# Papers and Originals

## Emphysema in Coal Workers' Pneumoconiosis

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**Summary: A correlation survey has been carried out between the pathological, physiological, and radiological findings pertaining to emphysema in 247 deceased coal miners and ex-miners, most of whom had been diagnosed as suffering from coal workers' pneumoconiosis during life. The pathological findings, which included large lung sections and detailed histology in every case, were compared with similar findings in a contrast non-mining population matched for age and sex.**

**The results indicated that emphysema was much more common among the coal miners, both with simple and with complicated pneumoconiosis, than among the contrast group. In addition the extent of the emphysema as measured by a recognized "counting" method carried out on paper-mounted lung sections was remarkably closely related to ventilatory impairment as evidenced by the forced expiratory volume in one second.**

**Extensive emphysema was more commonly found in those pneumoconiosis cases, both simple and complicated, showing the finer punctiform type of radiological change than in cases showing the larger micronodular and nodular opacities.**

### Introduction

Most workers in the pathological field of coal workers' pneumoconiosis have reported the finding of emphysema in significant degree, in both the complicated and the simple varieties, the presence of which they attributed to the disease (Gough, 1940: Gooding, 1946; Heppleston, 1947, 1954; Gough *et al.*, 1949; Duguid and Lambert, 1964). Though the precise role of this emphysema in terms of pulmonary malfunction has never been established, it has been generally accepted that it makes at least some contribution to any disability arising directly from the pneumoconiosis.

Recently, however, these concepts have been questioned and doubts have been expressed concerning the significance of such emphysema and the part played by pneumoconiosis in producing it. Reports from Chicago (Snider *et al.*, 1962), from Britain (Heard and Izukawa, 1964), and from other workers who found comparatively substantial degrees of often symptomless emphysema among the general population, have no doubt contributed to this.

Lynne Reid (1967), for instance, is not satisfied that the emphysema accompanying simple pneumoconiosis is due to the effects of coal dust, and she goes on to suggest that centri-acinar emphysema (in which she includes both the focal and the centrilobular varieties) may not be a cause of disability or airways obstruction.

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In addition the special committee set up by the Medical Research Council (1966) to investigate the role of occupation in the aetiology of chronic bronchitis and emphysema was unable on the present evidence to report that intensity of dust exposure was a significant factor in determining the prevalence of these diseases in coal workers. It should be pointed out, however, that this body was reporting on the combined disease of chronic bronchitis and emphysema rather than emphysema itself.

At a symposium in Birmingham in 1967, where these questions were discussed in some detail by a gathering of eminent pathologists and clinicians, Fletcher (1968) pointed out the necessity of obtaining relevant necropsy material on a large number of people who have had adequate physiological studies carried out during life. He also referred to the desirability of comparing the total amounts of emphysema in mining and non-mining populations with a view to establishing whether an excess was present in the former.

The present study, which throws some light on these questions, is based on findings arising from a survey carried out jointly by the Pneumoconiosis Medical Panel, Cardiff, and the pathology department of the Cardiff Royal Infirmary with the assistance of the university department of medical statistics. This survey was designed to correlate clinical, pathological, and physiological findings during life with post-mortem findings in the lungs, including Gough sections in the same individuals.

### The Population

The survey studies a population of 247 coal miners and ex-miners who died between July 1965 and May 1967, all of whom at the time of death resided within a definitive area comprising most of East Glamorgan and centred about 15 miles (24 km.) north of Cardiff City. Virtually all had been examined by the panel on several occasions during life; most had been in receipt of benefit for pneumoconiosis under the Industrial Injuries Act, and a necropsy had been completed on all of them by the university department of pathology at the Cardiff Royal Infirmary. The Industrial Injuries Acts cover all patients certified as suffering from pneumoconiosis who worked in the coal-mining industry subsequent to 1948. All such cases in this study were, in accordance with normal panel procedure, re-examined at regular intervals of up to but not normally exceeding three years. Those certified under the old Workmen's Compensation Acts, all of whom would have left the coal-mining industry before 1948 and were not normally required to be re-examined after that date, were excluded from the investigation, as were any others not seen by the panel within four years of death. These latter consisted almost entirely of a very small number who had been given life assessments under the Industrial Injuries Acts, and thus, as in the former cases, recent ante-mortem examinations would not have been carried out. The small number of men, 20 in all, who had been refused compensation by the panel and who died within four years of their examination were also included in the study.

With these exceptions all the necropsies carried out on any former panel patient who had resided in the defined area are included. It is believed that these must include most of the deaths occurring in men certified as suffering from pneumoconiosis under the Industrial Injuries Act because under that Act it is necessary to advise the local coroner of the death of any patient receiving compensation, and, moreover, it is in the financial interest of the widow or other dependants to try to establish that the pneumoconiosis played a significant part in bringing about death.

Many of the deceased were working at the time of their last examination, some up to the time of their death, and in 23% of cases the pathologists considered pneumoconiosis to be a primary cause of death, often in combination with another respiratory disease, usually chronic bronchitis and/or emphysema. In a further 5% of cases, usually where death was due to a non-respiratory cause, pneumoconiosis was considered to have made a material contribution also.

A contrast population comprising men examined at necropsy in the same hospital and matched for age and sex was also studied. This material was selected from 1,000 consecutive necropsies at the Cardiff Royal Infirmary 1964-6 carried out on patients either dying in the hospital or referred there by the local coroner for necropsy; females and male coal miners were excluded, the remaining cases being grouped by decade and chosen at random to match by age each of the pneumoconiosis post-mortem cases. The contrast population therefore consisted of 247 male non-miners matched for age but in all other respects unselected by disease, occupation, or residence. Death was certified as due to respiratory disease in 47 (19%), to chronic lung disease mainly chronic bronchitis and/or emphysema in 29, and to acute respiratory disease usually pneumonia either primary or terminal in 18.

## Ante-mortem Examinations

Clinical, radiological, and physiological examinations were available for all the miners. These in the main were carried out on the same day, and in the cases in receipt of benefit for pneumoconiosis were repeated at regular intervals throughout their remaining life-time. The clinical examination consisted of a physical examination, with special emphasis on the chest and cardiovascular systems. Sputum examinations were carried out on many of the progressive massive fibrosis cases and serological investigation was made on some suspected rheumatoid cases.

All the chest radiographs were taken by an experienced panel of radiographers, and the current film was normally available at the time of the examination to aid the panel in its diagnosis and assessment. For the purposes of this investigation the last *x*-ray film taken in life in all of the cases of simple pneumoconiosis, and including early (category A) progressive massive fibrosis, was reread by a group of five experienced senior medical officers in such a way that every film was read twice independently and blindly by at least two of them. The *Standard International Classification of Radiographs of Pneumoconiosis* issued by the International Labour Office, Geneva (1958), was used by the readers. In this, the category of simple pneumoconiosis is graded as 0, 1, 2, or 3, according to the extent and distribution of the nodulation, and the category of complicated pneumoconiosis by the additional letters A, B, or C, according to the extent of the progressive massive fibrosis. In addition, the types p=punctiform (size up to 1·5 mm), m=micronodular (size 1·5 to 3 mm), n=nodular (size 3 to 10 mm) recommended by the above classification to indicate the size of the nodular opacities was also used whenever possible, though many of the films could not be so typed, positively, because the opacities were mixed, were not readily identifiable, or were obscured because of the presence of severe emphysema.

The final film in respect of the more advanced progressive massive fibrosis cases (categories B and C) was read by one of us (J.P.L.). When disparities between the readings arose a pooled reading based on most of the readings available was determined. Category 2 simple pneumoconiosis is generally regarded as the earliest radiological stage which indicates the presence of significant disease, and the Pneumoconiosis Medical Panels normally accept cases showing at least these changes for purposes of diagnosis and compensation, irrespective of whether or not respiratory disability is detected.

The physiology consisted of ventilatory capacity tests with the Poulton spirometer in standardized conditions. Forced vital capacity (F.V.C.) and forced expiratory volume in one second ($F.E.V._1$) were recorded. Most of the examinations were conducted by the same highly experienced technician who had regularly carried out standardization trials with the Pneumoconiosis Research Unit at Llandough.

## Necropsies

A standard necropsy was completed to determine the cause of death. In addition the left lung of all cases was fixed in inflation by bronchial infusion of formol saline. When fixed a sagittal slice was taken through the mid-section of this lung and mounted on paper sections by the method of Gough and Wentworth (1960). From the lateral cut surface of the remainder of each lung 10 cubic blocks of tissue, each about 1 in. (2·5 cm.) cube, were removed. These were selected by means of a transparent plastic grid divided into 1 in. (2·5 cm.) squares which were numbered randomly by using a table of random numbers. From each left main bronchus a transverse block was taken immediately proximal to the terminal division. Standard histological sections were prepared from these tissues stained with haematoxylin and eosin, and when necessary special stains were made for collagen, elastin, and reticulin.

The presence of emphysema is readily detectable in whole lung sections. The main types in relation to the lung lobule (which measures 1-2 cm. in diameter, and is the smallest component of lung surrounded by connective tissue septa) are as follows:

*Centrilobular.*—This type occurs in the general population; anatomically, it consists of destruction of middle orders of respiratory bronchioles.

*Panlobular.*—This type also occurs in the general population; anatomically the air spaces throughout the lobule are dilated.

*Focal Dust emphysema.*—An occupational variety which, like centrilobular emphysema, also affects the centres of the lobules and which may usually be identified by the relation of dust foci to the emphysema.

The emphysema in our cases was measured by the method of Ryder *et al.* (1969), using a transparent grid which divides the paper-mounted section into 10 equal radial segments. In each of these segments an assessment of the size and number of the emphysematous lesions was scored on a scale 0, 1, 2, or 3, and the score was aggregated for the 10 segments, making a total score from 0 to 30, with 30 the most severe degree of emphysema measurable. The assessment of emphysema used in this study is a simple measurement of the magnitude and extent of abnormal air spaces distal to the terminal bronchiole. We use the term focal dust emphysema to include not only the early stages of development of emphysema but also the advanced stages where the size of the emphysematous spaces and the loss of lung structure, whether seen microscopically or macroscopically, indicate tissue destruction. For instance, in a lobule of lung where little remains except a large emphysematous space surrounded and traversed by strands of tissue impregnated by dense dust, the term focal dust emphysema is still used because of the excess dust present and also, by inference, from comparison with adjacent areas of lung when these show earlier recognizable focal dust emphysematous lesions.

Within these terms the emphysema seen in the miners was predominantly focal in type, and in only a minority of them did readily recognizable panlobular or centrilobular emphysema occur, and when these did occur it was mainly in areas containing little or no dust.

Broadly, the incidence of centrilobular and that of panlobular emphysema in the contrast population were roughly equal, and in most cases showing emphysema the two forms usually coexisted, with one or other form commonly predominating. For example, cases of pure centrilobular or panlobular emphysema were not common. A small miscellaneous group of indeterminate paraseptal, subpleural, and irregular (scar) emphysema was recognized, again often associated with panlobular and centrilobular emphysema or both.

The lungs of the miners and the matched contrast population were randomized and read separately by one of us (R.R.), each on two different occasions, and the mean value was used. The method has been shown to have a high degree of reproducibility both between and within observers (Ryder *et al.*, 1969), with an average difference of about 1 unit on this scale of 0 to 30. All the pathological investigations, including the emphysema count, were carried out without any knowledge of the ante-mortem data.

## Results

The age at death of all the 247 miners in the study, separated into decades of age and classified according to the International Labour Office Classification of the final *x*-ray film taken before death, is given in Table I. Though 20 of these are shown as category 0 and 37 as category 1, this does not imply that these men had not had significant pneumoconiosis during life but that when the *x*-ray films were reread in the manner described above there was no evidence of a higher category of dust in these particular final *x*-ray films. In fact, 10 of the 20 category 0 and 27 of the 37 category 1 had been considered by the Pneumoconiosis Medical Panel to have had at least one *x*-ray film during life showing category 2 or more. Only four of the category 0 cases were considered to have shown no radiological evidence of pneumoconiosis whatever by all of the readers and by the members of the medical boards who had examined them during life.

There is no statistical significance between the mean age at death of the miners with the varying grades of pneumoconiosis; it should be noted that those miners with category A progressive massive fibrosis were rather older than those with more advanced disease or than those with simple uncomplicated pneumoconiosis.

The interval of time between the final *x*-ray film and the date of death (Table II) shows that 46 (19%) were seen within a year of death, 112 (45%) less than two years before death, and 191 (77%) within three years. The miners with simple pneumoconiosis seem to have died at a longer time after the last examination than those with progressive massive fibrosis, but this could be explained by the policy of the panel to recall the latter cases more often than simple cases.

The emphysema counts at death by each decade of age are shown in Tables III, IV, and V. In lungs with massive fibrosis the presence of this complication may prevent us making any assessment of emphysema in a number of radial segments; consequently we have examined those miners with *x*-ray evidence of category B and category C separately from those with category A or simple pneumoconiosis. The control population is shown in Table V. The mean emphysema count in each decade of age in all three groups is shown in Fig. 1.

The F.E.V.$_1$ in litres as measured at the last examination is shown tabulated by the radiological categories in Table VI and by the post-mortem emphysema counts in Table VII. The mean values of the F.E.V.$_1$ for each category are shown in Fig. 2 and the mean values for each level of severity of emphysema counts are shown in Fig. 3.

TABLE I.—*Miners seen by Pneumoconiosis Medical Panel. Radiological Classification by Age at Death*

| Age at Death | Simple Pneumoconiosis | | | Progressive Massive Fibrosis | | | Total |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2, 3 | A | B | C | |
| Under 50 | 2 | 7 | 3 | 2 | 2 | 3 | 19 |
| 50-59 | 6 | 6 | 10 | 8 | 18 | 16 | 64 |
| 60-69 | 8 | 17 | 17 | 15 | 28 | 18 | 103 |
| 70-79 | 4 | 7 | 7 | 18 | 11 | 12 | 59 |
| 80+ | | | 1 | 1 | | | 2 |
| Total cases | 20 | 37 | 38 | 44 | 59 | 49 | 247 |
| Mean age | 61·7 | 61·4 | 63·3 | 66·9 | 63·0 | 62·2 | 63·2 |

TABLE II.—*Miners seen by Pneumoconiosis Medical Panel. Time between Last x-ray Film and Death*

| Time between Last *x*-ray Film and Death | Simple Pneumoconiosis | | | Progressive Massive Fibrosis | | | Total |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2, 3 | A | B | C | |
| Less than 1 year | 5 | 5 | 8 | 7 | 14 | 7 | 46 |
| 1 year | 2 | 9 | 6 | 17 | 15 | 17 | 66 |
| 2 years | 6 | 7 | 15 | 12 | 19 | 20 | 79 |
| 3 years | 2 | 13 | 8 | 7 | 10 | 3 | 43 |
| 4 years or more* | 5 | 3 | 1 | 1 | 1 | 2 | 13 |

*These miners were all examined by the panel within four years, but the last *x*-ray film may have been taken a short time earlier.

TABLE III.—*Miners with Pneumoconiosis Category O to A. Age at Death and Emphysema Count*

| Age at Death | Emphysema Count | | | | | | | | Total | Mean Count |
|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1— | 5— | 10— | 15— | 20— | 25+ | N.K. | | |
| 35-49 | 2 | 2 | 5 | 2 | 1 | — | 2 | — | 14 | 10·4 |
| 50-59 | 3 | 3 | 6 | 10 | 3 | 3 | 2 | — | 30 | 11·4 |
| 60-69 | — | 9 | 12 | 11 | 8 | 13 | 4 | — | 57 | 13·5 |
| 70-79 | 2 | 3 | 8 | 11 | 6 | 3 | 2 | 1 | 36 | 11·9 |
| 80+ | — | — | — | 1 | 1 | — | — | — | 2 | — |
| Total | 7 | 17 | 31 | 35 | 19 | 19 | 10 | 1 | 139 | 12·3 |

TABLE IV.—*Miners with Pneumoconiosis Category B or C. Age at Death and Emphysema Count*

| Age at Death | Emphysema Count | | | | | | | | Total | Mean Count |
|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1— | 5— | 10— | 15— | 20— | 25+ | N.K. | | |
| 40-49 | — | — | 2 | 1 | 1 | — | — | 1 | 5 | 10·8 |
| 50-59 | 1 | 2 | 5 | 9 | 5 | 8 | 3 | 1 | 34 | 14·8 |
| 60-69 | — | 5 | 17 | 10 | 8 | 4 | 2 | — | 46 | 11·5 |
| 70-79 | — | 2 | 5 | 5 | 4 | 5 | 2 | — | 23 | 14·4 |
| 80+ | | | | | | | | | | |
| Total | 1 | 9 | 29 | 25 | 18 | 17 | 7 | 2 | 108 | 13·2 |

TABLE V.—*Contrast Population from Cardiff Royal Infirmary. Control Cases Without Pneumoconiosis. Age at Death and Emphysema Count*

| Age at Death | Emphysema Count | | | | | | | Total | Mean Count |
|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1— | 5— | 10— | 15— | 20— | 25+ | | |
| 35-49 | 11 | 6 | 1 | 1 | — | — | — | 19 | 1·9 |
| 50-59 | 19 | 26 | 13 | 5 | 1 | — | — | 64 | 3·6 |
| 60-69 | 17 | 36 | 24 | 13 | 6 | 4 | 3 | 103 | 6·7 |
| 70-79 | 11 | 17 | 12 | 10 | 3 | 6 | — | 59 | 7·3 |
| 80+ | | 1 | 1 | | | | | 2 | — |
| Total | 58 | 86 | 51 | 29 | 10 | 10 | 3 | 247 | 5·6 |

TABLE VI.—*Miners seen at Pneumoconiosis Panel. F.E.V.$_1$ and Radiology at Final Examination*

| F.E.V.$_1$ Litres | Simple Pneumoconiosis | | | Progressive Massive Fibrosis | | |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2, 3 | A | B | C |
| <1·0 | 4 | 9 | 3 | 5 | 17 | 12 |
| 1·0-1·4 | 6 | 2 | 10 | 10 | 12 | 19 |
| 1·5-1·9 | 4 | 7 | 10 | 10 | 14 | 15 |
| 2·0-2·4 | 3 | 11 | 10 | 9 | 11 | 2 |
| 2·5-2·9 | 2 | 6 | 2 | 9 | 4 | 1 |
| 3·0+ | 1 | 2 | 3 | 1 | 1 | — |

TABLE VII.—*Miners seen at Pneumoconiosis Medical Panel. F.E.V.$_1$ at Final Examination and Emphysema Count at Necropsy*

| F.E.V.$_1$ Litres | Emphysema Count | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1— | 5— | 10— | 15— | 20— | 25+ | N.K. | |
| <1 .. .. | | 2 | 7 | 10 | 9 | 17 | 5 | | 50 |
| 1·0-1·4 .. | | 5 | 14 | 14 | 8 | 10 | 8 | | 59 |
| 1·5-1·9 .. | 1 | 5 | 13 | 17 | 12 | 6 | 4 | 2 | 60 |
| 2·0-2·4 .. | 3 | 7 | 11 | 15 | 7 | 2 | | 1 | 46 |
| 2·5-2·9 .. | 3 | 5 | 11 | 4 | 1 | — | | | 24 |
| 3·0+ .. | 1 | 2 | 4 | — | — | 1 | | | 8 |

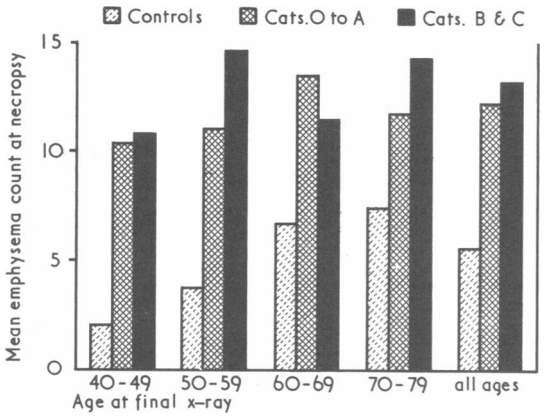


FIG. 1.—Mean emphysema count at necropsy for each decade of age.

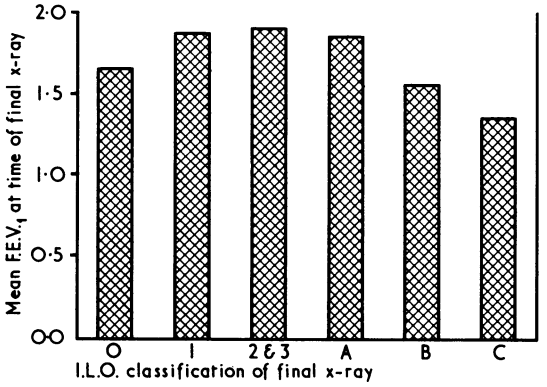


FIG. 2.—Mean F.E.V.$_1$ at final *x*-ray examination by I.L.O. classification of radiological pneumoconiosis.

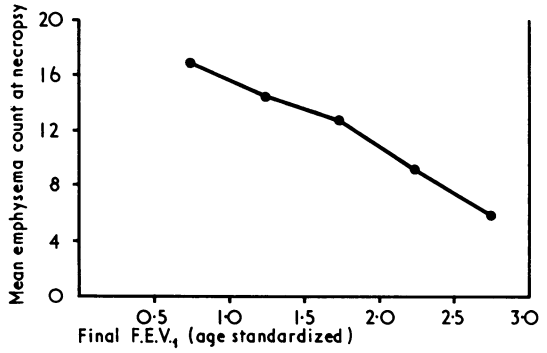


FIG. 3.—Mean emphysema count at necropsy by F.E.V.$_1$ at final *x*-ray examination (age standardized).

## Discussion

The population under study was selected at two stages; first by attendance at the Pneumoconiosis Medical Panel, and secondly by death. We do not believe that there can be a substantial group of miners in South Wales with undiagnosed compensatable pneumoconiosis at the present time. The National Coal Board, in the implementation of their periodic *x*-ray scheme, have surveyed the whole coal field at regular intervals, and it is their normal practice to advise any case showing radiological changes amounting to category 2 or more to apply to the panel for examination irrespective of the presence or otherwise of respiratory disability. For example, out of 9,842 men from 14 South Wales pits who were *x*-rayed under this scheme during 1964, 1,234 were considered to have compensatable pneumoconiosis, but 1,164 of these had already been certified by the panels. Also, as a result of the findings of the N.C.B. periodic *x*-ray surveys during 1965-7 inclusive, 254 cases from 30 collieries were advised to apply to the Cardiff Panel for examination, and at the time of writing at least 225 of them (92%) had done so. For these reasons we believe that our population can be considered to be reasonably representative of miners and ex-miners with pneumoconiosis in the area concerned.

A panel group such as ours has the advantage, not given to many other groups of coal miners so studied, of including the most disabled victims of the disease, such as the house-bound and the hospitalized cases, together with the drop-outs from the industry because of the disease. Once a man has been accepted for purposes of compensation by the Pneumoconiosis Medical Panel he is usually re-examined at regular intervals during his remaining life-time.

In addition to the above, the problems of dealing with possible bias in a population selected by death are always severe. This population of miners is, however, almost a complete sample of all deaths occurring in men with certified pneumoconiosis in a defined area and over a defined period of time. The disease has been prevalent for many years in the area. Coal workers' pneumoconiosis in itself in its earlier stages may not greatly influence mortality, though it can be disabling, especially in the more severe forms, and consequently there is no reason why these deaths should not provide a true sample of the experience of men with the disease. The contrast population is also a consecutive series of necropsies done on men in a teaching hospital unselected for any disease factor and from which only miners were excluded, hence they should give some evidence of the distribution of emphysema in non-miners during the terminal stages of their life.

Without broaching the question of the relationship between coal dust and emphysema and whether focal dust emphysema is or is not a distinct entity, it is clear from Tables III, IV, and V and Fig. 1 that there is a pronounced difference in the total amount of emphysema seen in the miners compared with the contrast group. In the contrast group there is a steady progression of the morbidity with age, the mean level increasing from about 4 in the fifth decade of life to about 9 in the eighth decade. The mean level among the miners with simple pneumoconiosis is never below 10 at any period and shows slight progress with age. In the miners with advanced progressive massive fibrosis there is surprisingly little further increase in the mean level compared with the simple pneumoconiosis; but it is probably mainly due to an artifact that it was not possible to count emphysema where the lung was completely fibrosed, and in these men the pattern of the mean emphysema score fluctuates between 10·7 and 14·7 with only a slight age trend.

The failure of the mean emphysema score in men with pneumoconiosis to increase with age is probably due to the progression of the fibrosis in these severe cases producing an apparent compensating decrease in the score as men move with age into the more severe forms of progressive massive fibrosis. This effect could, however, only have been to reduce the apparent score and hence to obscure any real differences present. Also it seems reasonable to suppose that the younger pneumoconiosis cases with the more severe degree of emphysema may have a lower incidence of survival into the higher age groups.

The smoking history of the contrast population is not available, but there should be no reason why they should have a lighter smoking experience in life than the miners, who are, of course, precluded from smoking when underground.

It is shown in Fig. 2 that there is little correlation between pulmonary function tests and radiological categories of *x*-ray films in simple pneumoconiosis up to and including category A of progressive massive fibrosis; it is only when the more advanced forms of progressive massive fibrosis intervene that a relationship becomes established. This is somewhat similar to the experience reported by Cochrane *et al.* (1961) when they used indirect maximum breathing capacity and concluded that there was little significant loss of function due to pneumoconiosis demonstrable until progressive massive fibrosis exceeded 20 sq. cm. In the present cases, though most of them do show impairment of ventilation, this again does not correlate with the radiological category until the development of progressive massive fibrosis category B.

This experience is in complete contrast to Fig. 3, where there is a strong correlation ($r=0{\cdot}74$) between the $F.E.V._{\cdot1}$ at the final examination and the emphysema count after death; not only is there a good correlation but there is a linear relationship over the whole range, so that the lower the $F.E.V._{\cdot1}$ was in life the greater was the emphysema score at death.

It is thus clear that the impairment of pulmonary function is closely related to the emphysematous changes. We have also data for the F.V.C. and for the F.E.V./F.V.C. ratio, which will be published later when the interrelationship between impairment of ventilation and pathological and radiological findings in coal workers' pneumoconiosis in the present survey will be discussed; but it can be said here that these results confirm that the impairment is largely obstructive in nature and in keeping with the presence of emphysema.

An interesting finding in this study is that those miners presenting with punctiform type of dust markings showed a higher excess of emphysema compared with the micronodular and the nodular types. These results are shown in Tables VIII and IX and the mean values of the emphysema count by type of opacity are seen in Fig. 4. This finding occurred both in simple pneumoconiosis and in the complicated cases, (Fig. 5) and was confirmed by an associated fall in the ventilatory capacity both at the last examination before death and at previous examinations—which indicates that those with the finer dust changes are more disabled than those with the coarser types, and it is tempting to attribute this to an increasing severity of emphysema (Figs. 6-9).

There may be a tendency in this survey or any other to place those *x*-ray films with the fine p type changes in a

TABLE VIII.—*Miners seen by Pneumoconiosis Medical Panel. Category of Pneumoconiosis and Type of Dust Reticulation*

| Type of Dust Opacity Qualitative Features | Category | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2, 3 | A | B | C | |
| Punctate | — | 9 | 5 | 11 | 5 | 3 | 33 |
| Micronodular | — | 12 | 29 | 8 | 8 | 1 | 58 |
| Nodular | — | 1 | 4 | 4 | 8 | 1 | 18 |
| Not typed | 20 | 15* | — | 21 | 38 | 44 | 138* |

*One patient was classified as type Z. One patient was classified as type L.

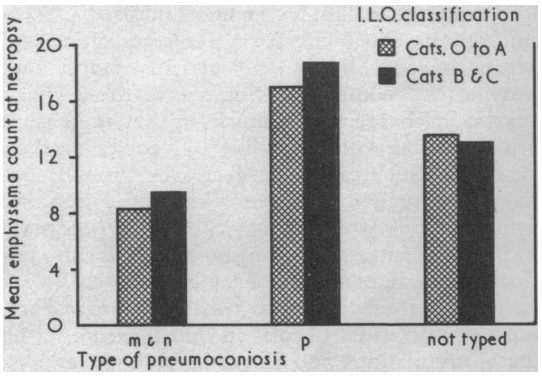


FIG. 4.—Mean emphysema count by type of opacity on final *x*-ray film.

TABLE IX.—*Miners seen by Pneumoconiosis Medical Panel. Type of Dust Reticulation at Last x-ray Examination and Emphysema Score at Necropsy*

| Type of Dust Opacity Qualitative Features | Emphysema Count | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1— | 5— | 10— | 15— | 20— | 25+ | N.K. | |
| Punctate | — | — | 4 | 5 | 13 | 4 | 7 | — | 33 |
| Micronodular | 6 | 10 | 19 | 12 | 4 | 4 | 1 | 2 | 58 |
| Nodular | — | 3 | 8 | 4 | — | — | 2 | 1 | 18 |
| Not typed | 2 | 13 | 29 | 39 | 20 | 28 | 7 | — | 138* |

*One patient was classified as type Z. One patient was classified as type L.

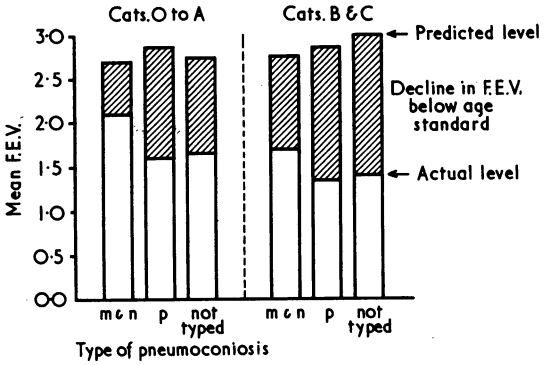


FIG. 5.—Mean $F.E.V._{\cdot1}$ actual and predicted (Cotes, 1965) for age by category and type of radiological pneumoconiosis.

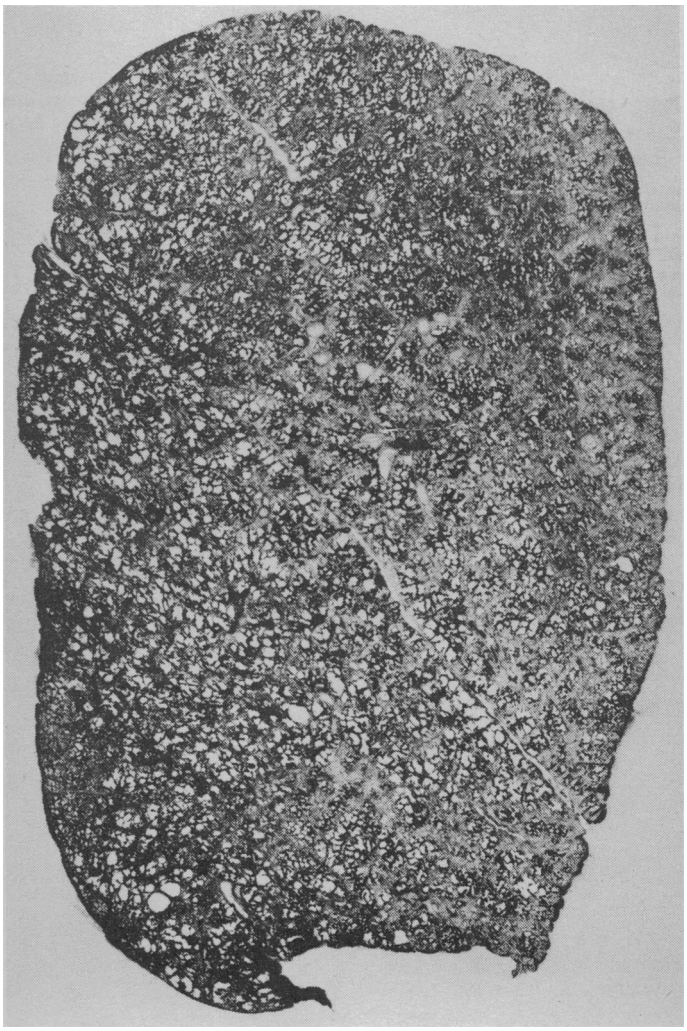

FIG. 6.—Simple pneumoconiosis with extensive emphysema and severe impairment of ventilation. Radiologically categorized variously as 1, 2p, and 3p.

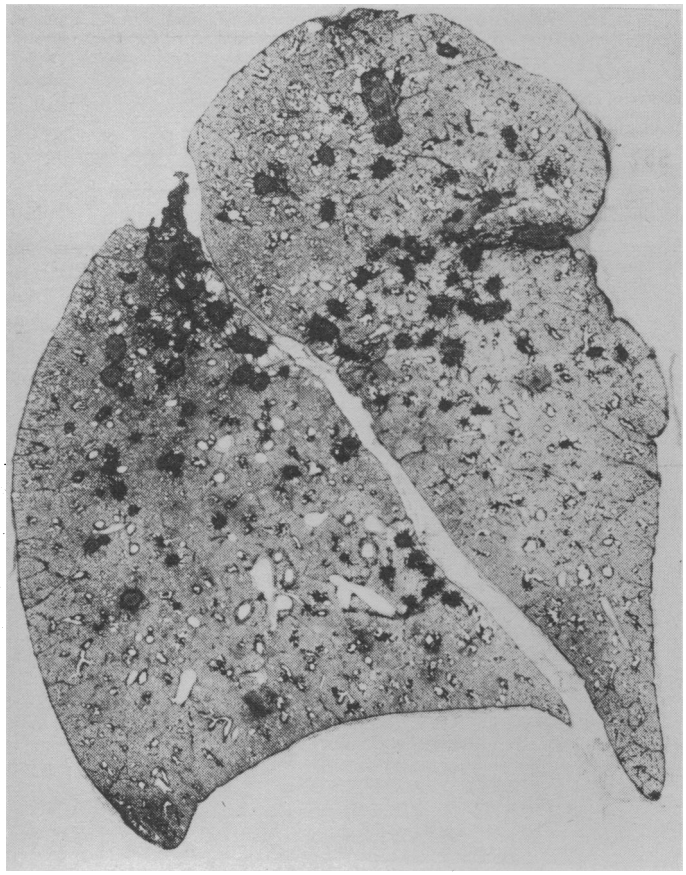

FIG. 7.—Nodular (Caplan type) pneumoconiosis. No emphysema, no impairment of ventilation. Radiologically categorized as n3 or n3A.

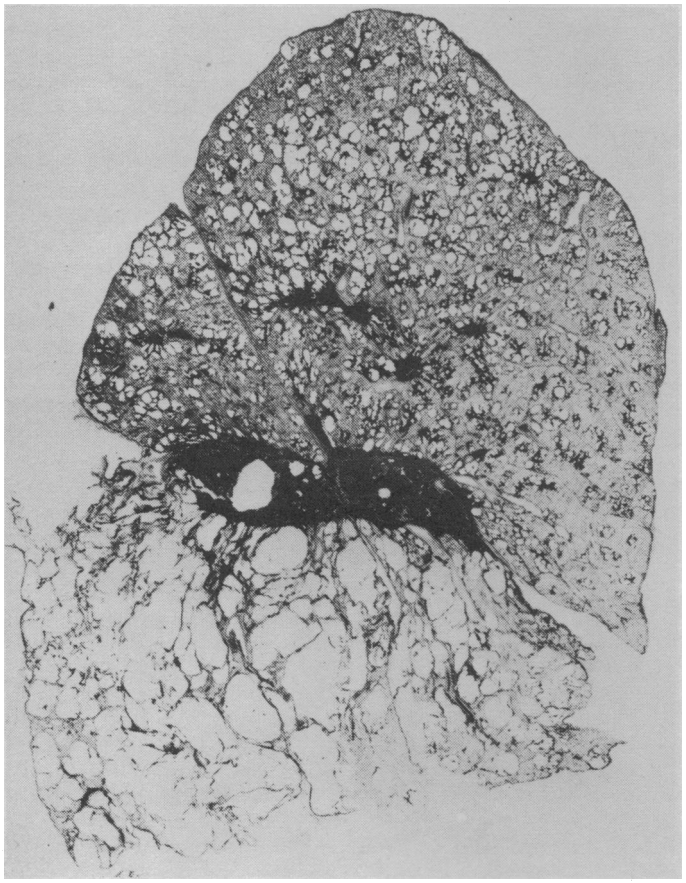

FIG. 8.—Complicated pneumoconiosis with severe emphysema and pronounced impairment of ventilation. Radiologically categorized as B (bilateral progressive massive fibrosis).

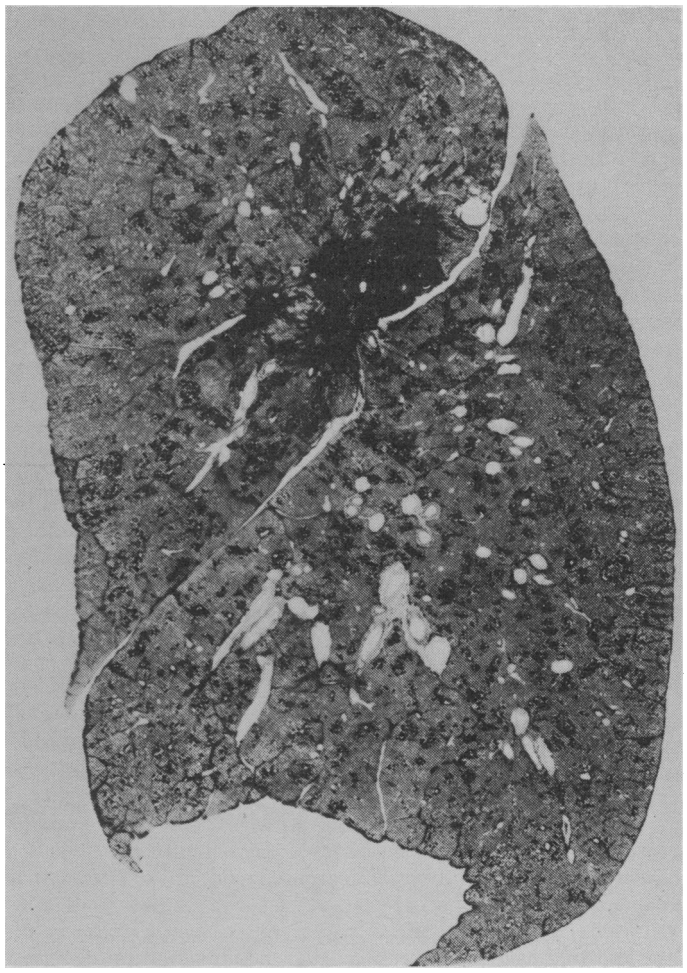

FIG. 9.—Complicated pneumoconiosis. No emphysema—no impairment of ventilation. Categorized radiologically B (with bilateral progressive massive fibrosis).

lower category than would be warranted either by the total dust in the lung or the total numbers of nodules found at necropsy. These finer nodules do not appear to be as striking as in the larger coarse n type of opacity, and this contrast may be further emphasized by emphysema in the surrounding lung or by a flat *x*-ray film; also the present International Labour Office Radiological Classification places emphasis on the size and distribution of the nodules rather than on the total numbers present. For these reasons films with the finer and less obvious nodulation may be placed in lower numerical radiological categories than those with the larger, more obvious, but not necessarily more numerous ones (Figs. 6-9). If, as is suggested by our findings, emphysema and impairment of ventilation are more likely to be associated with the p type changes, this might explain some of the difficulties experienced hitherto in correlating disability with radiological changes in simple pneumoconiosis.

Pneumoconiosis cases with p type changes often have varying degrees of fine linear and reticular type shadowing accompanying the nodulation. Sometimes these changes are almost cystic in character—so much so that the case may be diagnosed as one of fibrosing alveolitis rather than pneumoconiosis. Such cases, however, can normally be distinguished by the predominance of fine nodulation, which is always present and which, contrary to the changes usually seen in idiopathic interstitial fibrosis, often start in and nearly always include the upper zones of the lungs.

Clinically also, these cases are usually distinguishable from most forms of interstitial fibrosis in that they do not have the coarse basal crepitations and finger-clubbing often associated with these conditions, and though impairment of the transfer factor may be present in some of the pneumoconiosis cases

(Lyons *et al.*, 1967), this could well be due to the emphysema.

Nevertheless, the pathogenesis and detailed pathological features of the fine type of coal workers' pneumoconiosis may not be identical with those showing the coarser changes. It is already known, for instance, that many cases of simple pneumoconiosis with coarse nodulation have been shown to be rheumatoid in origin and thus have characteristic pathological features of their own (Caplan, 1953). Certainly the parenchyma adjacent to the nodules is more extensively involved in the former cases than in those with the coarser changes, and it may be that this difference is not solely due to the emphysema (compare Figs. 6 and 7). This aspect, which is very important, will be the focus of further study of the material, as will the findings relating to bronchitis.

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# Tissue Matching and Early Rejection of Cadaveric-Donor Renal Allografts: The Importance of Unidentified Donor Antigens

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**Summary: Tissue typing has been reviewed in a series of 100 technically successful cadaveric-donor kidney grafts. The criterion of transplant failure was immunological rejection causing total loss of function within three months of operation.**

**No significant correlation was observed between matching grade and graft failure due to early acute rejection. This is attributed to the failure to detect at least one "LA" or "4" antigen (as defined in our laboratory), representing a potential incompatibility, in 89% of the grafts, and in the remaining 11% to the lack of an available recipient with identical "LA" and "4" typing. Undetected antigens on the donor are usually incompatible, and probably these incompatibilities unfavourably influence early graft survival.**

**If the results of cadaveric-donor renal transplantation are to equal those of transplantation from well-matched living related donors it will be necessary to type with sera which can recognize individually all HL-A antigens, including those not yet identified, and to create an international pool of over 1,000 potential recipients.**

## Introduction

Since grafts exchanged between two siblings with an identical HL-A genotype are subject to a degree of rejection little greater than that occurring in transplants between identical twins (Stickel *et al.*, 1967), there can be little doubt that HL-A or a closely adjacent locus carries the most important genetic determinants for histocompatibility in man. That HL-A is indeed the major locus is confirmed by the demonstration that preimmunization of a recipient with cells carrying foreign HL-A antigens will cause accelerated rejection of a subsequent graft from a donor with these antigens (Dausset *et al.*, 1965; van Rood *et al.*, 1965; Kissmeyer-Nielsen *et al.*, 1966; Terasaki *et al.*, 1968; Patel and Terasaki, 1969; Stewart *et al.*, 1969), that purified preparations of soluble HL-A antigens can stimulate lymphocytes in culture (Viza *et al.*, 1968), and that donor-specific HL-A antibodies appear in patients at the time of rejection of renal allografts (Manzler, 1968; Morris *et al.*, 1969). When transplants are exchanged between unrelated donor-recipient pairs, however, it is not always possible to show a correlation between HL-A matching and early acceptance or rejection of renal allografts (Patel *et al.*, 1968).

Tissue matching has been used in Sydney for recipient selection in a city-wide collaborative programme of cadaveric-donor renal transplantation since 1967 (Sheil *et al.*, 1969). One-sixth of the grafts in this series underwent early acute rejection, but these rejections could not have been predicted from the tissue typing data obtained. This report analyses the incomplete nature of HL-A typing as at present carried out in a clinical laboratory.

## Methods

The analysis is based on 100 technically successful renal allotransplantations carried out between March 1968 and September 1969, and followed for at least three months after operation. Another 16 transplantations carried out in the same period have been excluded because of inadequate typing of the donor (four cases) or graft failure or death during the first two months due to causes other than rejection. Standard methods were used for clinical procedures and for immunosuppression (Sheil *et al.*, 1968; Tracy *et al.*, 1969). The diagnosis of rejection was confirmed by demonstration of

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