results, but in 1954 Adams reported two cases in patients with kwashiorkor.

We also believed megaloblastic anaemia of infancy to be a rare disease until 1953, when megaloblasts were recognized by one of us (S. H.) in the peripheral blood smears of some six patients with anaemia. Because of this a fuller investigation was instituted in 1954, and its results are reported here.

Material and Methods

The period of this investigation ran from February 17, 1954, to February 7, 1955, during which time 776 patients were admitted to the paediatric wards of the McCord Zulu Hospital. Children up to the age of 10 years are accepted in these wards, although the majority are under 3 years. A small daily hospital fee is charged, making this group somewhat selective, as free hospital care is available in Durban to those who wish to use it. About 90% of the patients admitted are of Bantu extraction, while Asiatic and Coloured (mulatto) make up the other 10%. Almost all come from very poor homes where sanitation is bad, poverty and ignorance are rife, and superstition flourishes, causing undernutrition and recurrent infections. The infants are usually breast-fed to begin with and are weaned on to maize porridge with very little milk or first-class protein; they may receive a little vegetable and sugar, and if milk is used it is usually well diluted. All patients with a suggestive clinical picture or with a haemoglobin level of less than 6.7 g./100 ml. were subjected to aspiration of bone marrow from the iliac crest as described by Rubinstein (1950). Later, local analgesia has not been used and no difficulties or complications have been encountered. The haemoglobin of 6.7 g./100 ml. was arbitrarily arrived at in 1953, when the first cases were discovered, and has served us well.

A megaloblastic bone marrow was found in 42 cases, 40 being African (Bantu), one Asiatic, and one Coloured. Of

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