OBSERVATIONS ON

THE NATURAL HISTORY OF ASBESTOSIS

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CONTENTS

INTRODUCTION

It is widely believed that asbestosis is a progressive form of pulmonary fibrosis carrying a poor prognosis.

A review of the literature provided a considerable amount of information about the mortality experience of asbestos exposed workforces but very little information on the mortality of clinical cases of asbestosis.

The literature relating to the clinical course of asbestosis was even more scanty and no systematic study was found which attempted to describe the progression of the intrapulmonary fibrosis.

In an attempt to provide information in these areas it was decided to follow up cases of asbestosis diagnosed by the London Pneumoconiosis Medical Panel between 1968 and 1974 which were seen at the Brompton Hospital at the time of certification.

The data has been used to describe:-

(1) The characteristics of cases of asbestosis diagnosed by the London Pneumoconiosis Medical Panel.

(2) The mortality experience of these cases and the factors associated with an adverse effect on mortality.

(3) The progression of the intrapulmonary fibrosis and the factors associated with progressive fibrosis.

It was found that in many cases the intrapulmonary fibrosis became arrested. If this observation is correct it raises interesting questions about why the fibrosing process should cease particularly if inhaled asbestos fibre is its immediate cause.

An attempt has been made to discuss the possible implications of this observation in the pathogenesis of asbestosis.

REVIEW OF THE LITERATURE

The heat resistant properties of asbestos have been known for over 2000 years and Pliny the Younger (61-114 AD) is said to have commented on the sickness of the slaves who worked with it but the modern exploitation of asbestos only began in the late 1870's.

The identification of the relationship between pulmonary fibrosis and asbestos exposure

The first known case of asbestosis was seen in 1899 by Montague Murray (1907) and he reported his findings to the Departmental Committee on Compensation for Industrial Diseases in 1906. His patient was a man of 33 who had worked in the asbestos industry for 14 years, the first 10 being spent in the carding room which the patient said was the most risky part of the work. Of the 10 men working in the room when he started he was the only survivor, the others having died around the age of 30. When he was seen by Montague Murray he was found to have marked pulmonary fibrosis but no evidence of pulmonary tuberculosis. He died in 1900 and at post mortem was found the have diffuse pulmonary fibrosis particularly affecting the lower parts of the lung. Spicules of asbestos were seen on microscopic examination of the lung. The Departmental Committee was unable to obtain evidence of additional cases but in the same year Auribault (1906) reported a high mortality rate in a French asbestos

textile factory and considered it likely to be a consequence of exposure to asbestos dust.

In 1910 a survey of the asbestos industry by the British Factory Department published in the Annual Report of the Chief Inspector for Factories and Workshops for 1910 (1911) found no evidence of a serious health hazard but in 1912 at the request of the Home Office J.M. Beattie conducted some experiments on guinea pigs and concluded that the inhalation of asbestos dust caused a mild degree of fibrosis (Royal Commission on Metalliferous Mines and Quarries, 1914). Little then happened until 1924 when Cooke (1924) reported the death of a 33 year old asbestos worker with pulmonary tuberculosis and a diffuse pulmonary fibrosis which he attributed to asbestos exposure. The case was more fully reported in 1927 (Cooke 1927) when McDonald (1927) made the first detailed description of asbestos bodies in the lung of Cooke's case. McDonald was convinced that these bodies originated from the asbestos dust.

In 1928 Seiler described an asbestos worker with diffuse pulmonary fibrosis and no evidence of tuberculosis. Full investigation failed to reveal a cause for the fibrosis other then asbestos exposure. At this stage the Factory Department set up a comprehensive investigation of the asbestos industry in the United Kingdom which lead to the "Report on Effects of Asbestos Dust on the Lungs" by Merewether and Price (1930).

At the time of this investigation it was estimated that 2,200 persons were exposed to the inhalation of asbestos in their daily work. A sample of 363 workers was examined and 95 (26.2%) showed definite evidence of fibrosis. Furthermore the prevalence of fibrosis increased with the duration and intensity of exposure to asbestos dust. No cases were seen among those with less than five years exposure to dust. This exposure-response relationship was strong evidence for a cause and effect relationship between asbestos exposure and pulmonary fibrosis.

Early attempts to prevent asbestosis

The report of Merewether and Price (1930) lead to the Asbestos Industry Regulations (1931) which aimed to prevent the disease by controlling asbestos exposure. The regulations did not apply to all the uses of asbestos and in particular the insulation trade was not included in its provisions. Conditions in the factories improved and in 1946 Wyers presented a thesis "That legislative measures have proved generally effective in the control of asbestosis". Wyers was over optimistic but his study indicates that considerable improvements came about after the introduction of the 1931 regulations.

Asbestosis: The Clinical Disease

Asbestosis is a form of pulmonary fibrosis caused by the inhalation of asbestos fibre. There are no features of the disease which are specific for asbestosis and the diagnosis is made where pulmonary fibrosis is found in the presence of an appropriate exposure to asbestos. Other causes of pulmonary fibrosis should be excluded as far as possible.

The disease will be discussed under the following headings:-

(1) Asbestos exposure
(2) Symptoms
(3) Signs
(4) Radiology
(5) Physiology
(6) Immunology
(7) Pathology
(8) Prognosis (a) Progression of fibrosis
(b) Mortality
(9) Management

(1) Asbestos exposure

In order to develop asbestosis it is necessary to be exposed to airborne asbestos fibre. Merewether and Price (1930)

were the first to try and determine how much asbestos exposure was required to cause fibrosis. They found no case of asbestosis in heavily exposed workers with less than five years exposure but it should be pointed out that they were examining a working population. The most severely affected cases were likely to have given up work and if this happened it would lead to an underestimate of the prevalence of disease. If those most vulnerable to the effects of asbestos exposure developed disease within five years and had to leave the industry then such cases would also be underrepresented in a working population. Furthermore the effects of short exposures in those who left the industry some years earlier could not be assessed.

Merewether and Price appreciated these problems and noted that cases had been described by others with exposures as short as 12 months. They pointed out that five years exposure could not be assumed to be safe.

Wood (1929) reported 16 cases of asbestosis seen by him in East London and noted that their exposures ranged from 1-14 years. In a later review of their first 100 cases of asbestosis Wood and Gloyne (1934) found 3 cases with less than 12 months exposure and one case that presented 20 years after ceasing exposure.

Merewether (1933) put forward the view that given exposure to a "fibrosis producing amount" of asbestos

the disease would eventually develop after a "maturation period". The greater the exposure the shorter the maturation period would be. He also believed there was a"dust datum" below which level of exposure disease would not occur.

The Asbestos Industry Regulations (1931) sought to limit exposure to levels below the "dust datum" which was defined as "the conditions arising from flyer spinning carried out without exhaust under good general conditions". This hygiene standard was not defined in easily measurable terms and this must have lead to difficulties in its application. Nevertheless conditions in the industry undoubtedly improved and in a review of secular changes in one asbestos factory Smither (1965) showed that the average length of exposure required to cause disease had risen from 7 years in 1930-34 to 17.5 years in 1960-64.

It is clear from the above that the development of asbestosis is dependent on the duration and intensity of exposure. As intensity of exposure has diminished so the duration of exposure before disease develops has lengthened. Wood (1929) noted that disease might be recognised for the first time long after exposure had ceased and there is now little doubt that disease can develop after exposure has ceased (Becklake 1979). These observations are in keeping with Merewether's (1933) concept of a 'maturation' period before fibrosis manifests itself.

These observations are of only limited value to the clinician in deciding whether sufficient asbestos exposure has occured to cause pulmonary fibrosis and the evaluation of the exposure history can be very difficult. It is made easier when the physician is well acquainted with conditions in the different parts of the asbestos industry and when there is information about the incidence of disease in the different workplaces.

Recently attempts have been made to relate the development of asbestosis to measures of airborne asbestos dust and fibre. These will be reviewed later. Whilst they provide good data on which to base hygiene standards they are rarely available to help the clinician assess the exposure of individual workers.

(2) Symptoms of asbestosis

Wood (1929) in his report on 16 cases regarded breathlessness as the cardinal symptom and considered that it was usually progressive. Cough sometimes occurred but sputum production was not excessive and might be absent. He commented on wasting and emaciation which he thought were more common in asbestosis than in fibroid phthisis.

In a later review Wood and Gloyne (1934) wrote that breathlessness was the first and last complaint. They regarded asbestosis almost as a one symptom disease but again commented on the stubborn cough with little sputum.

They also recorded that some patients complained of a dull pain in the chest.

Merewether (1930) reporting on the cases seen during his survey of asbestos workers reported breathlessness in only 51.6%. Cough was present in 59.3%, sputum production in 34.1% and pain in 10.6%. The apparently lower prevalence of breathlessness probably arises because Merewether was examining working men and women whereas Wood was seeing patients in hospital.

Wyers (1949) agreed with Wood about the pre-eminence of breathlessness but thought that anorexia, weight loss, fatigue and chest pains occurred infrequently.

Parkes (1974) again stresses the predominance of breathlessness. He states that cough occurs in almost all cases eventually but is often dry or productive of only small amounts of mucoid sputum. He considers that fatigue may occur particularly in advanced disease but is sometimes out of proportion to the clinical, physiological and radiological abnormality. He does not regard chest pain to be a feature of the disease but notes that some patients complain of a dull ache in the chest. Others complain of an inability to take a deep breath or to yawn.

In summary the main symptom of asbestosis is breathlessness and this has been a constant finding by all observers. Many cases will also have a dry cough.

(3) Physical signs

Wood (1929) noted fine dry crackling sounds at the lung bases and in the axillae. He found early finger clubbing in some cases but commented that it was never marked. He occasionally heard friction rubs, usually at the bases.

In a later report Wood and Gloyne (1930) again commented on the absence of marked finger clubbing and noted poor expansion of the chest.

In 1934 Wood and Gloyne reported an "earthy complexion" presumably cyanosis in advanced cases.

Merewether (1930) reported cyanosis in 55.9% of his cases. He also found the signs observed by Wood but regarded them as non-specific. In his view the most important single clinical sign was diffuse impairment of the percussion note. He found well marked finger clubbing in a few cases.

Wyers (1949) considered that basal crepitations were generally present but could be evanescent. Fifty-five percent of his cases had finger clubbing and Wyers (1946) thought that this sign developed early in the disease. He found an accentuated pulmonary second sound but no hepatomegaly or peripheral oedema in ambulant cases.

Smither (1965) reviewing four series of asbestosis cases from the same factory spanning the previous 35 years found that in the two most recent series basal crepitations were almost invariably present. In the two earlier series they were sometimes present in 1930-34 series and generally present in the second (Wyers series). Twenty percent of the 1930-34 series had finger clubbing compared with 55%, 84% and 69% in the three later series. Cyanosis was rarely seen in any of the series.

Parkes (1974) considers fine end inspiratory crepitations best heard at the lung bases or in the axillae and often localised to be the earliest sign of the disease. As the disease advances they become coarser and more widespread. He notes that 25% of cases never develop finger clubbing and observes that rapidly developing finger clubbing is often associated with similar progression of the pulmonary fibrosis. He thinks nailbed fluctuation is associated with actively advancing disease. Chest expansion is normal early in the disease but decreases as the fibrosis advances. Parkes considers cyanosis to be uncommon but sometimes seen after exertion in advanced disease. He does not recognise weight loss as a feature of the disease.

In summary the physical signs of asbestosis are not specific to the disease. Basal crepitations appear to be an almost constant feature and finger clubbing is seen in a high proportion of cases. Cyanosis and weight loss are uncommon.

(4) Radiology

The radiological changes seen in asbestosis were first described by Wood (1929). He observed shadows suggestive of diffuse fibrosis affecting the lower two-thirds of the lung fields. The shadows were fine and sometimes had the appearance of ground glass but he thought that mottling was always evident on close inspection. He observed prominent bronchial striations towards the lung base and noted that they spread out to form a fine network. The shadowing could lead to an irregular cardiac shadow especially on the left. He also commented on evidence of old basal pleurisy and on the frequency with which the costophrenic angles were obliterated.

These appearances were different to those he recognised in miners pneumoconiosis and fibroid pulmonary tuberculosis. He stressed the importance of good quality films if these abnormalities were to be recognised with certainty.

Wood and Gloyne (1934) commented on the value of oblique films in demonstrating the early changes of asbestosis which occur in the costophrenic recesses.

Merewether (1930) thought he could discern four grades of radiographic abnormality:

(1) A very doubtful stage of increased linear striations.

(2) Fairly definite dusty stippled appearance

(3) Courser mottling with increased striations

(4) Gross lesions with pleural changes and displacements due to the pull of the fibrosing lesions.

He thought the abnormalities tended to be more marked on the right.

Merewether (1933) pointed out that these appearances were not specific to asbestosis and like Wood stressed the importance of good radiographic technique. He commented on the difficulties caused by breast shadows and the even greater difficulties in pregnant women with raised diaghragms and engorged breasts. An observation which serves to stress just how early in life asbestosis could develop in the late 1920's and early 1930's.

These early descriptions and the comments on the problems of interpretation remain valid. Williams and Hugh-Jones (1960a) reviewing the radiology of asbestosis thirty years later again commented on the non-specific nature of the radiographic features and found poor agreement on the interpretation of the radiographs of certified cases of asbestosis by a panel of experienced readers.

Smither (1965) emphasised the difficulties of interpreting single films and recommended the value of serial films in assessing abnormality.

Fletcher and Edge (1970) described the early changes of asbestosis and noted various patterns of abnormality which included more small vessel markings than usual, thickening of the vessel markings where they branch, fine nodular opacities accompanying the peripheral vessels in the costophrenic angles and horizontal linear shadows resembling Kerley B lines but which do not always reach the pleura.

Soutar et al (1974) in a study of the radiology of asbestos induced lung disease noted that the shadows were usually small and irregular but an appreciable number were described as pinhead rounded lesions. These abnormalities were predominantly in the lower zones. A diffuse haze was seen in 18% of their cases and it was thought that this was not due to poor technique, overlying muscle or pleural disease.

Eyssen (1980) was able to study the first abnormality to appear in serial films from asbestos miners and millers where there was an earlier normal film. The chest radiographs were read by five readers and the first perenchymal change was recorded as round or irregular with roughly equal frequency by three readers. The other two

readers recorded mostly irregular opacities. The frequency of round as opposed to irregular small opacities is in keeping with the observations of Fletcher and Edge (1970) and Soutar et al (1974).

Involvement of the upper lobes alone as a manifestation of asbestosis is distinctly uncommon. Green and Dimcheff (1974) reported three cases. In the first case no relevant occupational history was taken but at post mortem ferruginous bodies were found in the lung. Occasional birefringent crystals compatible with talc were also found and it is perhaps more likely that the disease in this case was due to talc. The second case specifically denied asbestos exposure. No asbestos bodies were found in the lung but the ashed lung was found to contain asbestos fibres. The third case had been occupationally exposed to asbestos. The last two cases had been farmers for most of their lives but the possibility of farmers lung does not appear to have been excluded.

Nodular opacities have been reported by Nice and Ostrolenk and rheumatoid nodules have been described by Rickards and Barrett (1958), Telleson (1961), Morgan (1964) and Mattson (1971). The case described by Telleson died and on review after post mortem it was considered unlikely that asbestos exposure had played an important part in the disease (Greaves 1979). If nodular opacities of this nature are a feature of asbestosis it appears that they are uncommon.

The ILO-U/C International classification of the radiographs of pneumoconiosis (1971) provides a means of systematically recording the abnormalities found in asbestosis and other pneumoconioses. It also allows the pleural disease which often accompanies asbestosis but which may occur alone to be recorded. There is a set of standard films against which the type and degree of abnormality can be graded. It is hoped that this system will enable readers to detect and grade abnormalities in a consistent and reproducible manner. It does however tend to impose constraints on the description of atypical or unusual features. This may be relatively unimportant in epidemiological studies for which the classification was really designed but it could be important in the clinical situation.

(5) Pulmonary Physiology

The physiological abnormality in asbestosis consists of a restrictive ventilatory defect with reduced gas transfer.

Reduction of vital capacity was first noted by Wood (1929) and later confirmed by Stone (1940). The presence of impaired gas transfer was deduced by Baldwin et al (1949) who noted a fall in arterial oxygen saturation on exercise in a case of asbestosis.

It was not until 1960 that William and Hugh-Jones (1960b) published their observations in 21 cases of asbestosis and showed that diffusing capacity measured by the single breath carbon monoxide method was reduced in all but two cases. They also found a reduction in inspiratory capacity, vital capacity and total lung capacity. They noted that these features were not specific to asbestosis and might be found in any interstitial fibrosis. They commented on the lack of evidence of airflow obstruction but it is interesting that although the ratio of FEV_1 to FVC was in the normal range the ratio of residual volume to total lung capacity was raised. A year later Heard and Williams (1961) were able to report on the post mortem findings in six of these cases. In five who had reduced gas transfer in life there was no evidence of emphysema at autopsy.

Leathart (1960) made similar observations and again noted that the abnormalities were not specific to asbestosis. He considered measurement of pulmonary compliance and diffusing capacity to be of diagnostic value and thought that low pulmonary compliance was the outstanding feature of the disease. While these abnormalities did no more than confirm the diagnosis he felt that in the absence of both of them the possibility of asbestosis was almost certainly ruled out.

Bader et al (1961) confirmed the above observations.

These reports do not mention airways obstruction as a feature of asbestosis so it is of interest that Muldoon and Turner-Warwick (1972) found evidence of airflow limitation among cases seen by the London Pneumoconiosis Medical Panel. This may have been a consequence of cigarette smoking rather than asbestos exposure but Fournier-Massey and Becklake (1975) in studies of lung function in asbestos miners and millers found better correlations between obstructive physiological profiles and asbestos exposure than between restrictive profiles and exposure. There are difficulties in the interpretation of this data but it seems possible that asbestos has an effect on airway function. If this is so it is perhaps not surprising considering that the fibrosis in asbestosis begins around the respiratory bronchioles.

(6) Immunology

A number of immunological abnormalities have been found in asbestosis but none are specific to the disease.

Pernis et al (1965) found an increased prevalence of rheumatoid factors among asbestos workers with abnormal radiographs but the exact abnormalities were not specified. This observation was confirmed by Turner-Warwick and Parkes (1970) who detected rheumatoid factors in 28% of their cases of asbestosis and added their own observation that antinuclear antibody was present in 27% of cases.

Kagan et al (1977) found decreased cutaneous reactivity to M. tuberculosis, Candia albicans extract, streptokinase, streptodornase and 2,4-dinitrochlorobenzene. They also found decreased numbers of lymphocytes in peripheral blood with a depletion of the T lymphocyte sub-population. Immunoglobulins were raised.

Haslam et al (1978) observed decreased responses to phytohaemagglutinin in cases with severe fibrosis and proposed an association between defective T lymphocytes and fibrosis.

Pierce and Turner-Warwick (1980) found decreased cutaneous responses to tuberculin (PPD), Candida albicans and Trichophyton spp. in asbestosis. They regarded this as further evidence of impaired T cell function.

These findings are of only limited help in making the diagnosis of asbestosis and have so far shed little light on the pathogenesis of the disease.

(7) Pathology

The pathological changes in asbestosis were comprehensively described by Gloyne (1933) and Wood and Gloyne (1930, 1934) and more recently by Hourihane and McCaughey (1966).

In well developed disease the lungs are typically small and firm with thickening of the visceral pleura which is often most marked at the bases. The fibrosis is usually most marked subpleurally and in the lower parts of the lung. The fibrotic area may contain small cysts up to 3mm in diameter but more marked cystic change is rarely extensive (Hourihane and McCaughey). Bronchiectasis may occur particularly where there is severe fibrosis and right ventricular hypertrophy may be present.

Microscopically the fibrosis develops around the respiratory bronchioles and then spreads to involve the alveoli. Wood and Gloyne (1930) observed that the alveoli might contain desquamated cells and appearances similar to those of desquamative intertitial pneumonia have been associated with asbestos exposure (Corrin and Price 1972). Asbestos bodies are usually easily seen both in the alveoli and within the fibrotic tissue.

Asbestos bodies were first accurately described by McDonald (1927) and Gloyne (1932) showed that they consisted of an asbestos fibre surrounded by an iron containing protein. Gloyne realised that their presence in the lung merely indicated asbestos exposure and was not in itself an indication of disease. Asbestos bodies have subsequently been demonstrated in the lungs of city dwellers not occupationally exposed to asbestos (Doniach et al 1975)

(8) Prognosis

(a) Mortality

Merewether (1933) was in no doubt that asbestosis shortened life and he believed that infection occurring in already damaged lungs was the main cause of death. Pulmonary tuberculosis accounted for a good number of deaths but he tended to the view that unlike silicosis asbestosis did not especially predispose to pulmonary tuberculosis.

The first case of lung cancer complicating asbestosis was reported by Lynch and Smith (1935). In the same year Gloyne (1935) reported two further cases both occurring in women and both discovered as incidental findings at post mortem. All three tumours were squamous cell carcinomas arising in areas of fibrosis. Gloyne (1935) adds in passing that he had also seen an oat cell carcinoma complicating asbestosis.

Strong evidence that lung cancer was a hazard of asbestosis was produced by Merewether (1949) who found lung cancer at post mortem in 13.2% of cases of asbestosis compared with only 1.3% of cases of silicosis. Gloyne (1951) reported similar figures. He found lung cancer in 14.1% of his cases of asbestosis compared with 6.9% in silicosis. Asbestosis was proportionately more common in women who

were less likely to develop lung cancer so these figures probably underestimated the risk. Despite these findings the association between lung cancer and asbestosis was not universally accepted until Doll (1955) demonstrated an approximately tenfold increase in the risk of lung cancer among cases of asbestosis.

Buchanan (1965) showed two interesting secular trends in mortality from asbestosis. Firstly the average age at death had been increasing since the 1920's and secondly the proportions dying from lung cancer had been increasing.

Although there have been many mortality studies of asbestos exposed workforces there have been only two studies of mortality amoung those with the disease. Both studies examined mortality in cases diagnosed by the Pneumoconiosis Medical Panels.

McVittie (1965) found that 40% of deaths were due to lung cancer and mesothelioma and 30% to other respiratory causes. There is no obvious excess from any other causes in his data. The mean age at death was 57.

Berry (1981) found a mortality rate 2.6 times that expected for all causes of death. Lung cancer accounted for 36% of the deaths and the mortality ratio was 8.5 times expected. Three of the lung cancer deaths occurred in non-smokers. Nine percent of the 283 deaths in his series were due to mesothelioma.

Thus the mortality experience in asbestosis has probably changed over the last 50 years. In the early days death often occurred while the patients were relatively young and was frequently due to infection. As conditions in the industry improved and the disease took longer to develop more cases survived into the cancer age group and lung cancer became an increasing important cause of death. The association between asbestos exposure and mesothelioma was only recognised by Wagner et al in 1960 but the tumour has been increasingly recognised both in asbestos workers and in cases of asbestosis ever since. It is now an important cause of death in asbestosis. Its frequency in the past is uncertain but Wyers (1946) records a death due to endothelioma of the pleura which is probably the first record of the association.

(b) Progression of intrapulmonary fibrosis

There has been no systematic study of progression of intra pulmonary fibrosis but most authors regard the disease as relentlessly progressive even after exposure to asbestos has ceased (Morgan and Seaton 1975 Selikoff and Lee 1978). Parkes (1974) believes that in some cases the disease becomes arrested. The lung function studies of Britton et al (1977) suggested that in some cases physiological deterioration casesed and if correct this would support Parkes view.

The effect of ceasing exposure is unknown. Wood and Gloyne (1930) initially thought the disease continued to prgress but later modified their view after seeing cases that apparently became stable (Wood and Gloyne 1934).

Smith (1955) stated that progression halted after ceasing exposure but offered no data to support his view. It is now clear that disease can develop after exposure has ceased (Becklake 1979, Rossiter 1980), a finding which suggests that Smith's observations cannot apply in all cases.

(9) Management

There have been few attempts to influence the fibrosis with treatment. Leathart (1972) and Elder (1967) found that corticosteroids did not influence the course of the disease but it may be that the drug must be given early if it is to arrest or modify the fibrosing process. Without detailed knowledge of the natural history of the disease the results of uncontrolled trials are impossible to interpret.

In the absence of effective therapy only symptomatic treatment can be given. Infections should be treated promptly and patients should be encouraged to stop smoking.

Epidemiological Studies

In the 1960's there was a resurgence of interest in asbestos related problems and since then many epidemiological studies have examined different aspects of the effects of asbestos on health. Many of the investigations have attempted to relate responses to asbestos to measures of asbestos exposure.

The intention here is not to review the whole field because much of the literature is concerned with broader health problems than asbestosis alone. However some studies do have a bearing on the clinical aspects of asbestosis and these will be considered as they relate to morbidity and mortality.

Studies relating to morbidity

Two studies in the United Kingdom have investigated the relationship between measurements of asbestos fibre and the development of signs of asbestosis (B.O.H.S. 1968 and Berry et al 1979). In North America two groups have examined the relationships between asbestos dust counts and radiological and physiological changes (Weill et al 1973, 1975, Rossiter et al 1972, Becklake et al 1972). The Canadian group (McDonald et al 1972) also showed that the symptom of breathlessness was related to asbestos exposure while cough and sputum production were related to cigarette smoking.

There are difficulties in measuring both dose and response in studies of this kind. The problems involved in reconstructing exposure profiles have been discussed by Berry (1979). The difficulties in diagnosing asbestosis clinically and in interpreting the radiographic appearances have already been alluded to in the description of the clinical disease. Agreement on the presence or absences of crepitations is not always good and besides the sign is not specific to asbestosis. Despite these problems, convincing relationships were shown between measures of exposure and response in the studies quoted above and these provide further strong evidence of a cause and effect relationship between asbestos exposure and intrapulmonary fibrosis.

The study of radiographic changes in chrysotile asbestos mine and mill workers in Quebec (Rossiter et al 1972) is of particular interest. Five exposure measures were used but the best correlation coefficients were only 0.27. Although this figure is highly statistically significant it implies that only 7.4% of the total variation in radiographic appearance can be accounted for by dose. The correlations were much lower than those obtained in similar studies of coalworkers and imply that factors other than dose must be important. Differences in individual susceptibility have been suggested and a number of investigators have looked for immunological factors which might predispose to the development of asbesosis. The effects of cigarette smoking have also been studied.

Immunological Studies

The finding of an increased frequency of antinuclear antibody in cases of asbestosis (Turner-Warwick and Parkes 1970) prompted studies of asbestos exposed but non-diseased workers (Turner-Warwick 1973). The results showed that antinuclear antibody was associated with disease and not simply a consequence of asbestos exposure but the question as to whether non-diseased workers with antinuclear antibodies are more likely to develop asbestosis has not been answered.

White et al (1974) examined the relationship between rheumatic complaints assessed by questionnaire and radiographic change in 1,069 currently employed workers in the Quebec asbestos mines and mills. No relationship was found but the methods were crude and it is perhaps unlikely that men with symptoms of rheumatoid disease would be able to continue in that type of work. The study group may have represented a survivor population.

Histocompatibility antigens have been studied by Merchant et al (1975), Evans et al (1976), Matej and Lange (1976), Darke et al (1979), Gregor et al (1979) and Huuskonen et al (1979) but no consistent associations have emerged. Turner-Warwick (1979) reviewed the literature and concluded that no important differences had been shown between those with and without asbestosis.

In conclusion no immunological markers of increased susceptibility have yet been demonstrated.

Cigarette smoking

Two studies from the United Kingdom (Berry et al 1979, McMillan et al 1980) suggest the incidence of asbestosis is increased in cigarette smokers but the Canadian studies (Liddell and McDonald 1980) show no such effect. In the United States Weiss (1971) found that cigarette smoking and asbestos exposure were at least additive in causing pulmonary fibrosis while Samet et al (1979) found no evidence of synergism. The relevance of cigarette smoking in the development of asbestosis is still unclear after five studies so it seems likely that if an effect exists it is a small one.

Progression of Asbestosis

Most of the exposure-response studies have been cross-sectional and so do not shed light on the relationship between exposure and progression of asbestosis. Two studies have looked at progression of radiographic abnormality. The first by Liddell et al (1977) found poor correlations between exposure and progression of established disease. They recorded multiple correlations as high as 0.632 but the stimulus variable accounting for most of the total variation was not an exposure measure

but the status of the first radiograph. The authors point out that the causes of attack (the development of abnormality) and progression of established disease may be different.

Jones et al (1980) however have suggested that progression is dose related. Their evidence is based on a series of cross-sectional studies in an asbestos cement manufacturing plant. The prevalence of radiographic abnormality in the study population has increased and this has been regarded as progression. Progression was significantly correlated with measures of exposure. However most of the disease detected appears to have been attack (the development of abnormality) which is known to be dose related. The progression referred to appears to be a combination of attack and progression in an exposed population and not simply the progression of established disease. In the author's view this does not constitute good evidence that the progression of established asbestosis is related to dose.

Thus whilst dose might be expected to be a determinant of progression there is as yet no proof that this is so.

Studies relating to mortality

Lung cancer

Many studies have shown an increased mortality from lung cancer in asbestos workers. (11 studies are summarised

in Asbestos: Volume 2, 1979). The increase is correlated with measured airborne asbestos dust (Enterline 1973, McDonald et al 1971, 1980) suggesting that there is a close relationship between lung cancer and asbestos exposure.

Doll (1955) conclusively showed that asbestosis was frequently complicated by lung cancer and the question arises as to whether asbestos per se causes lung cancer or whether it is a complication of asbestosis. Few of the mortality studies give any information about the presence of asbestosis but Elmes and Simpson (1971) in their study of Belfast insulation workers found no case of lung cancer in the absence of asbestosis. Similar findings emerged from a study of Rochdale asbestos textile workers (Knox et al 1968). Liddell and McDonald (1980) analysed the relationship between excess mortality from lung cancer and small irregular opacities on the chest radiograph of Canadian asbestos miners and millers. They concluded that most but not necessarily all the excess mortality probably occurred in those with radiographic evidence of asbestosis.

These studies do not make clear whether an excess of lung cancer occurs in the absence of asbestosis but they do confirm that lung cancer is a complication of asbestosis.

Selikoff et al (1968) showed that smoking asbestos workers were at a greatly increased risk of developing

lung cancer and initially he thought that the excess risk was confined to smokers. However two recent reports suggest that the risk of lung cancer is increased in non-smoking asbestos workers (Hammond et al 1979, McDonald et al 1980) but again it is not known whether these cancers arose in cases of asbestosis. Berry (1981) observed three deaths in non-smokers among 102 lung cancer deaths in certified cases of asbestosis. It seems likely that the risk of lung cancer in asbestosis extends to non-smokers.

Gastrointestinal cancer

Many but not all mortality studies have found an excess of deaths from gastrointestinal cancer. (Asbestos Report: Volume 2, 1979). This has not been a feature of either of the two studies of mortality in certified cases. (McVittie 1965, Berry 1981). The reasons for the discrepancies are unclear.

Laryngeal cancer

Stell and McGill (1973) showed a relationship between laryngeal cancer and asbestos exposure in a case control study and there is some epidemiological data to support their observation (Newhouse and Berry 1973, Hammond et al 1979) but McDonald et al (1980) found no excess mortality from this cause nor did they find any evidence of a dose

response relationship with asbestos exposure but there was a relationship with cigarette smoking. Neither McVittie (1965) nor Berry (1981) reported deaths from laryngeal cancer. This may simply reflect the rarity of the disease even in those exposed to a predisposing cause but on the evidence available it is not possible to determine whether laryngeal cancer is commoner in those with asbestosis.

Mesothelioma

The association between mesothelioma and exposure to crocidolite was first observed by Wagner et al in 1960. Since then the disease has been increasingly recognised and although it often develops after exposures insufficient to cause pulmonary fibrosis (Whitwell et al 1977) it is not surprising given the long latent period before mesothelioma develops that some workers will accumulate sufficient exposure to develop pulmonary fibrosis. Both McVittie (1965) and Berry (1981) recorded deaths from mesothelioma among their certified asbestotics.

STUDY POPULATION AND STUDY METHODS

Study Population

One hundred and sixty seven patients with a diagnosis of asbestosis made by the London Pneumoconiosis Medical Panel between 1968 and the end of 1974 were reviewed between September 1978 and July 1979.

Diagnosis of Asbestosis

The diagnosis of asbestosis used in this study was that made by the London Pneumoconiosis Medical Panel. The guidelines used by the Medical Panels during the period 1968-1974 are set out in "Pneumoconiosis and allied occupational chest diseases" (HMSO 1967) in paragraphs 29 - 35.

Paragraph 34 states: "The diagnosis of asbestosis rests on six factors

(a) An exposure to asbestos
(b) Breathlessness
(c) Clubbing of the fingers
(d) Basal rales and crepitations
(e) Radiological changes
(f) Reduced transfer factor

Given the first factor (exposure to asbestos) the presence of any two of the others would be strongly suggestive of asbestosis."

Source of study population

Any person who has been exposed to asbestos at work and who thinks he may have asbestosis is entitled to make a claim for disablement benefit. Provided that the local insurance officer is satisfied that certain employment conditions have been fulfilled then the claimant will be examined by a medical panel.

In 1968 an arrangement was made with the London Pneumoconiosis Medical Panel whereby all claimants would attend the Brompton Hospital on the day they were examined by the Panel to have lung function tests performed. At this visit the opportunity was taken to obtain a clinical history and examine the patients. Blood was drawn for various immunological studies.

Claimants seen at Brompton Hospital between 1968 and 1974

Three hundred and thirteen claimants were seen and 167 were certified as having asbestosis by the Panel. During this period, panel records show that 369 claimants were examined and 180 were certified as suffering from asbestosis. An attempt was made to follow up all 313 cases previously seen at Brompton Hospital (See Appendix I).

Tracing of Claimants

The following details were extracted from Brompton Hospital and Panel case records:-

(1) Full name

(2) Date of birth

(3) Last known address

(4) Last known general practitioner

(5) Date of death when this was known to have occurred.

The general practitioners of all cases thought to be alive were contacted to determine:-

(1) Whether the patient was still alive and if not to obtain the date of death.

(2) Whether the general practitioner was agreeable to contact being made with the patient.

The help of the Office of Population Censuses and Surveys was gained in order to obtain death certificates and to trace those cases who had changed their general practitioner. The details 1-5 listed above were supplied to the National Health Services Central Register who then provided death certificates and the Family Practitioner Committee (F.P.C.) of those surviving cases who we had

been unable to trace. The F.P.C. were able to supply the general practitioner of the untraced cases and it was then possible to contact them through their general practitioner.

In this way it was possible to trace all the certified cases of asbestosis and all but two of the non-certified group. In two instances the general practitioner felt it would be inappropriate for a patient to be seen. Neither of these cases were certified.

An attempt was made to see all the remaining survivors. Where it was not possible to see the patient either at the Brompton Hospital or at home an attempt was made to obtain a recent chest radiograph. Details of the follow up are given in Appendix I.

Data Collection

Clinical Questionnaire

A clinical questionnaire was completed for each patient at first attendance (See Appendix II).

The following details were recorded:

Name

Date of Birth

Sex

Height in metres

Full occupational history with dates

Duration from first exposure to asbestos

Severity of exposure

Type of asbestos used

Exercise tolerance (Medical Research Council questionnaire on respiratory symptoms 1966)

Presence and severity of cough and sputum

Exercise tolerance (Brompton Hospital Grading)

Previous illnesses

Family History

Smoking History

The questions relating to cough and sputum were a modification of those used in the Medical Research Council questionnaire.

At follow up the same questionnaire was used but two further questions were included. The first question related to exposure to possible causes of extrinsic allergic alveolitis. The patients were asked whether they had ever lived in a house where anyone kept budgerigars or pigeons and whether or not they had ever worked with mouldy hay or rotting vegetable material. If an affirmative answer was given enquiry was made about chest symptoms related to these exposures.

The second question concerned the circumstances of the initial approach to the Pneumoconiosis Medical Panel. Patients were divided into two groups according to whether presentation followed a routine radiograph at work or by some other method. Cases which presented following a routine radiograph at work will be referred to as routine surveillance cases. This group does not include cases which were detected by the first radiograph taken when a regular surveillance scheme was initiated.

Physical Examination

The results of physical examination were recorded at presentation and at follow up on the questionnaire (Appendix II).

The following signs were specifically recorded:-

Finger clubbing
Cyanosis
Crepitations
Site of crepitations
Persistence of crepitations after coughing
Wheeze
Persistence of wheeze
Pulse rate
Blood pressure
Soft tissue swellings
other abnormal physical signs were recorded

No attempt was made to grade finger clubbing. It was merely recorded as present or absent.

The follow up clinical data was collected by the author without reference to the earlier data.

Pulmonary Physiology

The following measurements of lung function were selected for the purpose of this study. They were:-

(1) Forced expiratory volume in one second (FEV_1)
(2) Forced vital capacity (FVC)
(3) Vital capacity (VC)
(4) Transfer factor (D_LCO)

The measurements were all made with the patient seated, relaxed and wearing a nose clip.

At presentation FEV_1, FVC and VC were measured with a low inertia spirometer and transfer factor was measured by the single breath method (Ogilvie et al 1957) using a Resparameter Mark 3.

At follow up FEV_1 and FVC were measured with an Ohio 800 dry spirometer and transfer factor was measured using a resparameter (Transfertest Model C.) Vital capacity was measured in the body box.

The above measurements were chosen because they are reproducible and likely to have been measured in a consistent fashion over the eleven year period of this study. Other measurements were made on nearly all the patients and this allowed the lung function technicians to check that vital capacity manoeuvres gave reproducible results. All the patients were being examined for compensation purposes at the first examination and may have been less inclined to perform the tests as well as possible. This problem was well recognised and every effort was made to obtain accurate results.

The results obtained for FEV_1, VC and D_LCO have been expressed as percentages of predicted using the regression equations quoted by Cotes (1975).

Immunological Studies

Blood samples were collected from all willing subjects for the estimation of rheumatoid factor and antinuclear antibody. These tests were performed both at presentation and at follow up.

If a history of exposure to buderigars or pigeons was obtained at follow up serum was tested for avian precipitins.

Rheumatoid Factor

At presentation this was measured using the differential agglutination test (Rose et al 1948). At follow up it was measured using the RAHA test, a a commercial adaptation of the Rose-Waaler test produced by Fujizoki Pharmaceutical Co. Ltd. This test is more sensitive than the differential agglutination test and results in a tenfold increase in titre with respect to the differential agglutination test (Haslam, P.L. 1980).

Antinuclear Antibody

This was measured thoughout the study by the double layer immunoflorescent technique descrubed by Coons and Kaplan (1950). Only unequivocal positive results have been analysed, $\pm$ results were regarded as negative.

Avian Precipitins

Precipitin tests were made using the agar-gel double-diffusion Ouchterlony method (Pepys et al 1964).

All serum samples were coded, stored and tested in batches along with material from other sources without the laboratory being aware of clinical details.

The laboratory practice is to run known positive and negative controls with all test batches in an attempt to maintain consistent results.

Radiology

A full size postero-anterior chest radiograph was available for all the cases at presentation. Only cases for whom such a film was available at follow up were included in the study.

The initial films were taken either by the Pneumoconiosis Medical Panel using a grid or at the Brompton Hospital using low kilovoltage (60-70 kV). The majority of follow up films were taken at Brompton Hospital using a higher kilovoltage. They were either taken at 6 feet with 86-90 kV or at 10 feet with an air gap and 150 kV. The latter technique results in a slightly magnified image with respect to the other methods. A small number of follow up radiographs were obtained from other sources and the radiographic techniques varied.

Reading of Chest Radiographs

Three readers, all members of the Health and Safety Executive/Medical Research Council Panel on Survey Radiology, classified all the chest radiographs independently using the ILO-U/C International classification of radiographs

of pneumoconiosis (International Labour Office 1971) and a set of standard films. The reading form (Appendix III) was filled in by the author as each radiograph was read.

It was decided to read the chest radiographs of all 313 cases seen jointly by the Pneumoconiosis Medical Panel and Brompton Hospital irrespective of subsequent certification by the panel. A high proportion of these films were known to be abnormal in some way and so a number of chest radiographs known to be normal were added bringing the total to 340. The films were then randomised and every tenth film was withdrawn for use as a trigger film.

The readings were conducted in four stages.

Stage 1: The trigger films

This set of 34 films was read independently by each reader. The readers were then brought together to discuss their readings and to arrive at an agreed assessment for each of the radiographs. These films were then used as trigger films. That is to say they were included in all subsequent reading sessions and after they were re-assessed the reader was informed of the agreed assessment. It was hoped that this would reduce drift

in standard of classification. It also allowed an estimate of inter and intra observer variation to be made. Finally the joint discussion allowed differences in the interpretation of the instructions for use of the classification to be settled and a common approach adopted.

Stage 2: The reading of the chest radiographs at presentation

The 340 films described above were read independently by each reader. Every tenth film was a trigger.

Stage 3: The reading of the chest radiographs at follow up

The radiographs of all 177 cases seen at follow up, irrespective of certification, were randomised and the 34 trigger films were interspersed in such a way that every tenth film was a trigger. Not all 34 films were needed as triggers but all were re-read.

Stage 4: Side by side comparison of presenting and follow up radiographs

A side by side comparison of the presenting and follow up chest radiograph was made for all 177 cases. The films were presented in known order and the reading sheet (Appendix IV) was filled in by the author as the pairs were assessed.

The various features were recorded as follows:-

No change

Possible improvement

Definite improvement

Possible deterioration

Definite deterioration

Change in diaphragmatic level was measured in centimetres. Changes were recorded to the nearest centimetre and changes of less than one centimetre were ignored.

With the information gathered from the above readings it was possible to assess inter-observer and intra-observer variation and the results of this assessment in respect of small intrapulmonary opacities are shown in Appendix V. Overall agreement was good.

Score for small intrapulmonary opacities

As overall agreement between readers was good it was thought reasonable to classify individual radiographs using the median score given.

The type of small opacity recorded in the cases of asbestosis was generally irregular but occasionally round opacities or a combination of round and irregular were

recorded. In these cases the combined score for small opacities or the score for round opacities was used.

Determination of radiographic progression of small intrapulmonary opacities

This was determined from the results of the side by side comparisons. If a follow up film was considered by a reader to show definite increase in either the profusion or extent of small intrapulmonary opacities in either lung field then a score of two points was given. If possible deterioration was noted a score of one point was given. If a combination of possible and definite deterioration was recorded the film was given two points. Thus if all three readers recorded definite deterioration a score of six points resulted. If all readers agreed that no change had occurred a score of nought would result.

The results of this scoring system are shown in Appendix VI. It was decided that if a pair of films accrued three points or more then radiographic progression would be deemed to have occurred. In practice this meant that at least one reader had recorded definite progression.

Mortality data

Cause of death

The cause of death was obtained from the death certificate and it is this information which has been used in the analysis of mortality. The death of all persons suffering from an industrial disease should be reported to the coroner who will usually require a post mortem examination. In practice the majority but not all certified cases of asbestosis come to post mortem and the lungs together with any clinical and radiological data relating to the final illness are reviewed by the Pneumoconiosis Medical Panel who then make their own judgement about the cause of death. The agreement between these two sources in those certified as having asbestosis was good.

Histology of bronchial carcinomas

Details of the histology of bronchial carcinomas was culled from hospital notes and Panel records. In the latter case the histology was usually classified by Dr. K.F.W. Hinson.

Analysis of Mortality

Mortality was analysed using the subject years at risk method (Case and Lea 1955). The probability of death occurring between one birthday and the next was obtained from Life Tables: The Registrar General's decennial supplement for England and Wales 1970-72. These tables provide no basis for expectation of death from mesothelioma and so no mortality ratio can be obtained for this disease.

The subject years at risk method utilises the probability values provided in the Life Table to make a statement of expected mortality. If the age at presentation and the length of observation of each subject in a defined population is known it is possible to add together all the separate probabilities of dying and so provide a basis for expected mortality within that population. This can then be compared with the observed mortality.

Statistical Methods

Expert statistical help was obtained. Standard methods have been used throughout and will be indicated in the text.

DISCUSSION OF STUDY METHODS

The Study Population

The justification for studying the natural history of any disease is to gain information which will be of use in predicting the outcome and prognosis of similar cases. In order to do this a case must be defined as accurately as possible and the study population must be representative of those cases. To what extent does this study fulfil these criteria?

(a) Case Definition

Asbestosis may be defined as intrapulmonary fibrosis resulting from asbestos exposure. In order to make the diagnosis it is necessary to have evidence of intrapulmonary fibrosis and to show that asbestos is the likely causative agent.

The diagnosis of early intrapulmonary fibrosis is difficult and the earliest signs may precede radiographic changes. None of the signs or symptoms of asbestosis are unique to that disease and many ofthem commonly occur in other unrelated conditions. This problem lead Berry et al (1979) in a study of dose-response relationships in an asbestos textile factory to examine the relationship between dose and crepitations, possible asbestosis and certified asbestosis. The prevalance of all three categories rose with increasing exposure to asbestos.

It is known that some cases failed to attend at the Brompton Hospital. A few cases were initially seen at home by the Panel. No records of these visits are kept but the number is believed to be very small. A small number of cases diagnosed early in 1968 may never have been sent to the Brompton Hospital. It is unlikely that the failure to identify these 13 cases has seriously distorted the results.

Efforts are made within the Panel system to try and maintain a uniform standard of diagnosis. Berry's study (1981) of mortality rates in cases certified by the London and Cardiff Panels provides some evidence that comparability does exist at least between these two Panels. If the standard of diagnosis is fairly uniform then the results reported here should provide a general description of outcome in certified cases of asbestosis. It cannot be assumed that the description will apply to cases of asbestosis diagnosed by physicians but turned down by the Panels nor does it necessarily apply to cases of asbestosis who choose not to go before the Panels.

Problems of examining claimants.

All the cases at presentation were in the process of claiming compensation. This may well have had a disturbing effect on the study. It is conceivable, perhaps even likely, that patients may have exaggerated their symptoms and not

In the clinical situation the assessment of asbestos exposure can be particularly difficult especially in those who only intermittently used absestos or who did not handle it themselves but who worked in the vicinity of asbestos users.

Against this background any case definition is likely to be imperfect. In this study a case has been defined as a person certified by the Pneumoconiosis Medical Panel to be suffering from asbestosis. This at least has the virtue of defining an easily identifiable group but some might argue that it is too restrictive a definition.

(b) Is the study population representative?

One hundred and sixty seven of the 180 cases certified by the London Pnuemoconiosis Medical Panel between 1968 and 1974 were in the study group. In three cases no follow up chest radiograph was obtained but all three cases were known to be alive. A more serious threat to validity is posed by the 13 cases who were never seen. If all these cases were moribund and seen by the Panel at home or in hospital shortly before death then a serious underestimate of mortality might arise. The description of mortality in this study is similar to that obtained by McVittie (1965) and Berry (1981) who also investigated certified cases and so it seems unlikely that this happened.

cooperated fully in tests of lung function. If at follow up, when pension assessment was not involved, symptoms were reported more accurately and lung function tests were performed more adequately then a spurious impression of no change or even improvement might be gained. It is not known how accurately patients reported their symptoms but steps were taken to ensure that reliable lung function results were obtained.

A false impression of radiographic abnormality may be gained when the radiograph is exposed without the patient taking a full inspiration. (Plate 1) In retrospect it seems likely that a number of patients did not or could not inspire fully when their chest radiographs were taken. The number of such cases was small and it is thought unlikely to have been a deliberate ploy on the part of the claimants.

Drawbacks of the follow up study

The study examined two aspects of asbestosis. Firstly the mortality and secondly the progression of the intrapulmonary fibrosis.

At present the mortality of this group can only be incompletely described as 101 cases are still alive and it may be the patterns of mortality observed so far will change.

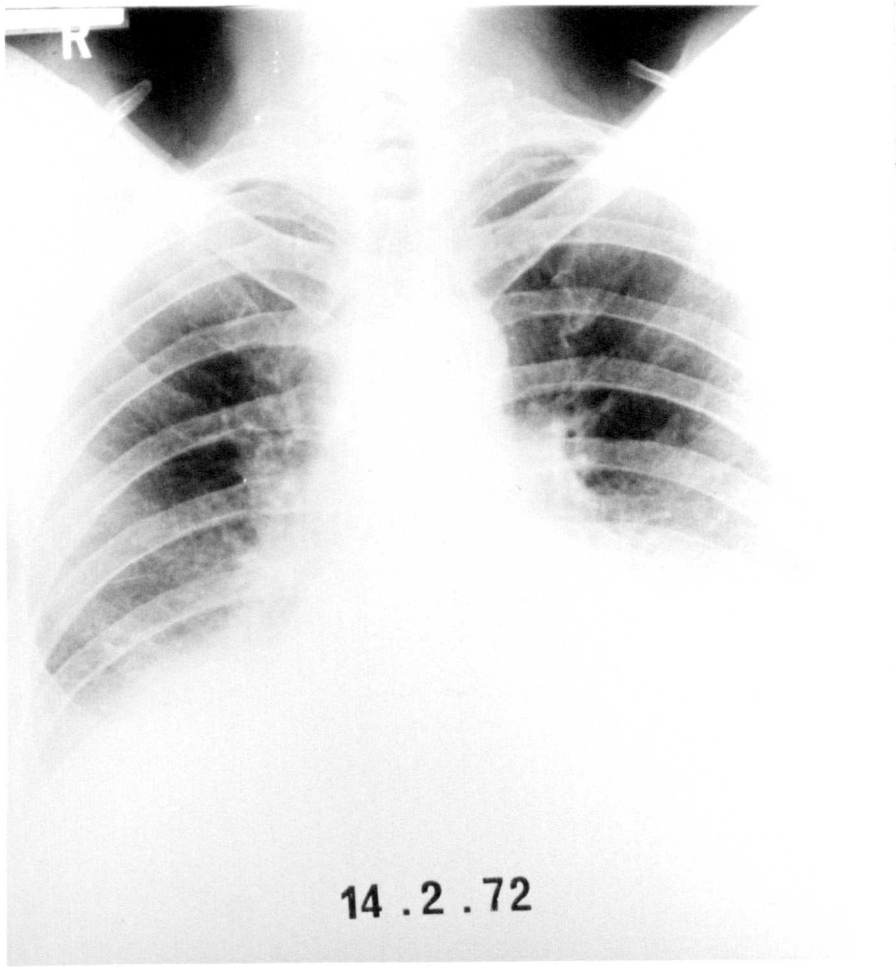
PLATE 1

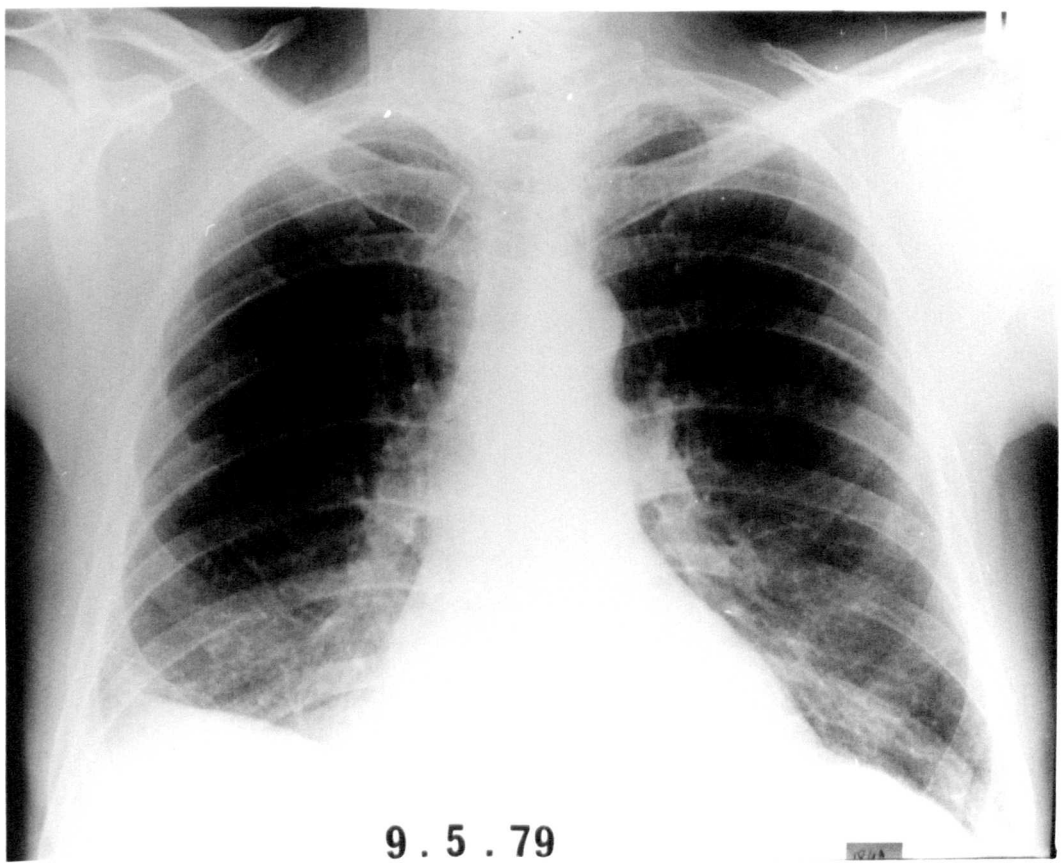
Chest radiographs of a patient at presentation (top) and follow up (bottom) who either could not or did not take a full breath when the earlier film was taken.

The independent and paired readings are set out below:

Reader	Presentation radiograph	Follow up radiograph	Paired reading
MTW	2/1	1/1	Definite improvement
IHK	2/2	1/1	No change
JCG	0/0	0/1	No change

It is of interest that reader JCG has handled this film differently to the other readers (See Appendix V).


R
14 . 2 . 72


9 . 5 . 79

The study of progression is based on a group of patients who have survived 4-11 years from diagnosis. No information is available on the progression of the non-survivors.

The results obtained must be interpreted in the light of these limitations.

Data Collection

Any method of collecting information should be repeatable. It should give the same results when used again on the same subject. It should also be valid. That is to say it should measure what it purports to measure. Repeatability is easy to measure and if it is poor then validity must also be poor. However, repeatability alone does not ensure validity and in many clinical situations where patients are asked to grade symptoms it is not possible to assess validity fully. Interobserver and intraobserver variation is well known to occur. It is one of the components of repeatability and it can be measured.

Repeatability, observer variation and validity were not for the most part systematically assessed in this study. This is a weakness and in discussion of the methods of data collection an attempt will be made to locate the possible sources of bias.

Clinical Questionnaire

The study group was collected over seven years and most of the cases were seen by the same clinician. No attempt was made to measure the repeatability of the questionnaire and whilst in theory it might seem easy to have done this, in practice it would have involved recalling a random sample of claimants and repeating the same questionnaire. It was felt that this might arouse considerable hostility. The asbestos workers around London form a number of closely knit groups and any suggestion that their truthfulness in answering our questions was in doubt might have resulted in the loss of their future cooperation.

At follow up the patients were seen by the author. Any assessment of inter-observer variability would have had to be carried out on the cases seen at follow up. The results would reflect current inter-observer variation but would not necessarily give an accurate assessment of the variation between current observations and those made in the past.

Exposure to asbestos

Occupational history

Prior to appearing before the Pneumoconiosis Medical Panel claimants have to write out an occupational history

giving the dates of all their jobs and stating those which involved exposure to asbestos. This statement is scrutinised by the Insurance Officer who can check its accuracy against company employment records in cases of doubt. This exercise is likely to have increased the accuracy of the occupational history obtained at the Brompton Hospital. There was close agreement between exposure histories obtained by the Panel and at Brompton Hospital.

Severity of exposure to asbestos

An attempt was made to grade the severity of exposure. In practice this was an assessment of the heaviest period of exposure. Many cases had a variety of jobs with differing exposures but nearly all the cases had suffered what was considered to be heavy exposure at some time. There was a small group of cases whose exposure was difficult to grade. This occurred particularly with workers who did not themselves handle asbestos but who worked in the vicinity of those who did. Such cases commonly came from the dockyards and power stations.

Exposure to different fibre types

Many workers did not know what fibre types they had been exposed to. From what is known of local work practices

Insert on page 63 before Measures of Exposure

Little is known about the propensity of different asbestos fibres to cause asbestosis in man. Weill et al (1977), in the only epidemiological study which has addressed this problem, suggested that crocidolite may be more fibrogenic than chrysotile. Animal studies have not supported this finding. Both Wagner et al (1974) and Davis et al (1978) found chrysotile to be more fibrogenic than crocidolite in the rat. Further information on the fibrogenicity of different types of asbestos in man is clearly desirable but it cannot be obtained from this study.

Weill, H., Rossiter, C.E., Waggenspack, C., Jones, R.N. and Ziskind, M.M. (1977)

Differences in lung effects resulting from chrysotile and crocidolite exposure.

In: Inhaled Particles IV Ed. Walton, W.H.
Pergamon Press, Oxford pp 789-798.

Davis, J.M.G., Beckett, S.T., Bolton, R.E., Collings, P., and Middleton, A.P. (1978).

Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats.

British Journal of Cancer, 37, 673.

it is unlikely that many had exposure to single fibre types. One factory in the London area has used amosite almost exclusively but even there some usage of chrysotile and crocidolite has occurred.

Measures of Exposure

It is likely that the occupational histories are accurate. They allow exposure to be defined in two ways:-

(1) Duration of exposure

(2) Time from first exposure

It is considered unlikely that significant exposure to asbestos occurred after 1970 in the small number who continued in the industry after that date and so duration of exposure has been calculated to 1970 in the analysis of progression.

These measures of exposure are crude but they have allowed exposure-response relationships to be demonstrated in populations of asbestos workers. Newhouse (1969) demonstrated increasing mortality with increasing duration of exposure. Selikoff et al (1979) have shown a relationship between the time from first exposure to asbestos and subsequent mortality from lung cancer and mesothelioma in a cohort of insulation workers and Berry et al (1979) in a study of asbestos related morbidity found that time from

first exposure to asbestos correlated with the response data as satisfactorily as cumulative exposure measured in fibre-years/cm^3.

Although these indices of exposure have proved satisfactory in some epidemiological studies it is likely that more refined measures would be better still. One possible way of improving this exposure data would be to try and produce an index which combined duration and intensity of exposure. This would involve ranking all the different jobs done by each worker and would require knowledge of the varying working conditions in a wide range of employments over the last sixty years. This would be a formidable task. Even if it could be satisfactorily achieved it would only be a measure of exposure and not necessarily an index of the biologically active dose. It would take no account of the residence time of asbestos in the lungs and it is known that disease may appear after exposure has ceased. (Becklake et al 1979). Nor would it be possible to validate any intensity/duration index other than by its ability to produce biologically plausible results. This begs the question as to what is biologically plausible? For example if progression of asbestosis is dose-related then those with the highest intensity/duration index should demonstrate most progression. Alternatively the more susceptible individuals may develop disease with a relatively lower intensity duration index and because of

their increased susceptibility progress more rapidly. Finally although the development of asbestosis is dose-related (Rossiter et al 1972, Weill et al 1973) the subsequent progression may be independent of dose. Thus in this population it could be argued that many different results might be biologically plausible.

The problems of ranking the exposures and more particularly of validating any derived intensity/duration index were such that they were felt to outweigh its possible value and so this type of exposure measure was not attempted.

Assessment of Symptoms

Symptoms were recorded using a modified form of the Medical Research Council questionnaire (1966) with the addition of a Brompton Hospital breathlessness question and questions on the amount and character of sputum. No validation of these questions has been possible in this study. The questions relating to cough and sputum have been condensed and an attempt made to assess the duration of symptoms. In the authors experience answers to the questions on duration of cough and sputum were extremely vague and it might have been better to have asked whether the symptoms had been present for a certain period of time, say 2 or 3 years. An attempt was made to assess the amount and character of any sputum produced. Fletcher et al (1959) have shown that answers to questions about the character

of sputum are unreliable. Moreover the answers elicited by male and female interviewers may be different and the answers may vary at different times of the year.

Some validation of the exercise grade (Brompton) question has been gained from the study. Evidence will be presented to show that an increasing grade of breathlessness on this scale correlates with radiographic progression of asbestosis.

Smoking history

This was collected using a modified form of the MRC questionnaire. Patients may have underreported their tobacco consumption but as nearly all admitted to smoking cigarettes regularly at some time the division into life long non-smokers and those who had ever smoked should be accurate. It was possible to check whether ex-smokers at presentation had continued in that category at follow up.

Physical examination

No studies of inter-observer or intra-observer variation were made but the cases were seen by experienced chest physicians.

Pulmonary physiology

Various physiological measurements were made on these patients over the eleven year period. During this time there were changes in equipment, techniques and laboratory staff. Because of this it was decided to use measurements which were (a) likely to have been made consistently despite the aforementioned changes and (b) were reproducible and relatively independent of effort on the part of the subject.

A determined effort was made to obtain reproducible vital capacity measurements. Forced expiratory volume measurements are largely independent of effort and transfer factor is not appreciably dependent on lung volume.

Immunological studies

These tests were carried out in the same laboratory throughout the study period and only a relatively small number of staff have carried out the tests. Although positive and negative controls have been included in each batch of tests no studies of long term comparability have been made but it seems unlikely that the results obtained on similar samples for anti-nuclear antibody have changed over the last 11 years.

Variation in film quality

Film quality was graded 1-4 (Appendix III). The percentage of films placed in each category is set out below along with the readers assessment of whether parenchymal detail was clearly visible.

		MTW	IHK	JCG
Film quality	1	84%	74.5%	60.5%
	2	13%	21.75%	33.25%
	3	2.5%	3.5%	6.25%
	4	0.5%	0.25%	0
Parenchyma clearly visible		97%	93%	70%

The readers varied in their assessment of film quality but few radiographs were placed in categories 3 or 4. All three readers had wide experience in survey radiology and commented independently that the film quality was considerably better than that generally encountered in epidemiological work.

Parenchymal detail was considered to be clearly visible in over 90% of cases by two of the readers, in 70% by the third; suggesting that pleural shadows were not a major problem when assessing the profusion of small opacities.

The high level of inter and intra observer agreement on profusion scores (Appendix V) suggests that variation in film quality and the presence of pleural shadows did not have a marked effect on the readers assessments.

Radiographic Assessments

(1) Technical variations in the radiographs

There were wide variations in the radiographic methods used but in general the follow up radiographs were taken with a higher kilovoltage (kV) than the earlier films. The high kV techniques give better definition of the lung fields and it was noticeable that some radiographs read consistently as 0/0 at presentation were read as 1/1 at follow up but were regarded as unchanged on paired assessment (Plate 2). The trigger films readings were higher in the follow up series and the better film quality of that series may have contributed to this.

(2) Trigger Films

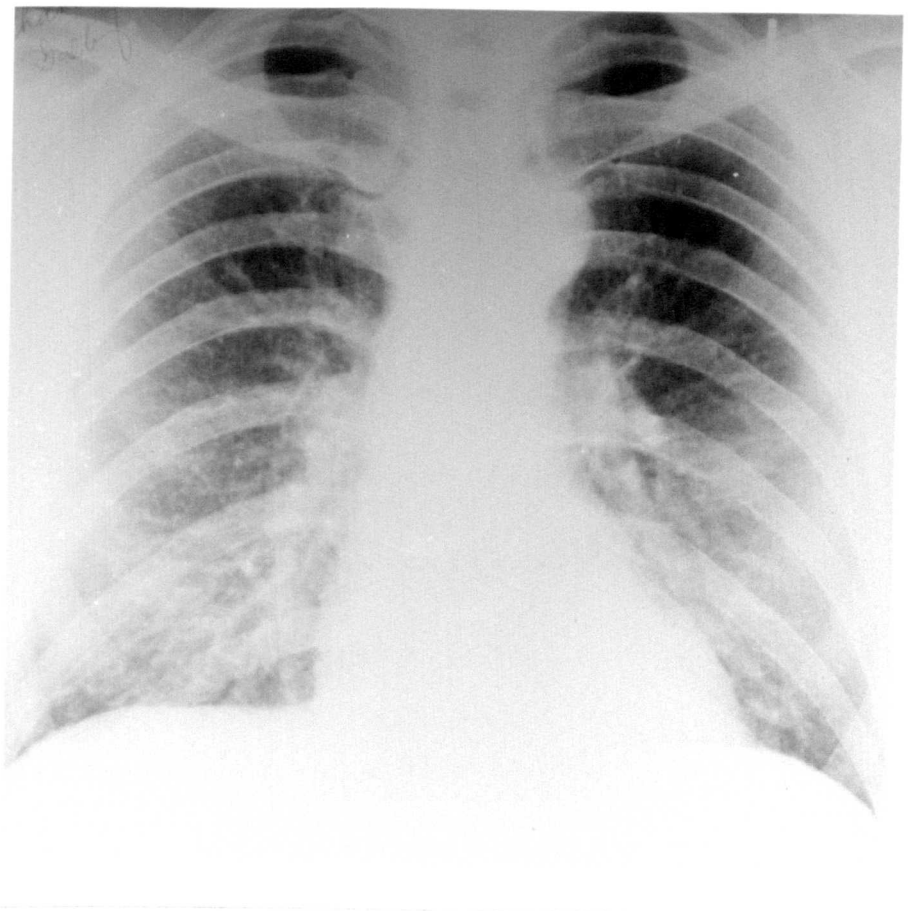
It was hoped that the inclusion of a set of trigger films with an agreed reading would help to prevent drift in the level of categorisation. In practice there was good agreement at all three reading sessions on the profusion of small intrapulmonary opacities and so it is not certain whether the triggers helped in this respect.

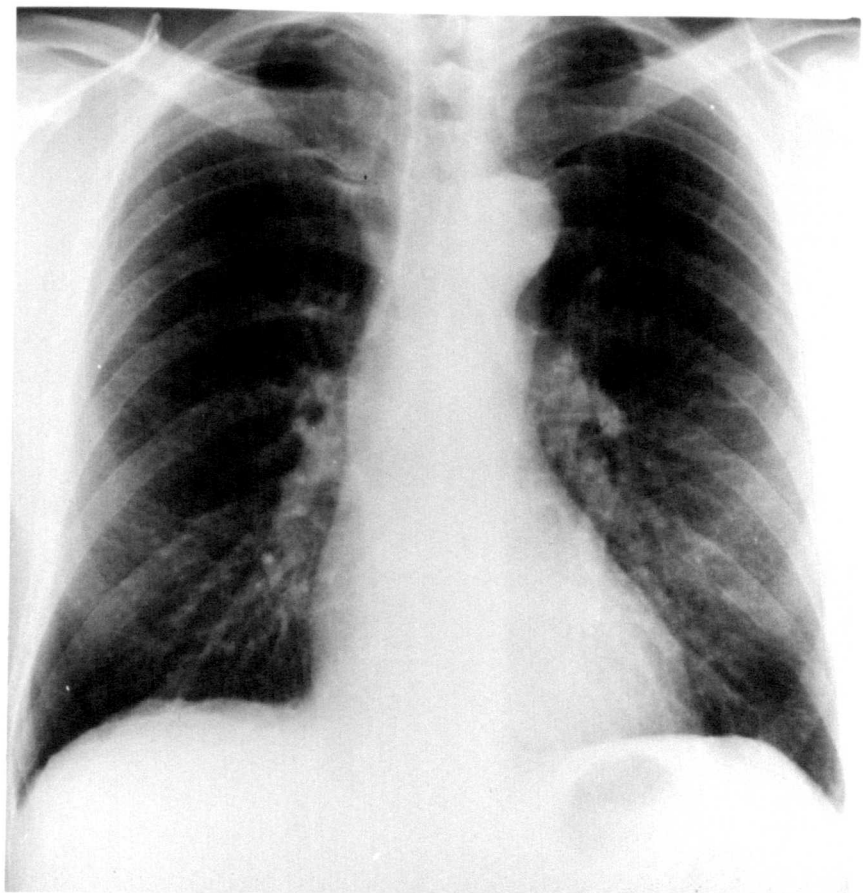
The mean score for the trigger films (see Appendix V) was around the 0/1 - 1/0 boundary. This area at the border between normality and abnormality is one where inter-observer and intra-observer variation is at its highest and so the triggers provided a particularly severe examination of reader variability.

PLATE 2

An example of a chest radiograph where the better quality of the follow up film (bottom) resulted in higher profusion scores being given by all three readers but where progression was not recorded on paired assessment.

Reader	Presentation radiograph	Follow up radiograph	Paired reading
MTW	0/1	1/1	No change
IHK	0/0	1/1	No change
JCG	0/1	1/1	No change





(3) The reading of paired chest radiographs

If paired chest radiographs are read in known order then there may be bias towards reading progression in the later film. Amandus et al (1973) have shown that when pairs of radiographs are assessed there is a tendency to read progression in the right hand film. In their study the effect was most marked at low levels of abnormality. Despite this finding they still decided that reading paired films in known order was the best method available and it was the one chosen by Jones et al (1980) and Becklake et al (1979) in their studies of radiographic change in asbestos exposed subjects.

The variations in radiographic technique were such that experienced readers would easily have been able to identify the chronological order and so presenting the films in random order would not have eliminated this bias.

(4) The determination of radiographic progression

This could be assessed either on the basis of the independent readings or on the paired readings.

There are arguments for and against both methods. Although paired readings may result in bias towards progression in the later film and perhaps towards not reading regression it does permit the readers to make

allowance for differences in technique and this appeared to happen judging from the comments made as the pairs were assessed.

Independent readings should be free of bias and this is strongly in their favour. Greater variation is seen with this method and it is possible that spurious regression may be recorded. The instructions for use of the ILO-U/C classification state that the reader should average the profusion of small opacities over the affected zones. If progression occurs by slight encroachment on a previously unaffected zone then the averaging procedure may reduce the profusion score. Furthermore in this study there was reason to believe that the readers were assessing profusion more severely in the follow up films (Appendix V).

On balance it was decided to assess progression on the basis of the paired assessment. Cases were only labelled as progressers if at least one reader thought definite progression had occurred and a second reader considered progression possible. This may have helped to counteract any bias towards over-reading.

Alternative reading strategies

The prosentation and follow up radiograph series were read seperately. The follow up series were probably read more severely and whilst this may have been due to the

Possible effects of pleural disease

Many of the cases had pleural disease (Table 5). This could potentially effect the study in two ways.

Firstly, pleural disease in the absence of radiologically apparent intrapulmonary fibrosis may lead to a small decrement in lung function (Lumley, 1977). Progression of pleural disease might lead to further loss while intrapulmonary fibrosis remained unchanged. In this study progression of asbestosis was determined radiographically and significant deterioration in lung function only occurred in the group of cases where an increase in small opacities was observed (pp120-126).

Secondly, the presence of pleural shadows may create difficulty in scoring the profusion of small opacities. Extensive pleural shadowing may obscure parenchymal disease and lead to an under-recording of profusion whilst minor pleural changes seen enface, particularly when small amounts of calcium are present may mimic intrapulmonary disease and result in the over-reading of profusion.

There is no way of knowing how great the effect of accompanying pleural disease is on the scoring of profusion but the good agreement on profusion categories in this study suggests that at least the readers behaved consistently. It is of note that in most cases the readers considered the parenchymal details to be clearly visible even though a high proportion of the cases had pleural disease.

A probable advantage of assessing progression by paired film analysis is that the readers have an opportunity to assess any pleural changes which may have confounded the scoring of profusion on independent readings.

An attempt was made to validate radiographically determined progression of asbestosis (pp 120-126). The results suggest that pleural disease is unlikely to have distorted the analysis of progression.

Lumley, K.P.S., (1977).

Physiological changes in asbestis pleural disease.

In: Inhaled Particles IV Ed. Walton W.H.
Pergamon Press, Oxford pp 781-788.

better quality of these radigraphs it may also reflect bias. The readers knew they were reporting the follow up films.

If all the radiographs had been randomised and read at one session the level of reading might have been more even although it is likely that the later films would still have been easily recognised and their better quality would still be unchanged. If this strategy had been adopted it might not have been possible to detect the tendency towards higher reading of the follow up films.

Mortality data

There are a number of sources of bias in this data. Firstly, the expected mortality experience has been calculated on the basis of all men or women in England and Wales using the 1970-72 Life Table. This does not make allowance for social class, geographic area or smoking habits. The standardised mortality ratio for lung cancer in the Greater London Area is higher than that for England and Wales overall and so the use of national mortality statistics leads to a slight overestimate of the lung cancer risk in a largely London based group of cases. It is also likely that the cigarette consumption of the group is higher than the national average. If this is so it leads to a further over-estimate of lung cancer mortality.

Secondly, comparability with mortality data derived from the general population is further diminished by the higher post mortem rate among the cases of asbestosis.

Conclusions

The methods used in this study were far from perfect. It would, for instance, have been better if all the radiographs had been taken using the same technique with the same equipment and same radiographer. Similar comments could be made about the lung function tests, the immunological investigations and clinical assessment. Such high standards are rarely possible but an attempt has been made to highlight the defects of the methods and the likely sources of bias.

RESULTS

Description of cases at presentation

Age

Figures 1 and 2 show the distribution of ages at presentation in the male and female cases. The mean age at presentation was higher in the female cases but the majority of cases in both sexes presented after the age of 50.

Exposure to asbestos

Figure 3 shows the duration of exposure to asbestos in the male cases. The mean exposure was 20.7 years but the range of exposures was very wide (0.75-54 years). The cases with short exposures had acquired these many years earlier and often before 1933 when the Asbestos Regulations came into force. Figure 5 shows the time from first exposure to diagnosis. In this study the Panel did not diagnose asbestosis in any case before nine years had elapsed from starting exposure and the mean time for the male cases was 28.4 years. This histogram (Fig. 5) has the appearance of bimodality. Data collected while following up the survivors suggests that this may have arisen as a consequence of periodic medical examinations at work leading to earlier recognition of disease. This could give rise to the first mode. The second mode arising as cases gradually present by other routes. This explanation must remain speculative.

The female cases generally had short exposures (Fig. 4) often before 1933. The mean interval from first exposure to diagnosis (40.54 years) is longer than for the men and the distribution is unimodal (Fig. 6).

Table 1 shows the occupations of the cases. All the women were factory workers. Most of the male cases were factory workers or insulation workers but a small number of cases arose in men working in the vicinity of insulation workers in power stations, dockyards and boilerworking. Only two cases had more than one type of exposure and in both cases they had both lagged and done factory work. They are classified according to which type of work was done for the longest time. Four men were exposed while handling imported asbestos fibre cargoes and seventeen cases were exposed in other ways. This group includes construction workers and pipe fitters who had apparently used asbestos products and perhaps more importantly had to remove lagging and occasionally apply it. A number of men exployed in the chemical industry had used asbestos as a filler in the manufacture of plastics and a further three men had been involved in manufacturing battery cases. One of these men had not personally used asbestos but the fibre was stored in hessian bags in his workshop.

Symptoms (Table 2)

Over half the male cases reported little or no breathlessness at presentation. Only two male cases were

breathless at rest. Twentyfive (16.3%) cases were breathless walking on level ground.

Eighty per cent of the male cases reported cough and 60% produced sputum. Rather fewer women reported cough and sputum production.

Smoking history (Table 3)

Only five male cases claimed never to have smoked and 65% were smoking at presentation. Five of the women had never smoked and only three were smoking at diagnosis.

Physical signs (Table 4)

All the female cases and 81% of the male cases had crepitations in the lung fields at presentation. Forty three per cent of the male cases and a similar proportion of the females had clubbing of the fingers.

Chest Radiographs

The distribution of profusion scores for small opacities for males and females is given for each reader (Figs 7-12). The median profusion score for males and females is given in Figs. 13 and 14. Many of the analyses to be described use only the four point scale of the shortened ULO-U/C

classification and so it is of note that relatively few radiographs are classified as 0/1. Most of the cases in category 0 are 0/0 films.

Table 5 gives details of pleural disease as recorded by each reader. About two thirds of the cases had pleural thickening irrespective of sex. Pleural calcification appears to be commoner in the women possibly reflecting the longer time from first exposure to asbestos.

Pulmonary Function Tests

Forced expiratory volume in one second (FEV_1), vital capacity (VC) and transfer factor (D_LCO) have been expressed as percentages of predicted values. Figures 15 and 17 show the distributions of percentage predicted FEV_1 and VC respectively in the men. The mean value for both measurements is similar leading to a normal mean value for FEV_1/FVC ratio (Fig 19) but a small number of cases have a low FEV_1/FVC ratio.

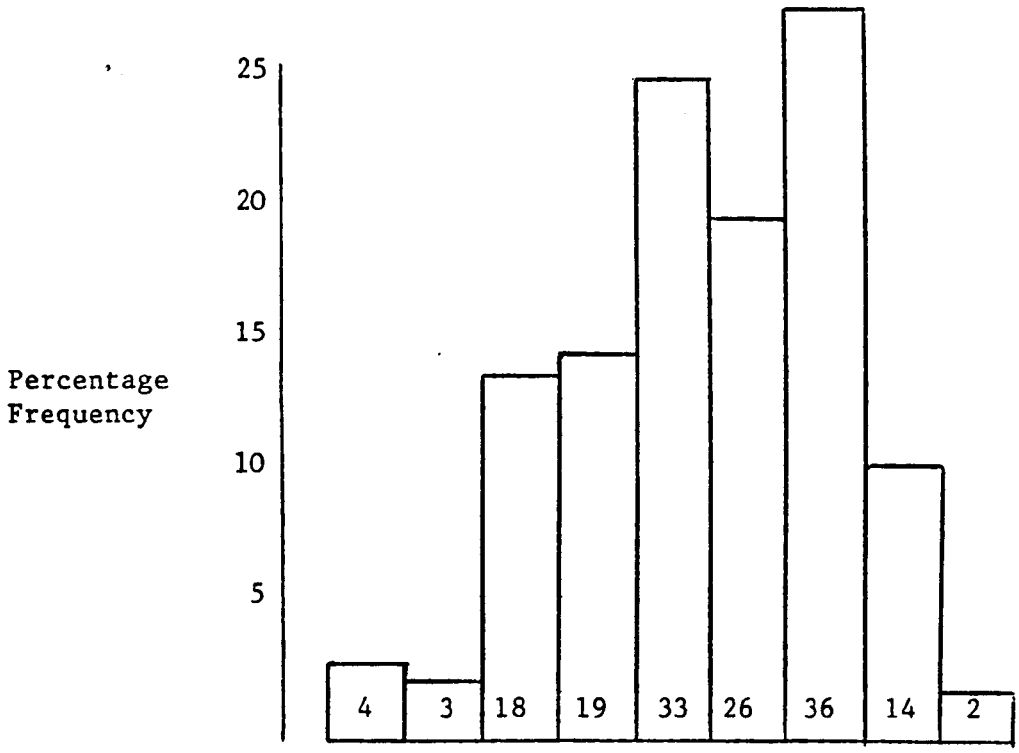
The female cases have a proportionately greater fall in VC (Fig 18) than in FEV_1 (Fig 17) resulting in a higher mean FEV_1/FVC ratio.

Figures 21 and 22 give the distribution of transfer factor in the male and female cases. The mean value is lower in the male than the female cases.

Immunological investigations (Table 6)

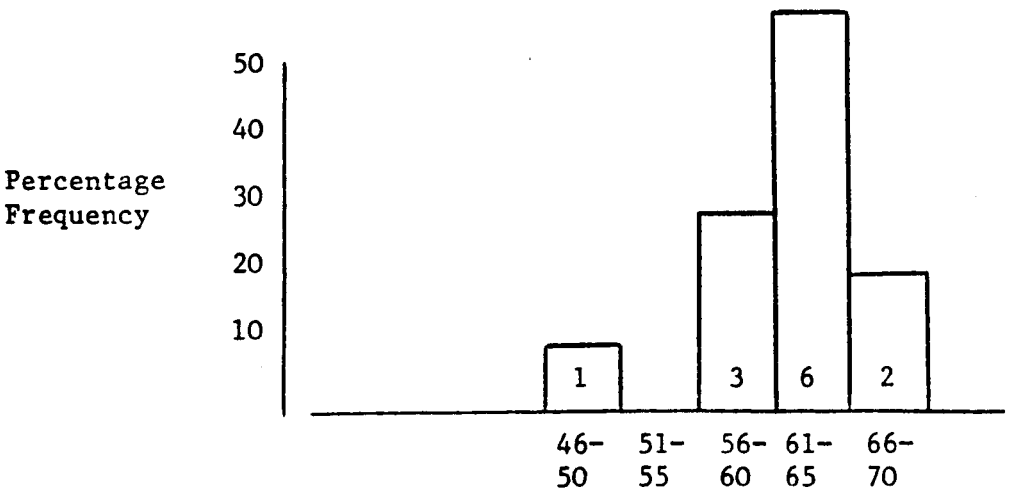
Positive tests for antinuclear anitbody occurred in 50% of female cases and 26.6% of the male cases. None of the women had a differential agglutination titre of $\geqslant$ 1/32 while 7.3% of the males were positive.

FIG. 1 - AGE OF MALE CASES AT PRESENTATION



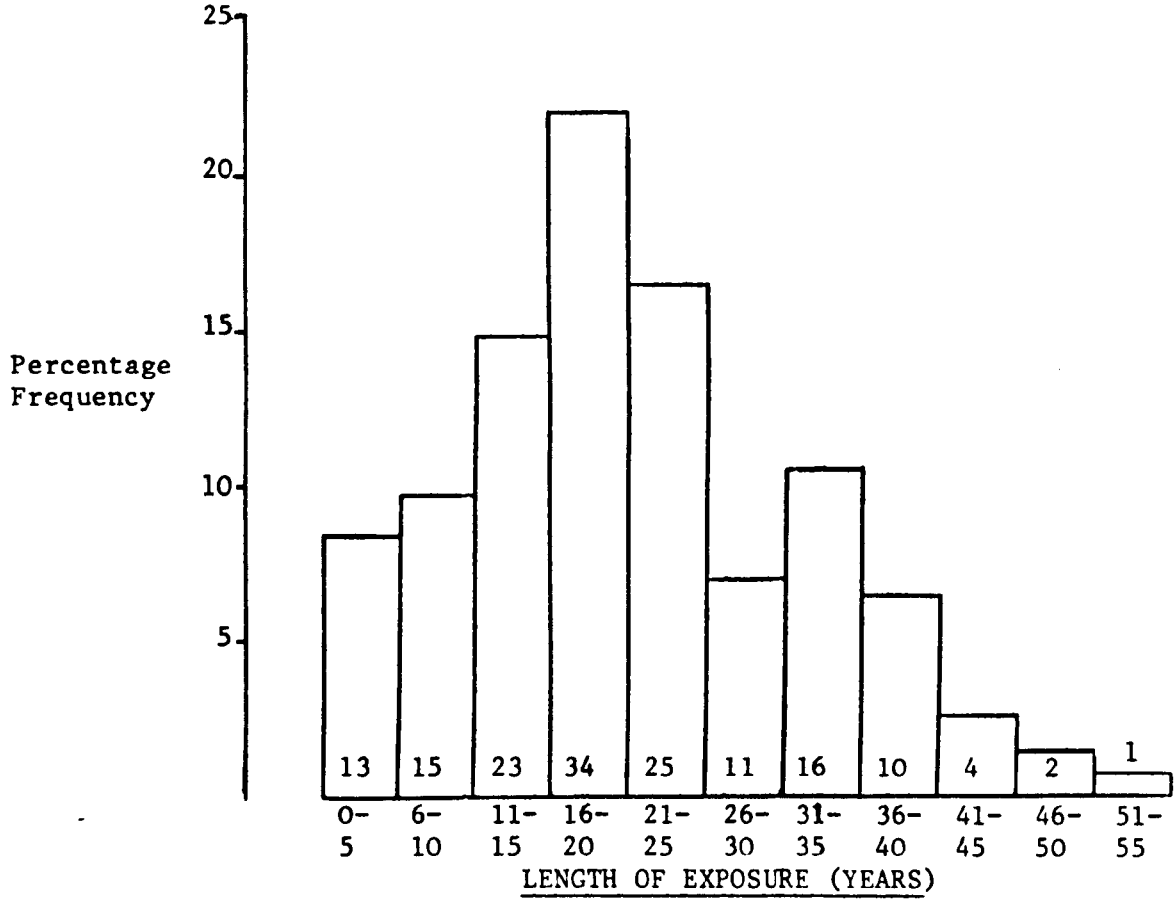
Total cases	155
Mean Age	52.2
Standard Deviation	8.83

FIG. 2 - AGE OF FEMALE CASES AT PRESENTATION



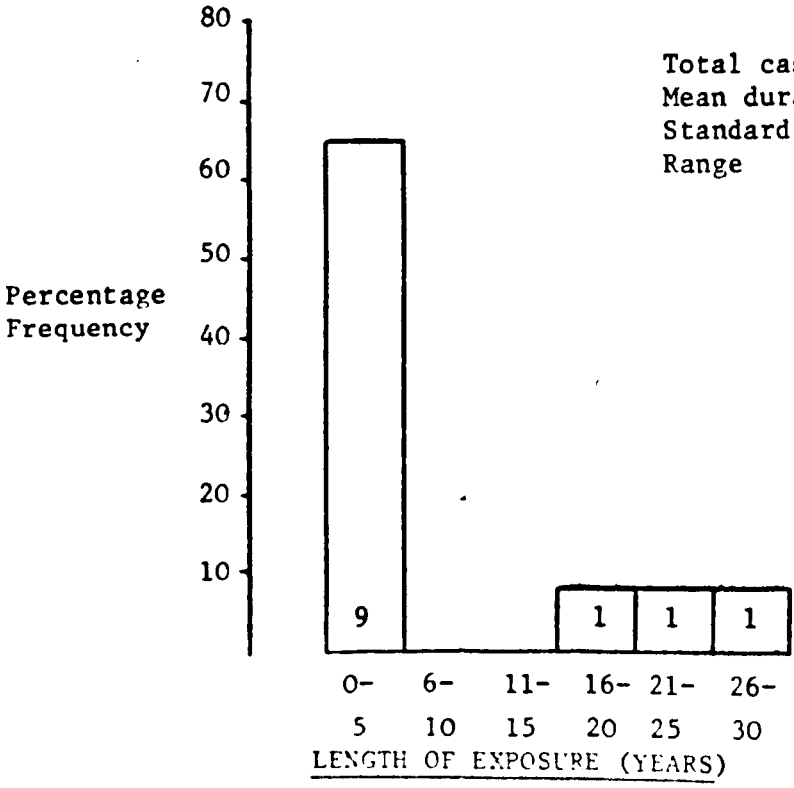
Total cases	12
Mean Age	58.3
Standard Deviation	5.36

FIG. 3 - DURATION OF EXPOSURE TO ASBESTOS IN MALE CASES AT PRESENTATION



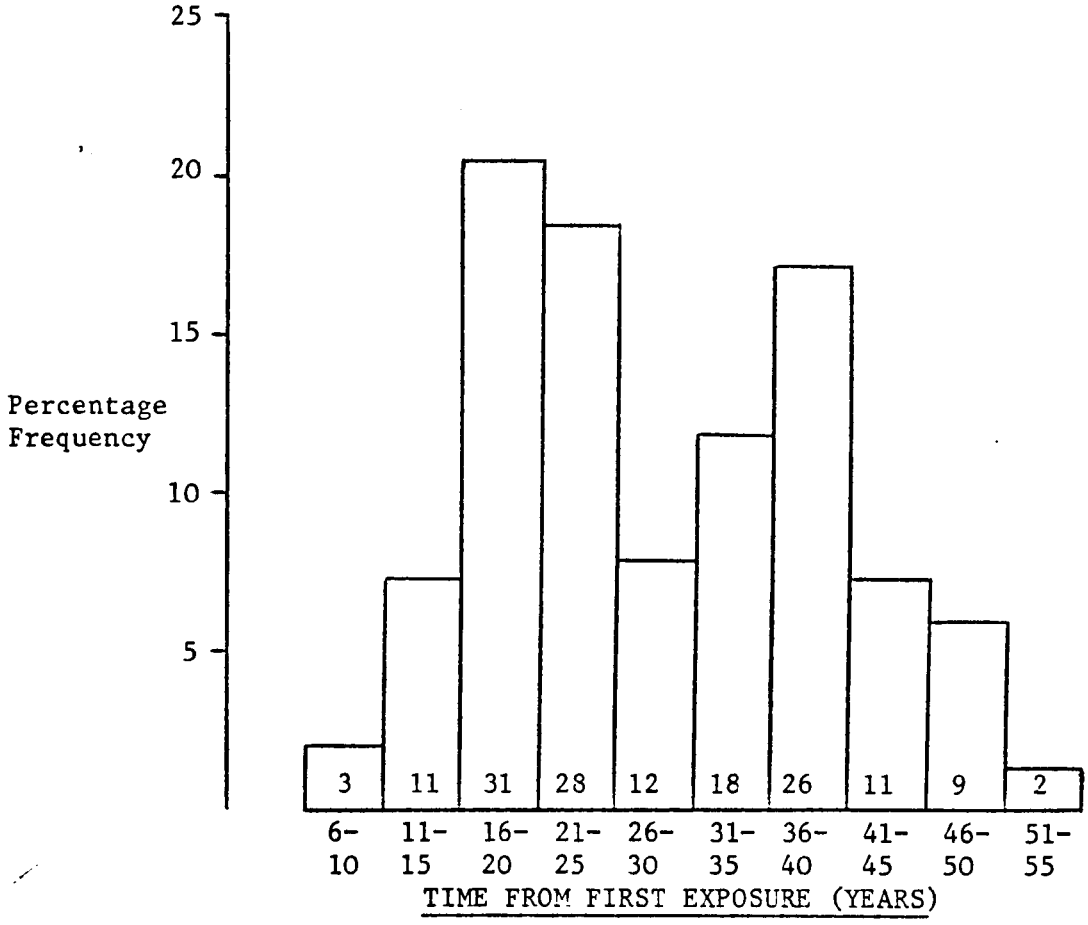
Total cases	154
Mean duration of exposure	20.7 years
Standard deviation	12.72
Range	0.75 - 54

FIG. 4 - DURATION OF EXPOSURE IN FEMALE CASES AT PRESENTATION



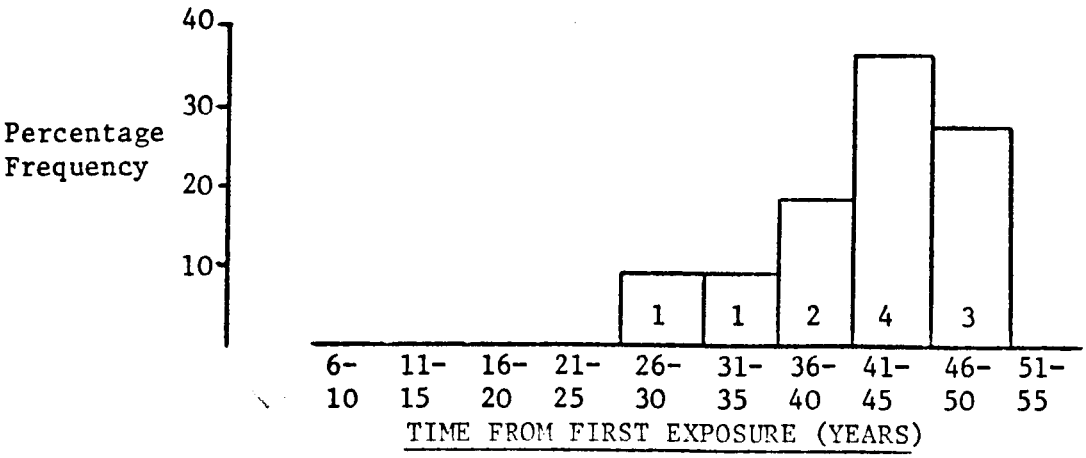
Total cases	12
Mean duration of exposure	7.5 years
Standard deviation	10.08
Range	1 - 30

FIG. 5 - TIME FROM FIRST EXPOSURE IN MALE CASES AT PRESENTATION



Total cases	151
Mean time from first exposure	28.4 years
Standard deviation	10.70
Range	9 - 54

FIG. 6 - TIME FROM FIRST EXPOSURE IN FEMALE CASES AT PRESENTATION



Total cases	11
Mean time from first exposure	40.54 years
Standard deviation	6.53
Range	27 - 48

TABLE 1

Occupations of Male Cases

		%
Laggers	59	38.0
Asbestos factory workers	49	31.6
Asbestos sprayers	9	5.8
Dockyard workers excluding laggers	8	5.2
Powerstation workers excluding laggers	5	3.2
Boiler workers, not in dockyards or powerstations	4	2.6
Dockers	4	2.6
Others	17	11.0
	155	100%

Occupations of Female Cases

Asbestos factory workers	12	100%

TABLE 2

Symptoms

Exercise tolerance	Males (153)	Females (12)
Normal	27 (17.7%)	1 (83%)
Breathless climbing hills or 2 flights of stairs	53 (34.6%)	4 (33.3%)
Breathless on a slight incline or 1 flight of stairs	46 (30.1%)	4 (33.3%)
Breathless walking on level ground	25 (16.3%)	3 (25%)
Breathless at rest	2 (1.3%)	0 (0%)
Cough for at least 3 months of the year	122 (80%)	6 (50%)
Sputum for at least 3 months of the year	63* (60%)	3 (25%)

*Information on the presence or absence of sputum was available for only 105 cases

TABLE 3

Smoking History

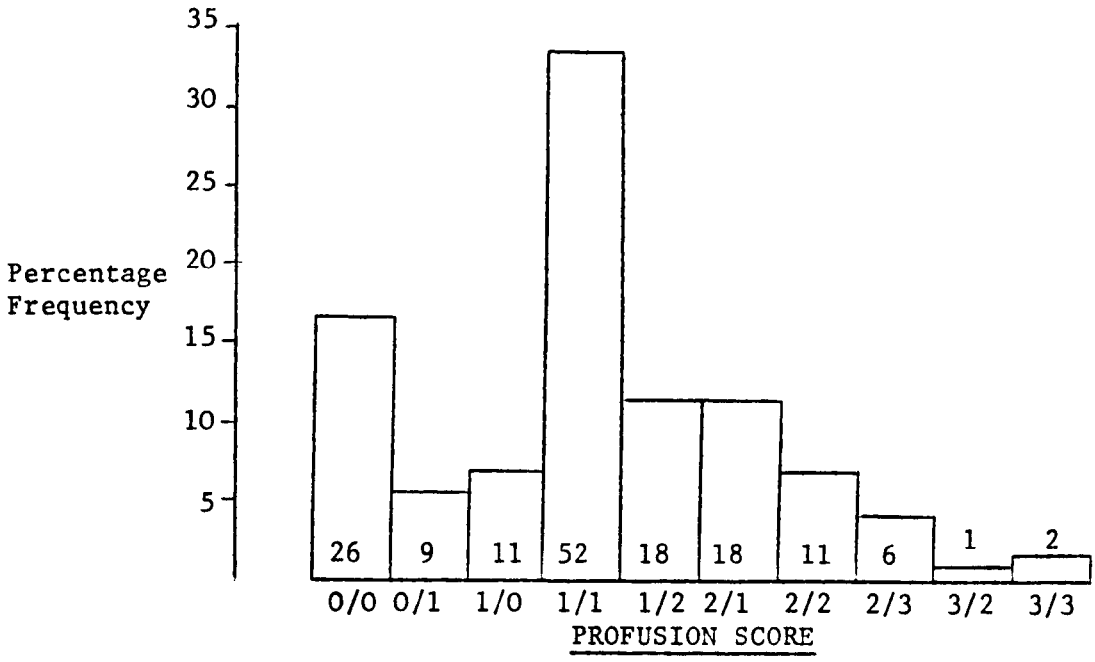
	Males (155)	Females (12)
Smoking at diagnosis	101 (65%)	3 (25%)
History at regular cigarette smoking	150 (97%)	7 (58%)

TABLE 4

Physical Signs

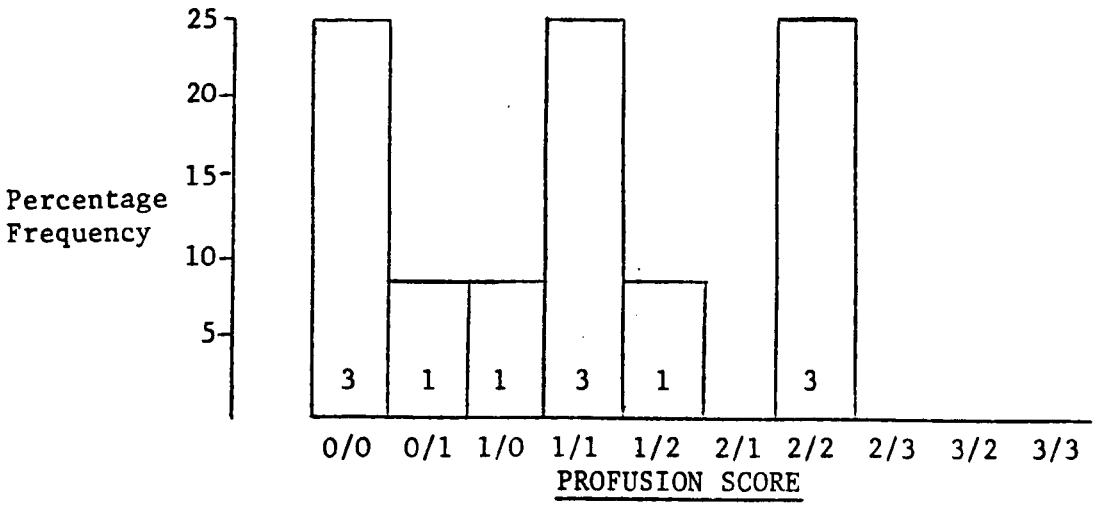
	Males (155)	Females (12)
Crepitations	126 (81%)	12 (100%)
Finger clubbing	67 (43%)	5 (42%)

FIG. 7 - DISTRIBUTION OF SMALL OPACITIES IN MALES



Total cases 154
Reader MT-W

FIG. 8 - DISTRIBUTION OF SMALL OPACITIES IN FEMALES



Total cases 12
Reader M T-W

FIG. 9 - DISTRIBUTION OF SMALL OPACITIES IN MALES

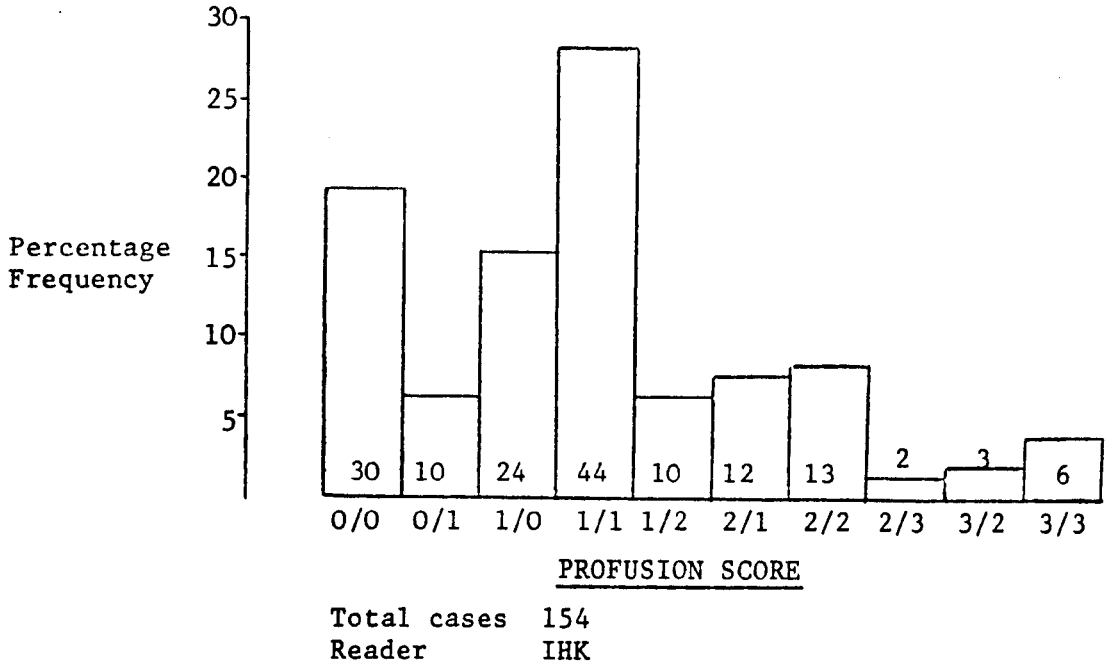


FIG. 10 - DISTRIBUTION OF SMALL OPACITIES IN FEMALES

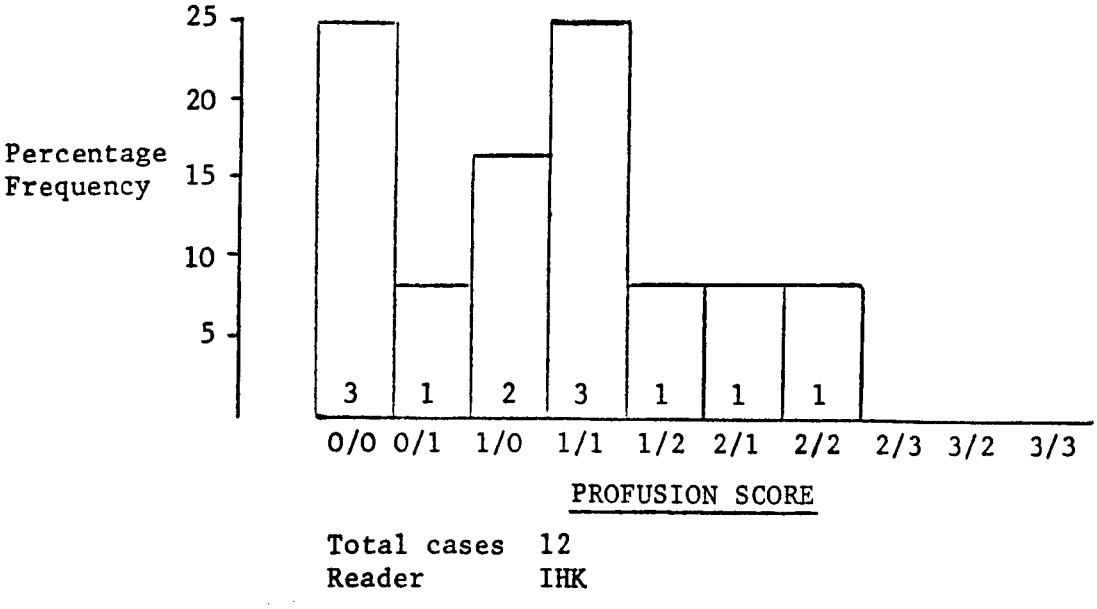


FIG. 11 - DISTRIBUTION OF SMALL OPACITIES IN MALES

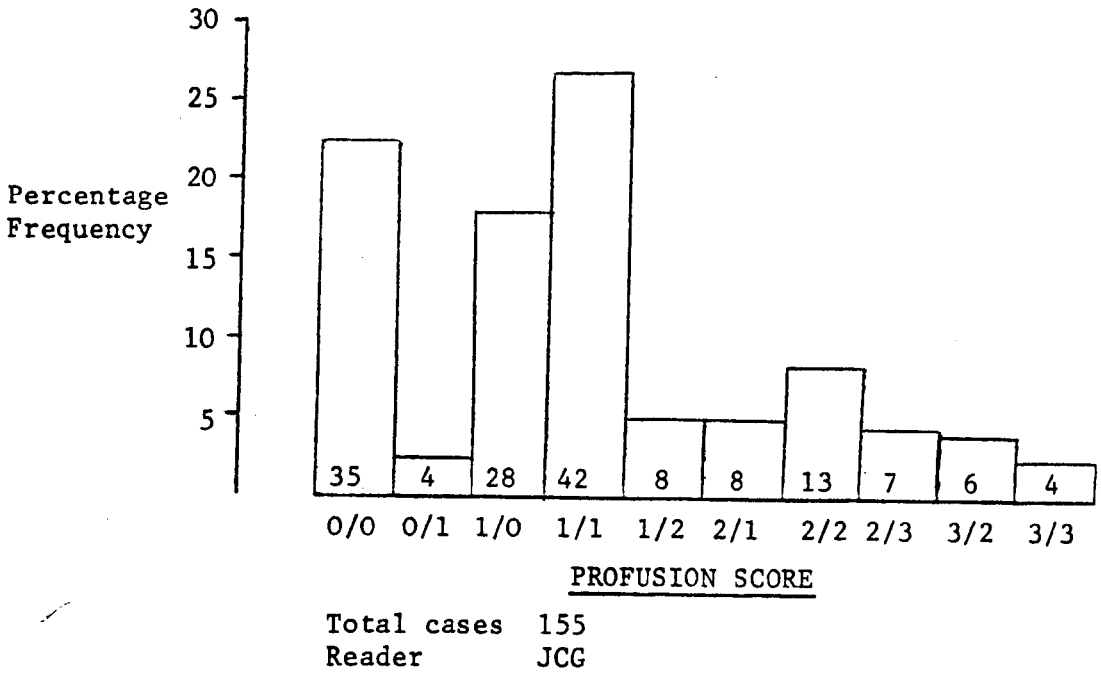


FIG. 12 - DISTRIBUTION OF SMALL OPACITIES IN FEMALES

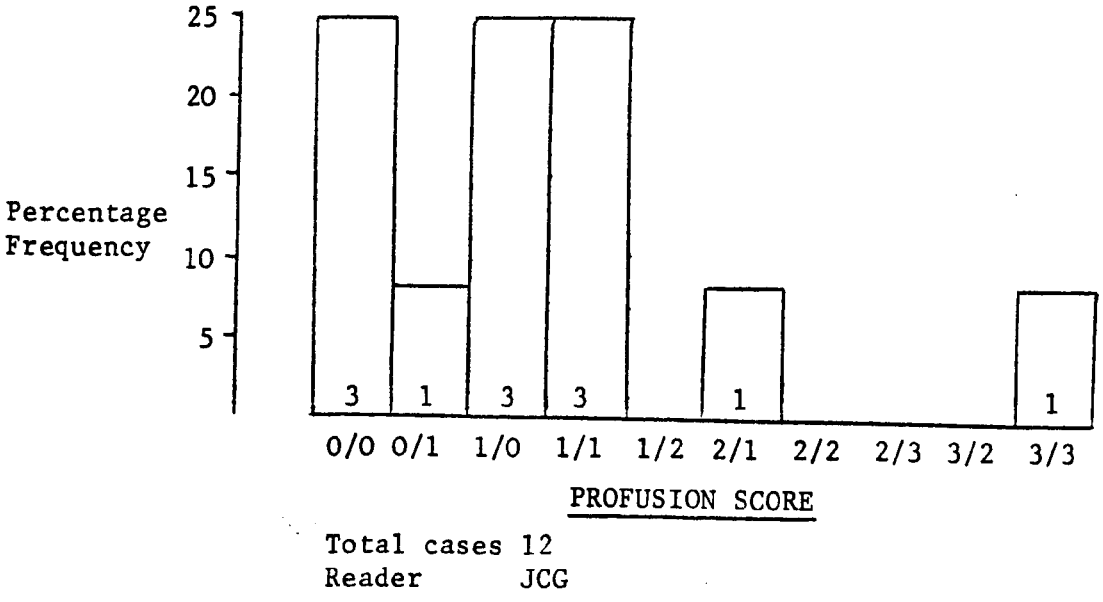


FIG. 13 - DISTRIBUTION OF SMALL OPACITIES IN MALES USING MEDIAN OF THREE READINGS

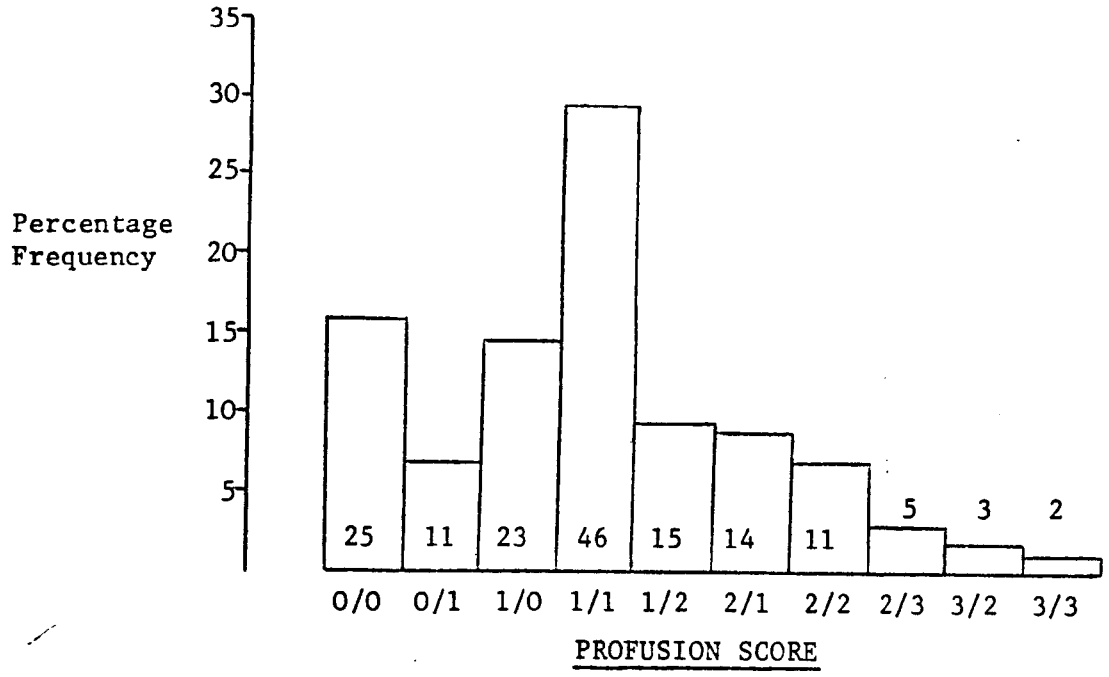


FIG. 14 - DISTRIBUTION OF SMALL OPACITIES IN FEMALES USING MEDIAN OF THREE READINGS

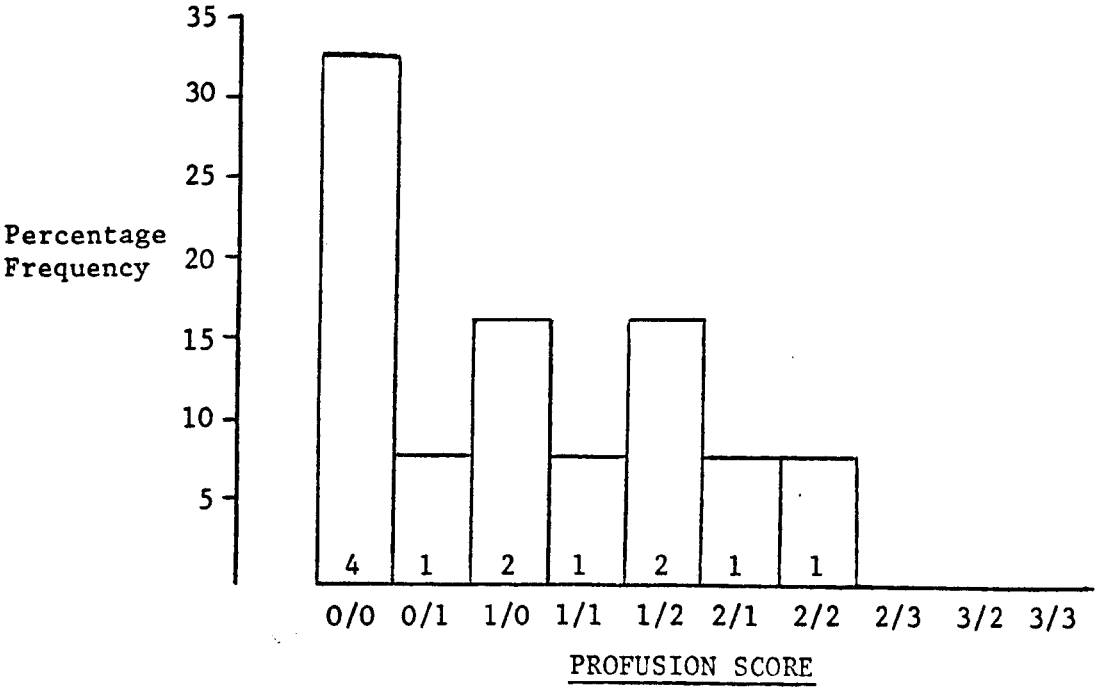


TABLE 5

Percentage Showing Pleural Thickening and Pleural Calcification

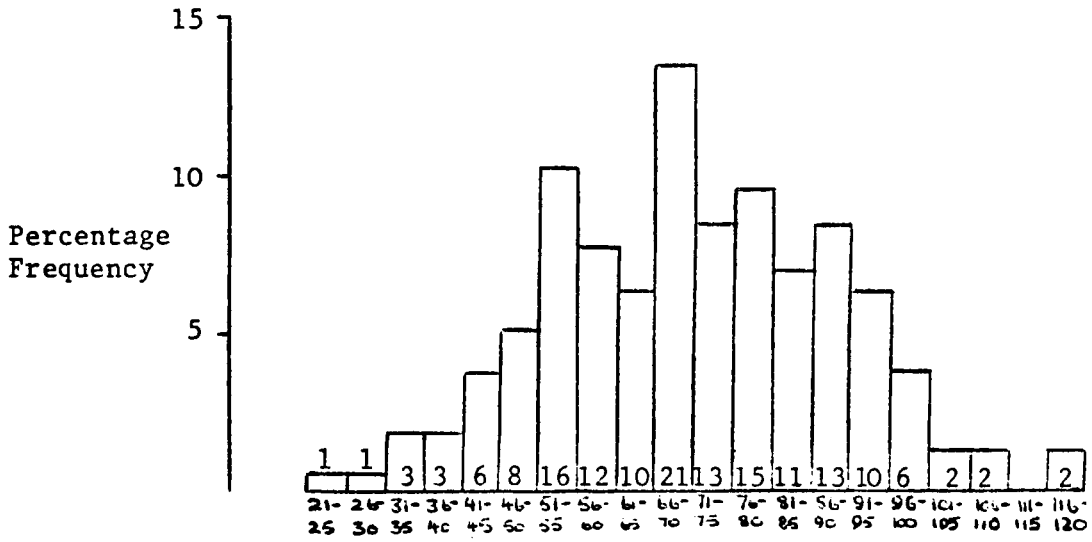
Male Cases (155)

Reader	Pleural Thickening	Pleural Calcification
MTW	63	25
IHK	70	34
JCG	63	32

Female Cases (12)

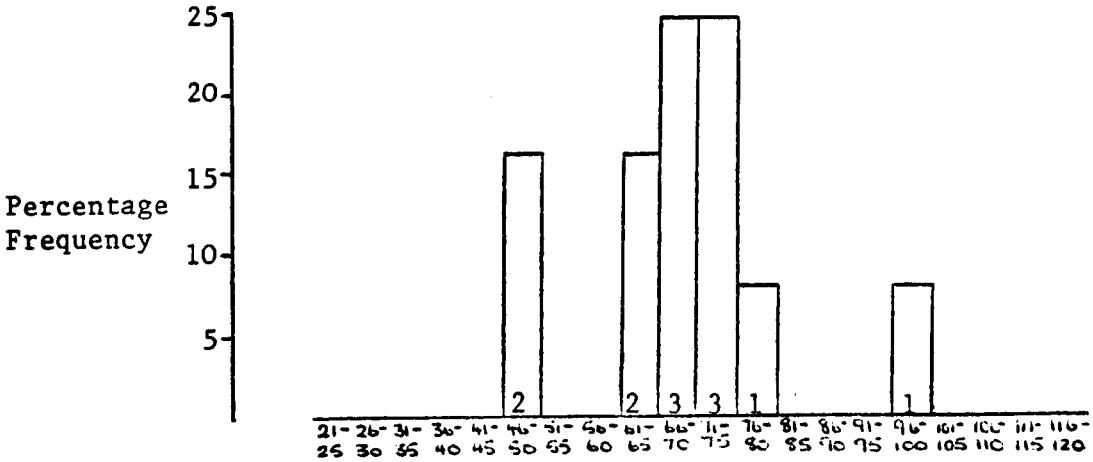
MTW	58	42
IHK	75	50
JCG	67	42

FIG. 15 - PERCENTAGE OF PREDICTED FEV1 AT PRESENTATION IN MALE CASES



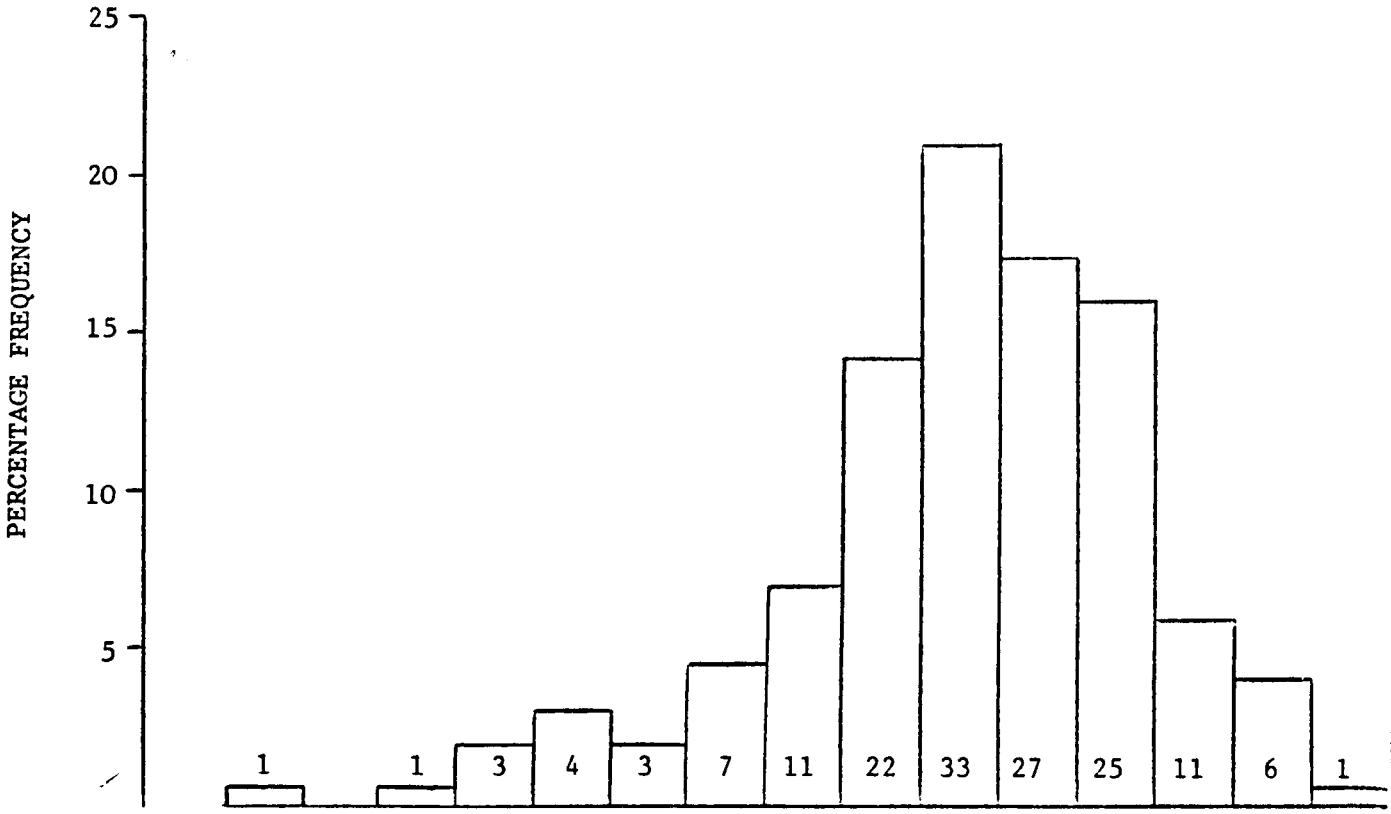
Total cases	155
Mean percentage predicted FEV1	67.06
Standard deviation	18.57

FIG. 16 - PERCENTAGE OF PREDICTED FEV1 AT PRESENTATION IN FEMALE CASES



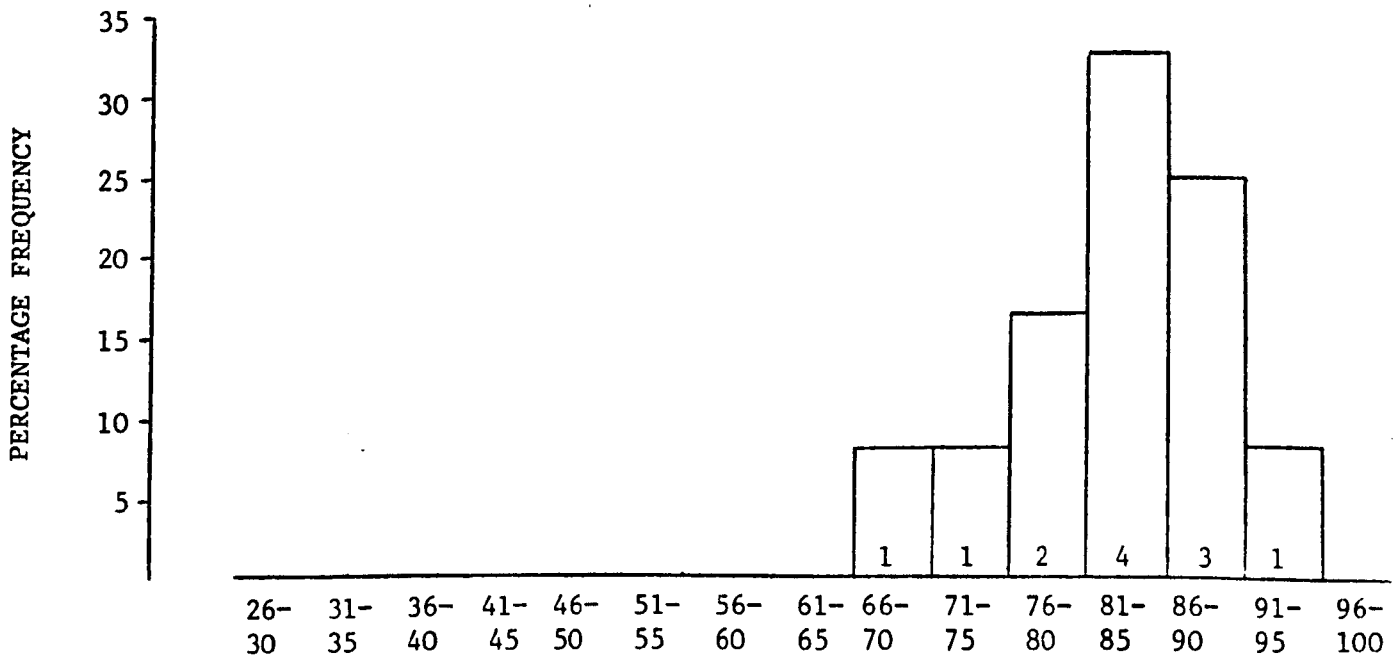
Total cases	12
Mean percentage predicted FEV1	65.42
Standard deviation	13.22

FIG. 19 - FEV1/FVC% RATIO AT PRESENTATION IN MALE CASES



Total cases 155
Mean FEV1/FVC% 70.26
Standard deviation 11.83

FIG. 20 - FEV1/FVC% RATIO AT PRESENTATION IN FEMALE CASES



Total cases 12
Mean FEV1/FVC% 79.16
Standard deviation 7.02

FIG. 17 - PERCENTAGE OF PREDICTED VITAL CAPACITY (VC) AT PRESENTATION IN MALE CASES

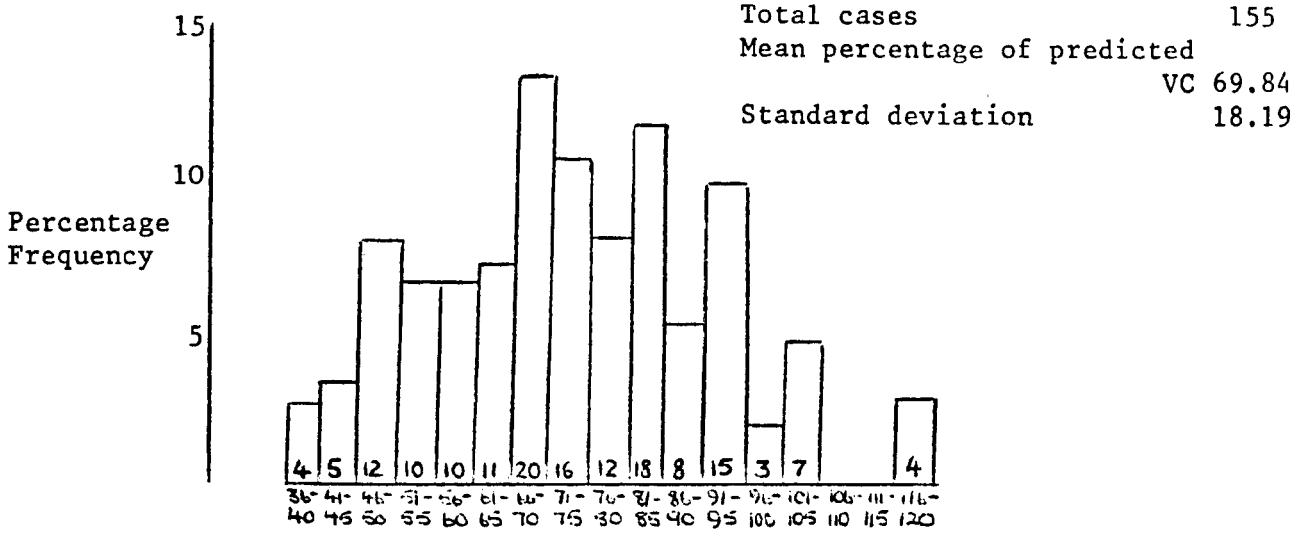


FIG. 18 - PERCENTAGE OF PREDICTED VITAL CAPACITY (VC) AT PRESENTATION IN FEMALE CASES

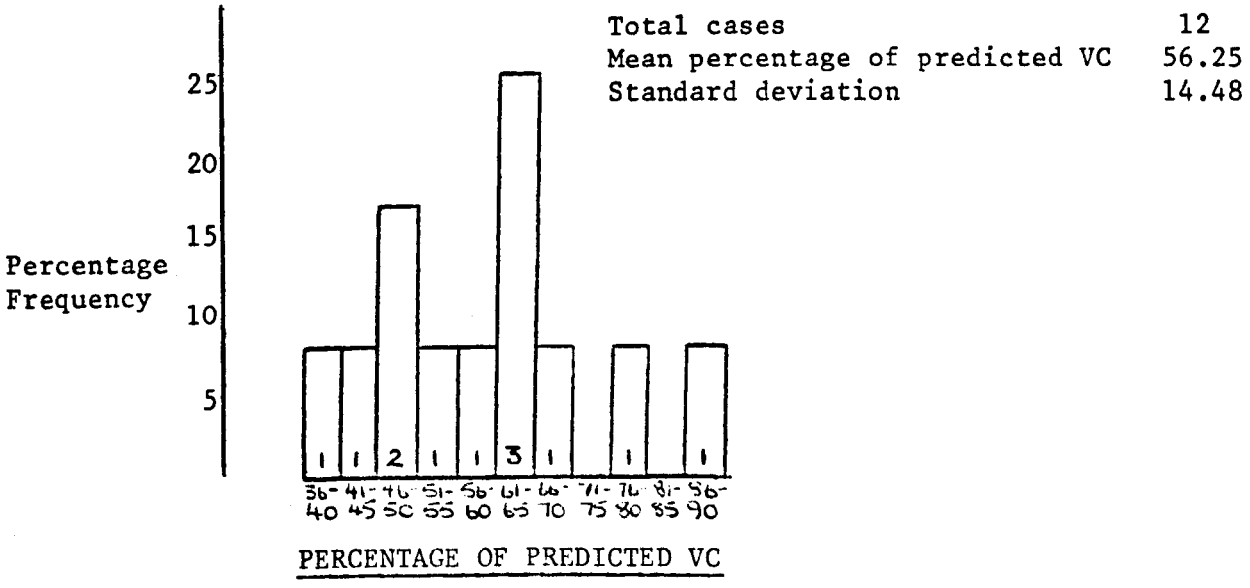
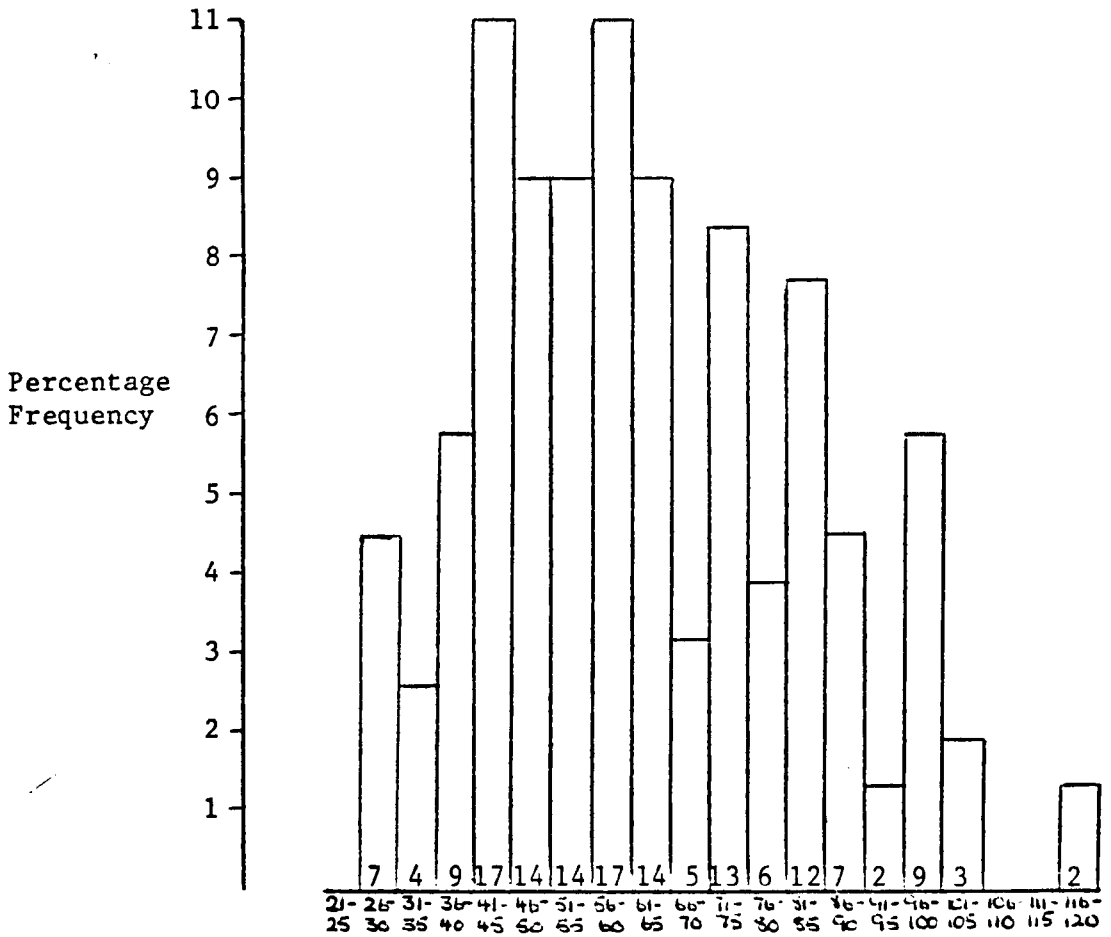


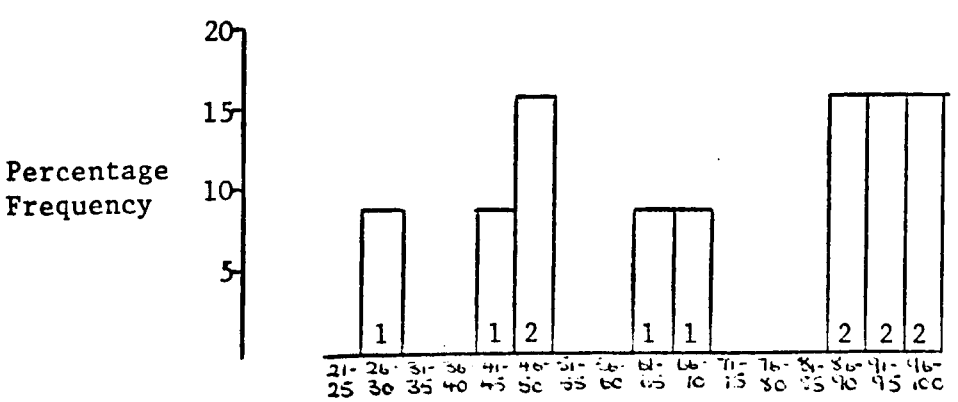
FIG. 21 - PERCENTAGE OF PREDICTED TRANSFER FACTOR (DLCO) AT PRESENTATION IN MALE CASES



PERCENTAGE OF PREDICTED DLCO

Total cases	155
Mean percentage predicted DLCO	59.35
Standard deviation	20.54

FIG. 22 - PERCENTAGE OF PREDICTED TRANSFER FACTOR (DLCO) AT PRESENTATION IN FEMALE CASES



PERCENTAGE OF PREDICTED DLCO

Total cases	12
Mean percentage predicted DLCO	68.34
Standard deviation	24.8

TABLE 6

Immunological Studies

Antinuclear antibody

Titre	Females (12)	Males (150)
	5 (41.7%)	106 (70.6%)
±	1 (8.3%)	4 (2.7%)
+	1 (8.3%)	25 (16.7%)
++	4 (33.3%)	14 (9.3%)
+++	1 (8.3%)	1 (0.7%)

Differential agglutination test

0	11 (91.7%)	122 (81.3%)
1/4		3 (2%)
1/8		2 (1.3%)
1/16	1 (8.3%)	11 (8%)
1/32		6 (4%)
1/64		
1/128		1 (0.7%)
1/256		1 (0.7%)
1/512		3 (2%)

Mortality

Of the 167 cases in this study 66 (59 men and 7 women) died before follow up could be obtained.

Mortality in asbestosis: Males

Causes of death in males (Table 7)

Twenty-three cases had a death certificate diagnosis of lung cancer. Pathological material was examined by the Pneumoconiosis Medical Panel in twenty of these cases and there was complete agreement about cause of death. The panel found lung cancers in a further three cases where death had been ascribed to other causes on the death certificate.

Six death certificates recorded mesothelioma and again the diagnosis was confirmed by the panel.

Eleven cases died from respiratory disease other than lung cancer or mesothelioma. The remaining cases died from other causes. No excess of gastrointestinal cancer was seen and no case of laryngeal cancer occurred.

Fig. 23 compares the mortality experience of the 155 male cases of asbestosis with that of the general male population of a similar age. The overall mortality experience of the asbestotic men is worse.

Mortality ratios in asbestosis

Tables 9 and 10 show the mortality experience after 5 and after 10 years observation of the 155 male cases. There is an excess mortality at 5 and at 10 years from all causes ($p < 0.001$) and this comes about because of an excess of deaths from lung cancer ($p < 0.001$), respiratory disease ($p < 0.001$) and mesothelioma. There is no basis of expectation for death from mesothelioma but the six cases seen in 1107 man years of observation is clearly excessive for what is a rare disease.

Table 11 examines the mortality ratios in different decades. The mortality ratio is highest in the sixth decade and then falls off in the seventh and eighth decades.

The mortality ratios are lower at the ten year point than at the five year point. The mortality ratio for all causes of death in those who survive into the second five year period after diagnosis is 1.51 (18/11.9031). This suggests that risk diminishes with time. Two factors may contribute to this. Firstly, the cases with a category 0 profusion score do not have an increased overall mortality ratio (Tables 9 and 10) and so are likely to form an increasing proportion of the at risk population as time elapses. Secondly, Table 11 shows that the mortality ratio falls in the higher age groups again suggesting that those who survive are at less risk.

Mortality in relation to profusion of small opacities on chest radiograph

Table 8 gives details of the male deaths by radiographic category. Relatively few deaths occurred in category 0 but over 40% of cases died in each of the other two categories. Although the mean age at presentation and at death rises with increasing profusion score these differences are not statistically significant. There were no statistically significant differences in duration of exposure to asbestos amongst either the deaths in each category or amongst all cases in each category. (Mean exposure of category 0 cases 21 years, range 1-47, category 1 mean of 20 years, range 1-47 and category 2 and 3 mean of 17 years, range 1-46).

Tables 9 and 10 give mortality ratios after 5 and after 10 years observation for three radiographic categories 0, 1 and 2+3. Mortality from all causes is not increased among the 36 category 0 cases but on the basis of small numbers of deaths the mortality ratio for lung cancer and respiratory disease is increased.

The mortality ratio for all causes of death is increased in category 1 ($p < 0.001$) and in categories 2+3 ($p < 0.05$) at both the 5 and 10 year points. This is due to high mortality ratios for lung cancer and slightly less high ratios for respiratory disease. Five mesothelioma deaths occurred in category 1 cases and one in category 2.

Mortality ratios are seen to increase as radiographic category increases only in the case of respiratory disease at the ten year point and the number of deaths (11) is too few to show any statistically significant trend. Otherwise the highest mortality ratios for all classes of death are seen in category 1 cases both at the five and ten year points.

Effect of cigarette smoking

It was not possible to investigate this. Only one of the male deaths occurred in a life long non-smoker and only five of the 155 male cases were life long non-smokers. The death was due to pleural mesothelioma.

Factors predicting mortality in asbestosis

In order to determine whether any features present at the time of diagnosis were of value in predicting mortality a discriminant analysis of the survivors and the deaths was performed to assess the importance of the following features:

Age at presentation
Finger clubbing
Duration of exposure to asbestos
Time from first exposure to asbestos
Percentage of predicted D_LCO.
Percentage of predicted VC
Percentage of predicted FEV_1
Score for small opacities using the twelve point scale.

Finger clubbing ($p < 0.05$), age at presentation ($p < 0.025$) and percentage of predicted FEV_1 ($p < 0.01$) were found to be of value in discriminating between survivors and non-survivors. The separation achieved by the discriminant function involving all eight factors resulted in an estimated misclassification of 28% of the cases.

When the analysis was re-run using only the significant variables the following probability values were obtained:

Age at presentation	$p < 0.01$
Finger clubbing	$p < 0.01$
Percentage of predicted FEV_1	$p < 0.01$

The discriminant function resulted in misclassification in an estimated 35% of cases.

Table 12 compares the lung function results at certification in the surviving and non-surviving cases. It can be seen that their is a large difference between the percentage of predicted D_LCO in the two groups. This variable does not appear to be of value in the discriminant analysis because of an association between it and finger clubbing. This association will be discussed further in the section on finger clubbing.

Fig. 30 sets out in life table form the mortality experience of the cases with and without finger clubbing at presentation. The two groups appear to be moving apart throughout the twelve year period but the possibility that the difference is all due to early deaths from lung cancer in the cases with finger clubbing needs to be considered.

Thirty-three of the male deaths had finger clubbing at diagnosis and 17 of these had a death certificate diagnosis of lung cancer. A further death was certified due to another cause but a pulmonary carcinoma was found when the Pneumoconiosis Medical Panel examined the lungs. In six of the 26 deaths in cases without finger clubbing death was certified as due to lung cancer and two further cases of lung cancer were found when the panel examined the lungs.

Of the 26 cases in which lung cancer was present at death 12 occurred within three years of diagnosis. Two in the first and third years and eight in the second. Finger clubbing was present in 10 of the 12 cases. Two of the cases with finger clubbing were known to have lung cancer when asbestosis was diagnosed and these cases were identified by each of the 3 film readers. Three further cases, two with finger clubbing and one without had chest radiographs which were recorded as showing other disease by one reader in two cases and 2 readers in the third. On review these abnormalities were considered compatible

with but not diagnostic of lung cancer. Review of all twelve radiographs with the possibility of lung cancer in mind revealed a sixth film which had a possibly abnormal right hilum with a shadow in the right costoprenic angle. It has not been possible to correlate the findings in these four cases with post mortem information.

Despite the greater mortality ratio in the younger age groups (Table 11) the association between increasing age and the absolute risk of death was to be expected.

No association was found between increasing profusion of small opacities and increased mortality and this is in keeping with the results in Tables 9 and 10.

No discernible effect was found of increasing duration of exposure or increasing time from first exposure when allowance was made for age at presentation.

Histology of bronchial carcinomas

Histology was available for 24 of the cases who developed lung cancer (Table 13). Adenocarcinoma was the commonest cell type closely followed by squamous cell carcinoma. Although the incidence of adenocarcinoma appears to be higher than that generally reported no appropriate series of post mortem cases is available to allow statistical testing to be carried out. However

after 10 years observation 3.1 deaths were expected (Table 10) from lung cancer and so adenocarcinoma cannot be responsible for all the excess cases.

Table 14 shows the distribution of the various histological types by radiographic profusion category. This suggests that adenocarcinoma is the commonest tumour in cases with category 2 and 3 profusion scores.

Mortality in femalecases

Seven of the 12 female cases died. Details of the cause of death obtained from the death certificate, age at death, radiographic profusion of small opacities and exposure are given in Table 15. Five of the seven cases had short exposures many years before certification. Only three of the cases smoked and there were no deaths from lung cancer. Despite this the mortality ratios were high both after five and ten years observation. At five years 4 deaths had occurred against 0.71 expected (O/E 5.63) and at ten years 7 had occurred against 1.29 expected (O/E 5.42). These mortality ratios are higher than those for the male cases but the number of female cases and the subject years of observation (54 subject years at 5 years and 82 subject years at 10 years) are too small for any firm conclusions to be drawn about female mortality experience in asbestosis.

SUMMARY

(1) Mortality is increased in these cases of asbestosis as a result of an excess death rate from lung cancer, mesothelimoma and respiratory disease.

(2) Finger clubbing and percentage of predicted FEV_1 are of value in predicting death.

(3) Duration of exposure to asbestos and time from first exposure to asbestos did not predict death after making allowance for age.

(4) Overall mortality was increased in cases with a category 1 or higher profusion score but increasing profusion score above category 1/0 (using the 12 point scale of the ILO U/C classification) was not associated with increasing mortality.

(5) There was a suggestion of an excess of adenocarcinoma but it did not account for all the extra cases of lung cancer seen.

TABLE 7

Cause of Death Appearing on the Death Certificate in 59 Male Deaths

Lung Cancer	23	(39%)
Mesothelioma - pleural	3	(10%)
- peritoneal	3	
Cor pulmonale	7	
Bronchopneumonia	3	(19%)
Asbestosis	1	
Cardiovascular disease	10	
Peritonitis	2	
Cirrhosis of the liver	1	
Carcinoma of the rectum	2	(32%)
Carcinoma of oesophagus	1	
Carcinoma of penis	1	
Carcinoma of rectum	1	

FIG. 23

SURVIVAL AFTER DIAGNOSIS IN MEN WITH ASBESTOSIS

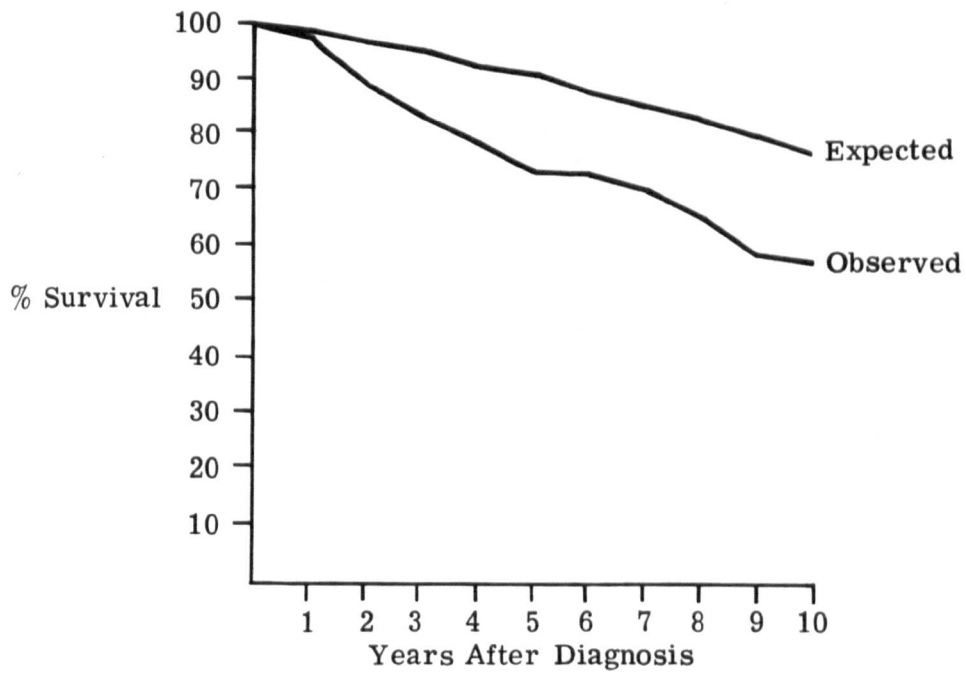


TABLE 8

Male Deaths in Asbestosis: details of age at presentation and at death, duration of exposure, time from first exposure and radiographic category

Radiographic Category	0	1	2+3*
Total Male Cases (155)	36 (23%)	84 (54%)	35 (23%)
Male deaths (59)	6	38	15
Age at presentation			
Mean	53	57	60
Range	38-61	42-72	47-68
Age at death			
Mean	58	60	64
Range	45-67	43-75	50-72
Exposure in years			
Mean	13	21	18
Range	2-46	3-37	1-44
Duration from first exposure			
Mean	31	29	29
Range	12-46	13-50	12-46

*Only 5 cases were in category 3 at presentation and these have been combined with category 2.

TABLE 9

Observed and Expected Mortality of Men by Radiographic Category in the Five Years after Certification

Radiographic Category	Years of Observation	ALL DEATHS			LUNG CANCER DEATHS			RESPIRATORY DEATHS			OTHER DEATHS (excluding mesothelioma)		
		Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E
0	173	3	2.9078	1.03	2	0.3710	5.39	1	0.3571	2.80	0	2.1797	-
1	373	28	6.8652	4.07	13	0.8732	14.89	3	0.8713	3.44	9	5.1206	1.76
2+3	151	9	3.9754	2.27	3	0.5022	5.97	2	0.6218	3.22	3	2.8514	1.05
ALL	697	40	13.7484	2.91	18	1.7464	10.31	6	1.8502	3.24	12	10.1337	1.18

4 mesothelioma deaths occured in 697 man years of observation, 3 in category 1 and 1 in category 2.

TABLE 10

Observed and Expected Mortality of Men by Radiographic Category in the Ten Years After Certification

Radiographic Category	Years of Observation	ALL DEATHS			LUNG CANCER DEATHS			RESPIRATORY DEATHS			OTHER DEATHS (excluding mesothelioma)		
		Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E	Observed (O)	Expected (E)	O/E
0	297	6	5.9710	1.00	3	0.7400	4.05	2	0.7842	2.55	1	4.4468	0.22
1	579	38	12.2782	3.09	16	1.5030	10.65	5	1.6647	3.00	12	9.1106	1.31
2+3	231	14	7.4023	1.89	4	0.8665	4.62	4	1.1179	3.58	5	5.4178	0.92
ALL	1107	58	25.6515	2.26	23	3.1095	7.39	11	3.5668	3.08	18	18.9752	0.95

6 mesothelioma deaths in 1107 man years of observation, 5 in category 1 and 1 in category 3

TABLE 11

Observed and Expected Mortality of Men by Age

AGE GROUP	5 YEARS OBSERVATION				10 YEARS OBSERVATION			
	Years of Observation	Observed Deaths (O)	Expected Deaths (E)	O/E	Years of Observation	Observed Deaths (O)	Expected Deaths (E)	O/E
30 - 39	24	-	0.0350		33	-	0.512	-
40 - 49	128	2	0.6016	3.33	173	3	0.8140	3.69
50 - 59	259	17	3.0946	5.49	400	22	4.8397	4.55
60 - 69	255	18	7.8389	2.30	405	24	13.2582	1.81
70 - 79	31	3	1.9183	1.56	96	9	6.4284	1.40
ALL	697	40	13.4884	2.97	1107	58	25.3915	2.28

TABLE 12

Comparison of Percentage of Predicted DLCO, VC and FEV1 at presentation in those who survived to Follow-Up and those who died

LUNG FUNCTION TEST	STATUS	NUMBER OF CASES	MEAN	STANDARD DEVIATION	T VALUE	PROBABILITY VALUE
% age predicted DLCO	ALIVE	92	62.90	19.55	2.83	0.005
	DEAD	56	53.94	17.17		
% age predicted VC	ALIVE	96	72.40	16.86	1.47	0.143
	DEAD	55	68.21	16.79		
% age predicted FEV1	ALIVE	96	72.29	17.27	2.65	0.009
	DEAD	58	64.50	18.35		

TABLE 13

Histology of Bronchial Carcinoma in 26 Cases with Asbestosis

Adenocarcinoma	11	41%
Squamous cell	9	33%
Oat cell	4	15%
Undifferentiated	1	3.5%
Unknown	2	7.5%

One case had two primary lung tumours, the histology of one being adenocarcinoma and the other a squamous cell carcinoma

TABLE 14

Histology of Bronchial Carcinoma According to Radiographic Category

Radiographic Category	Adeno-Carcinoma	Squamous Cell	Oat Cell	Undifferentiated	Unknown
0	1	1		1	
1	1	1	4		2
2	3	1			
3	1				
TOTAL	11	9	4	1	2

TABLE 15

Details of Female Deaths

Case	Radiographic Category	Cause of Death	Age at Death	Duration of Exposure	Time from first Exposure	Smoking Status
1	1	Coronary thrombosis	69	2	43	NEVER
2	1	Bronchopneumonia	64	2	43	NEVER
3	2	Cor pulmonale	75	30	37	NEVER
4	1	Asbestosis	69	3	46	NEVER
5	0	Coronary thrombosis	61	1	41	SMOKER
6	1	Peritoneal mesothelioma	69	1	48	SMOKER
7	0	Cancer of oesophagus	63	21	27	SMOKER

Progression of intrapulmonary fibrosis

Validation of radiographically determined progression

Radiographically determined progression has been validated by comparing change in symptom scores for breathlessness and change in lung function in the progressing and non-progressing groups.

Change in breathlessness

Table 16 compares the results of the Brompton Hospital breathlessness question (Appendix 11) at follow up with those at presentation. 43.1% of the non-progressors and 72.7% of the progressing cases in whom data was complete show an increase in breathlessness. Breathlessness apparently improved in 2 progressors and 12 non-progressors. If those showing deterioration are compared with those showing either improvement or no change then there is a significant trend towards increasing breathlessness in those showing radiographic progression (x^2 5.93 $p < 0.02$).

The increase in breathlessness in 43.1% of the cases showing no radiographic progression is high but perhaps not surprising in a group of men with an average age of 61.7 who had impaired lung function when first seen 4-11 years earlier.

Changes in lung function

Figures 24-26 compare changes in percentage of predicted FEV_1, VC and D_LCO at presentation and at follow up in the radiographic progressors and non-progressors. All three measurements of lung function fell significantly in the progressor group (t test comparing difference between presentation and follow up values against zero). The only statistically significant change in the non-progressing group was a small fall in percentage of predicted FEV_1.

The mean value for percentage predicted FEV_1 and VC in the progressors is higher at presentation than in the non-progressors. This difference is statistically significant for FEV_1 ($p < 0.05$) but not for VC.

The change in percentage predicted D_LCO followed a different pattern. At presentation the mean value was similar in the two groups but at follow up the mean value had fallen significantly in the progressors (non-progressors 62.08 ± 16.46, progressors 47.43 ± 17.43, $p < 0.001$).

Conclusions

The results of the comparison of lung function between the two groups show marked changes in the radiographic

progressors but little or no change in the radiographic non-progressors. This coupled with the trend towards increased breathlessness in the radiographic progressors provides reasonable validation of the method of determining progression which will be used in subsequent analyses.

TABLE 16

Changes in Breathlessness Score at Follow-up

	Progressors (37)	Non-Progressors (61)
Improved	2 (5.4%)	12 (19.7%)
Unchanged	7 (18.9%)	17 (27.8%)
Deteriorated	24 (64.9%)	22 (36.1%)
No data	4 (10.8%)	10 (16.4%)

FIG. 24

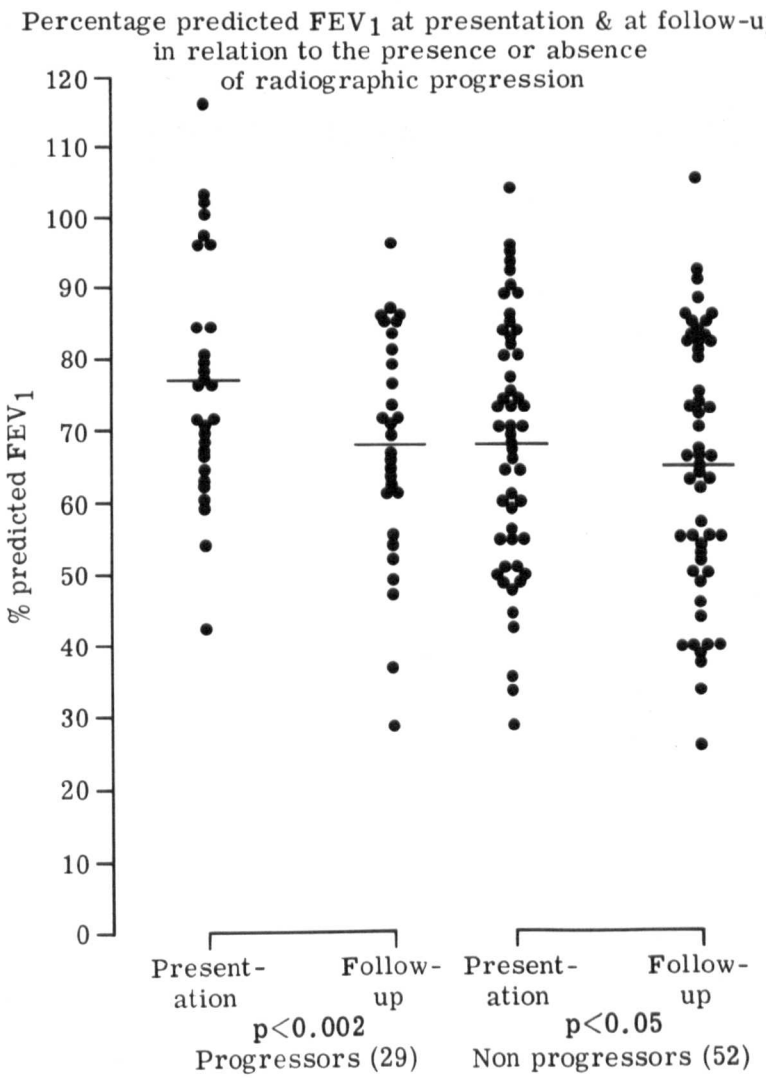

Percentage predicted FEV1 at presentation & at follow-up
in relation to the presence or absence
of radiographic progression
% predicted FEV1
120
110
100
90
80
70
60
50
40
30
20
10
0
Present-
ation
Follow-
up
Present-
ation
Follow-
up
p<0.002
Progressors (29)
p<0.05
Non progressors (52)

FIG. 25

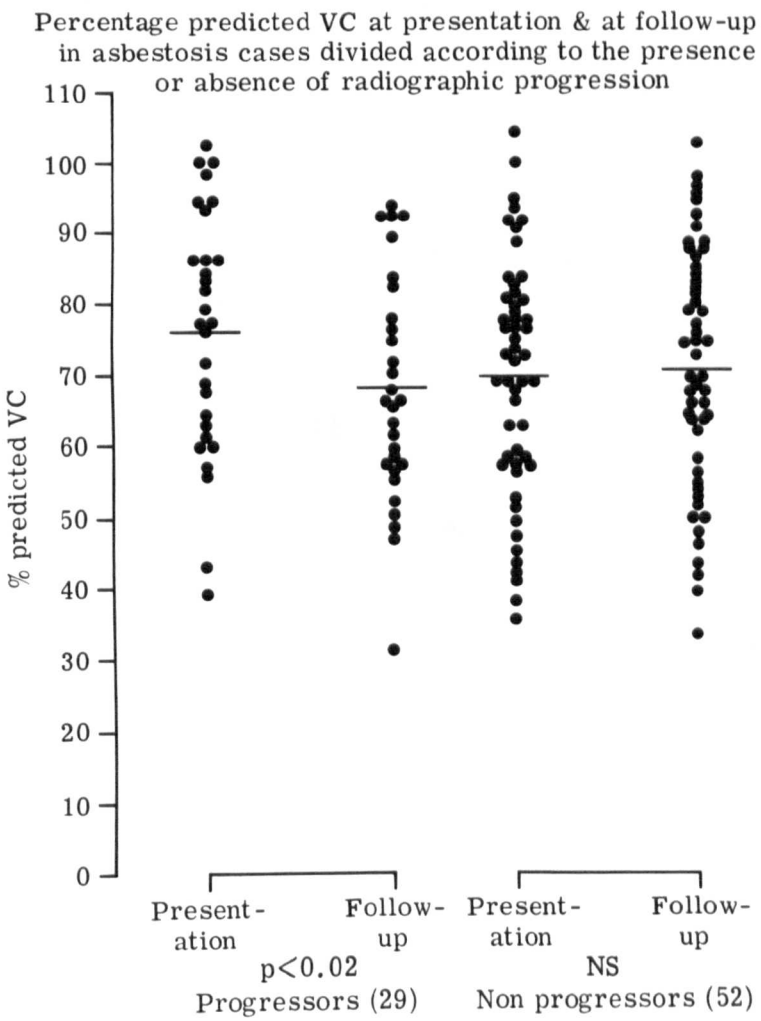
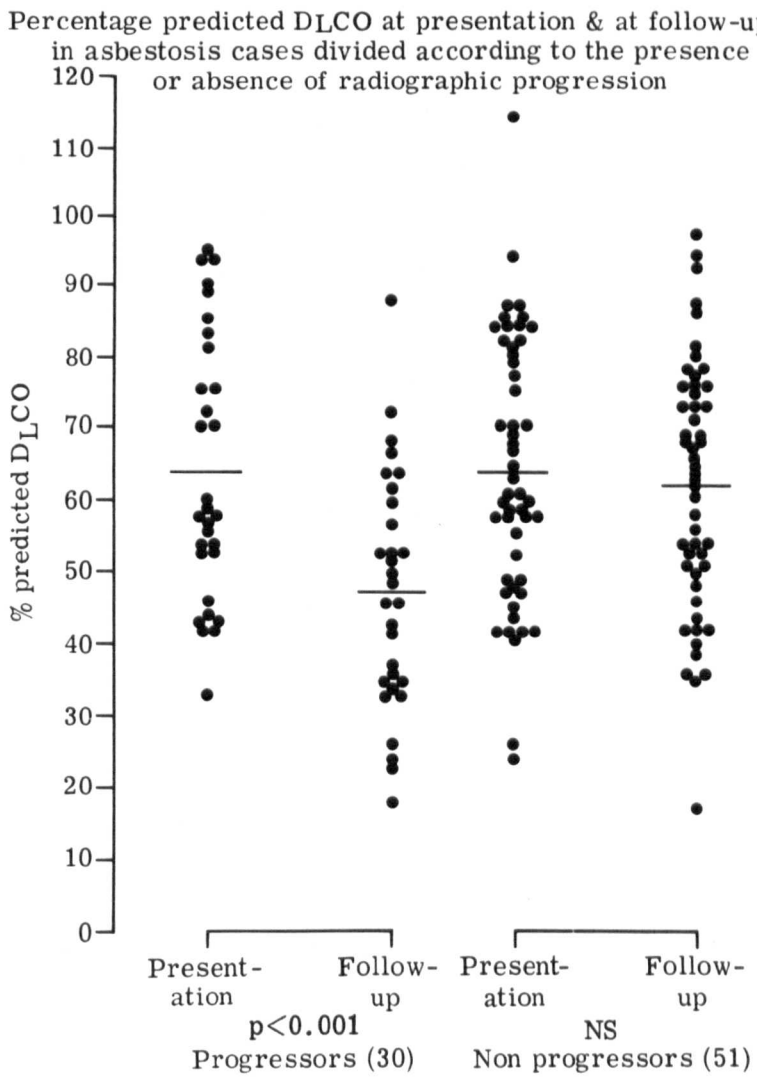

Percentage predicted VC at presentation & at follow-up
in asbestosis cases divided according to the presence
or absence of radiographic progression
% predicted VC
110
100
90
80
70
60
50
40
30
20
10
0
Present-
ation
Follow-
up
Present-
ation
Follow-
up
p<0.02
NS
Progressors (29)
Non progressors (52)

FIG. 26


Percentage predicted DLCO at presentation & at follow-up
in asbestosis cases divided according to the presence
or absence of radiographic progression
% predicted DLCO
120
110
100
90
80
70
60
50
40
30
20
10
0
Present-ation
Follow-up
p<0.001
Progressors (30)
Present-ation
Follow-up
NS
Non progressors (51)

Progression of asbestosis

Radiographic follow up was achieved in 98 of the 101 surviving cases. The group consists of 94 male cases and 4 female cases. The mean follow up period was 7.49 years and the range 4-11 years. Thirty-seven cases showed evidence of radiographic progression.

Progression in relation to length of follow up (Table 17)

There was no significant linear correlation between length of follow up and progression. Of the 30 cases seen 9-11 years after diagnosis only 50% had progressed and in many cases the degree of radiographic change was modest (Plate 3).

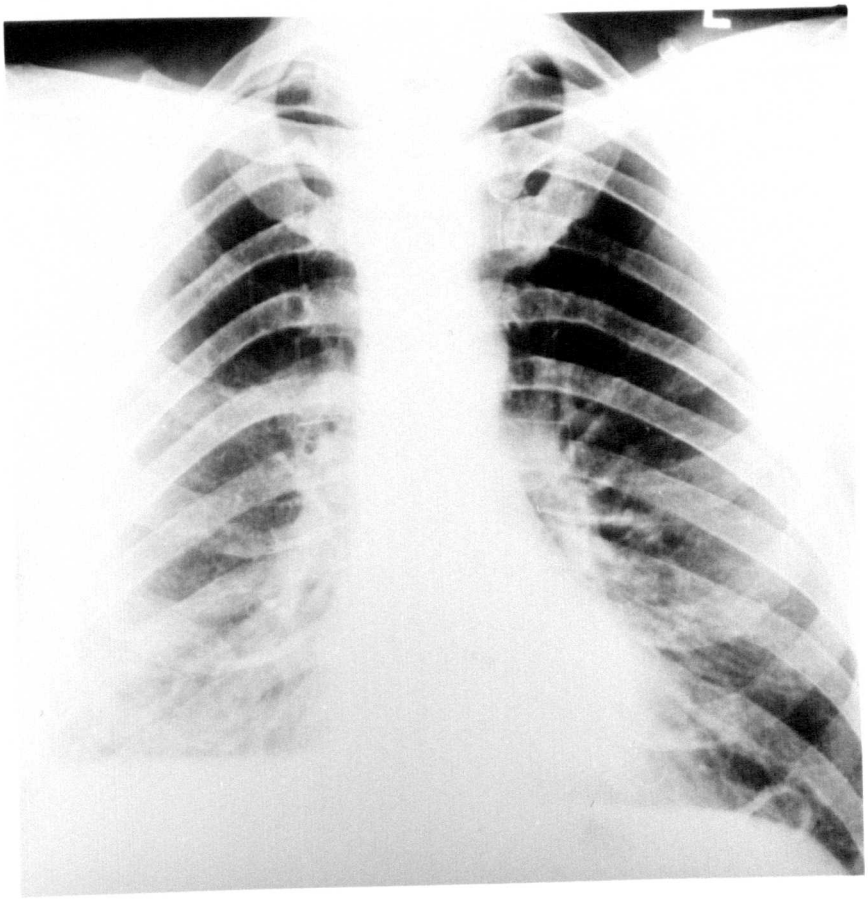
Progression in relation to radiographic category at presentation (Table 18)

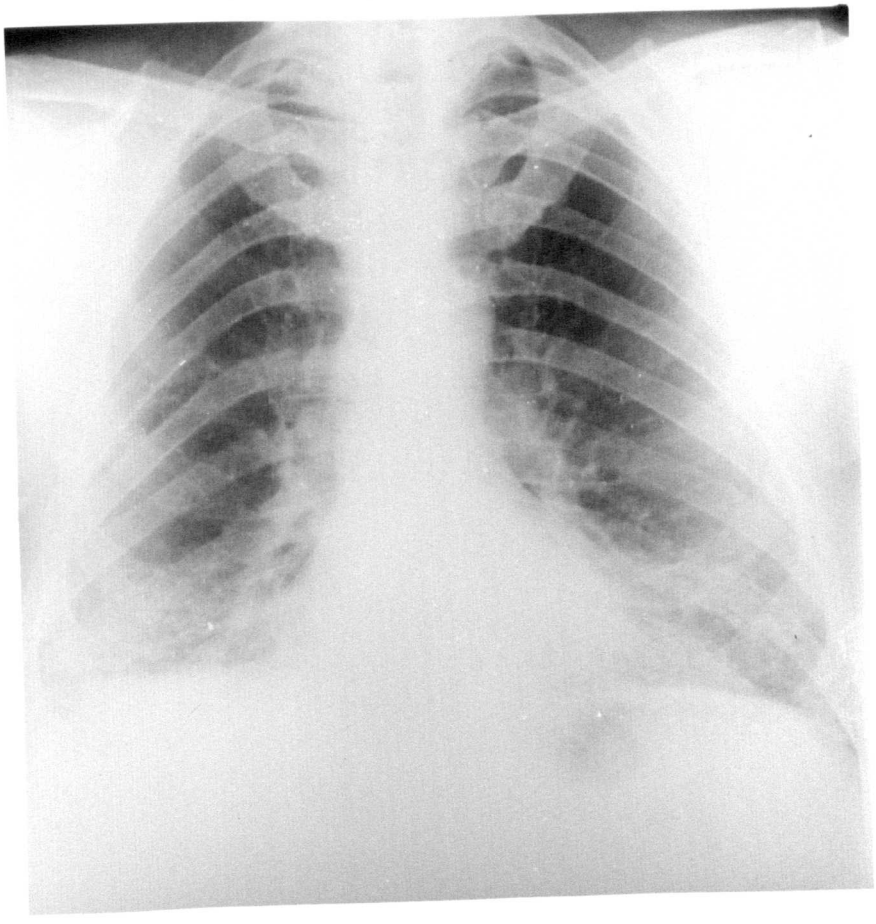
Radiographic progression was more likely to occur in the presence of a category 1 or greater profusion score for small opacities at presentation but there was no evidence of increasing liability to progression with increasing category thereafter.

It might be argued that failure to detect radiographic progression could occur in cases with a category 2 radiograph at presentation on the basis that increases in fibrosis which are detected radiographically in less

PLATE 3a Chest radiograph at diagnosis in 1968.

PLATE 3b Chest radiograph at follow up in 1978 showing increased shadowing at the left base. Definite progression recorded by all 3 readers.





abnormal films might be obscured in severely abnormal ones. Lung function tests were carried out at presentation and at follow up on 10 of the 11 category 2 non-progressors. The results are shown in Table 19 for D_LCO, VC and FEV_1. None of these indices show any significant change.

Comparison of progressors and non-progressors (Table 20)

The mean age at presentation, mean duration of exposure to 1970, meantime from first exposure to follow up and mean duration from last exposure to follow up are all less but not significantly so in the progressors. The mean length of follow up was longer for the progressors but not significantly so. Finger clubbing was observed more frequently ($p < 0.01$) at presentation in cases that subsequently progressed. This finding is discussed more fully in the section on finger clubbing.

Only three cases had never smoked. Two were non-progressors and one a progressor. Smoking histories were examined to see if continuing to smoke after diagnosis influenced progression. Although there were proportionately more smokers amongst the progressors the difference was not statistically significant.

The presence or absence of antinuclear antibody at presentation did not predict progression. This is discussed more fully in the section on immunology.

Method of detection of cases

An attempt was made to find out how the cases came to present. Twenty-five cases were found to have presented as a result of periodic examinations at work. These will be referred to as routine surveillance cases and they have been compared with the remaining 73 cases who presented in other ways or in whom there is no information on the method of presentation. (Table 21a, b and c). As might be expected surveillance detects cases when they are younger and have had less time from first exposure to asbestos. The surveillance cases also had a shorter duration of exposure to asbestos but this difference is not statistically significant.

The surprising finding is the higher incidence of progression in the routine surveillance cases. Although the difference in progression rates between the two groups does not reach statistical significance the comparisons of change in percentage of predicted FEV_1, VC and D_LCO shown in Figs. 27-29 suggest that this is a biologically significant observation. The surveillance cases have a higher mean value for each lung function test at presentation but by follow up have fallen to a similar level to the other cases.

As routine surveillance is likely to detect cases early in the course of the disease these findings suggest that the disease is more active in its early stages.

Tables 22 and 23 examine the relationship between progression and length of follow up and radiographic category at presentation (c.f. Tables 17 and 18) but excludes the routine surveillance cases. The findings are similar to those already described but the lack of progression with increasing length of follow up is even more apparent.

Effects of co-existent diseases

It was thought possible that associated diseases might influence the likelihood of progressive intrapulmonary fibrosis.

(1) Rheumatoid Arthritis

Five cases had or developed rheumatoid disease during the study. Three progressed and two did not. The presence of rheumatoid factor at presentation did not predict progression but its appearance during the study was associated with progressor status. See section on immunology.

(2) Chronic active hepatitis

One case had this disease and his fibrosis progressed. Chronic active hepatitis is itself associated with pulmonary fibrosis but its relevance to this case is unknown.

(3) Von Recklinghausen's neurofibrosis

One non-progressing case had this disease. His case was unusual in a number of respects. Firstly his pulmonary function tests showed severe airways obstruction with an FEV_1/FVC ratio of 40% at presentation and 35% at follow up. Chest radiograph (Plate 4) showed large apical bullae and lower zone shadowing, findings which are reported in neurofibromatosis. The man had been heavily exposed to asbestos both as a lagger and as a factory worker. He had been a lagger during the second world war when exposure was likely to have been heavy. Again distinction between the two diseases is a matter for speculation.

(4) Extrinsic allergic alveolitis

A history of exposure to pigeons or budgerigars was obtained in 29 of 78 cases. The exposure was often many years earlier but serum was examined in all cases for precipitins to pigeon and budgerigar antigens. Only one case had precipitins and they were present to both pigeon and budgerigar antigens. The case was a progressor and the chest radiograph was unusual in the degree to which the upper lobes were involved (Plate 5). In this case the possibility of additional damage due to avian hypersensitivity must be very high.

PLATE 4 A case of Von Recklinghausen's Neurofibromatosis and Asbestosis.

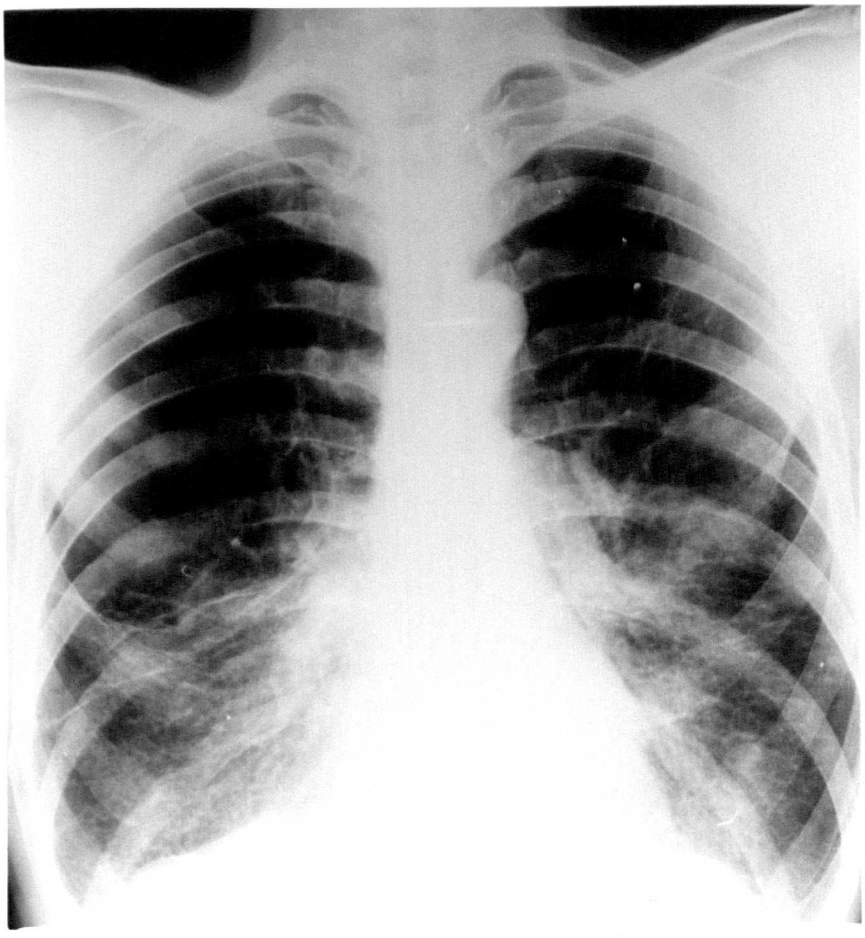
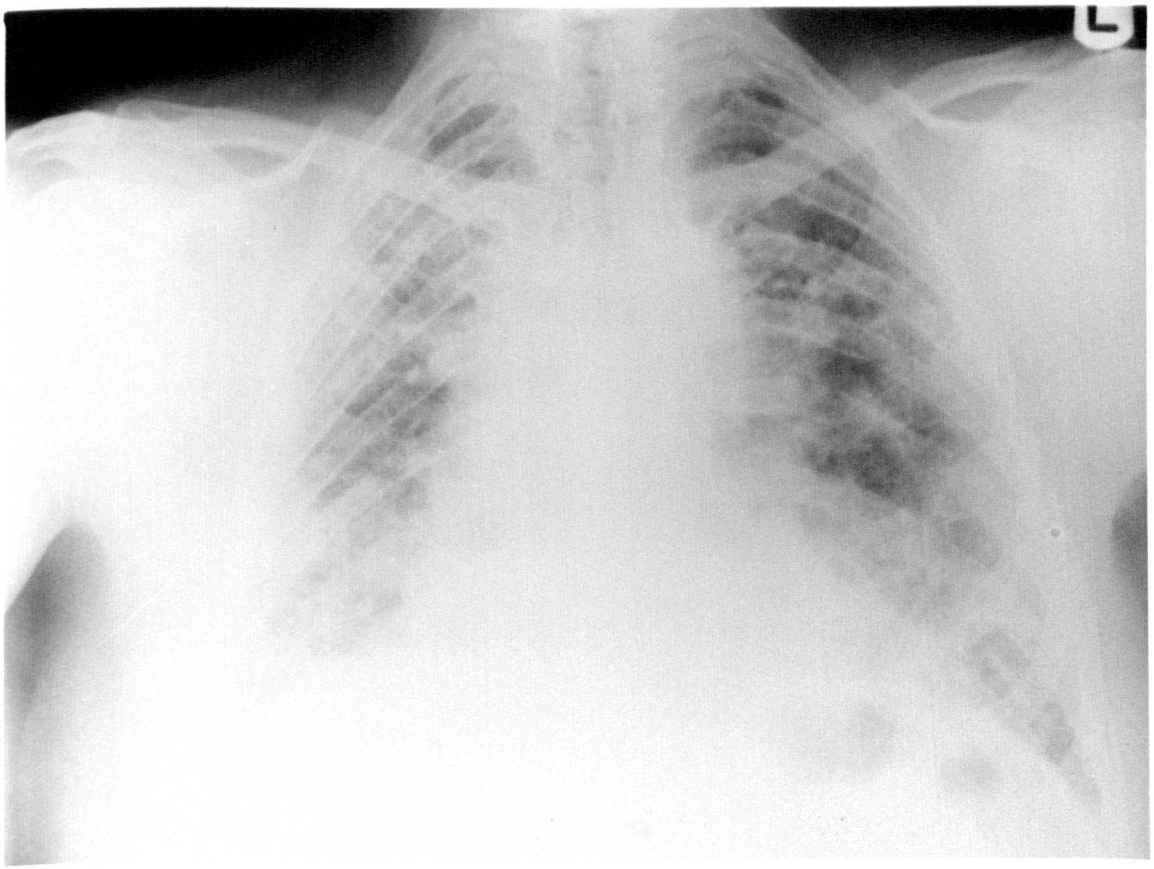


PLATE 5 Asbestosis in a man with precipitins to pigeon and budgerigar antigens. The radiographic shadowing is unusual for asbestosis both in extending throughout the lung fields and in its coarseness.



Factors predicting progression in asbestosis

In order to try and determine whether any features present at diagnosis were of value in predicting progression a discriminant analysis was used to investigate:-

Age at presentation
Duration of exposure to 1970
Time from first exposure to follow up
Length of follow up
Method of presentation (Routine surveillance or other)
Presence or absence of finger clubbing
Score for small opacities using 12 point scale
Percentage of predicted FEV_1
Percentage of predicted VC
Percentage of predicted D_LCO

The analysis confirmed the lack of association between age, duration of exposure, time from first exposure, length of follow up and small opacity score.

Finger clubbing was significantly associated with progression ($p < 0.01$). No further support was obtained for the notion of an early progressive stage in the disease.

SUMMARY

(1) 37 of the 98 survivors of the original 167 cases had evidence of progressive intrapulmonary fibrosis.

(2) Progression occurred more frequently in those with at least a category 1 profusion score but increasing profusion category thereafter was not associated with a greater likelihood of progression.

(3) Progression was not related to age, length of follow up, duration of exposure or time from first exposure.

(4) There is some evidence that progression is more common early in the disease.

(5) Finger clubbing is of value in predicing progression.

TABLE 17

Progression in Relation to Length of Follow-Up

Follow-Up (yrs)	4	5	6	7	8	9	10	11	TOTAL
Cases	4	17	10	23	14	7	16	7	37
Progressors	1	4	3	10	4	3	8	4	98
% Progressing	25	24	30	43	29	43	50	57	38

r = 0.2638 t = 0.669 p NS

TABLE 18

Progression in Relation to Radiographic Category at Presentation

Small Opacity Score	0/0	0/1	1/0	1/1	1/2	2/1	2/2	2/2	3/3	3/3
Cases	23	10	13	28	4	8	7	4	1	
Progressors	4	3	2	17	2	2	5	1	1	
% Progressing	17	30	15	61	50	25	71	25	100	
	7/33		21/45			8/19			1/1	
% Progressing	21%		47%			42%			100%	
						45%				

TABLE 19

Details of Change in Percentage of Predicted DLCO, VC and FEV_1 in 10 non-progressing cases with Category 2 Profusion Scores

Lung Function Test		Mean	T Value	Probability Value
% Predicted DLCO	Presentation	57.5		
	Follow-Up	54.6	0.62	NS
% Predicted VC	Presentation	71.5		
	Follow-Up	76.0	1.26	NS
% Predicted FEV1	Presentation	70.2		
	Follow-Up	68.4	0.44	NS

TABLE 20

Comparison of Progressors and Non-Progressors

	Progressors (37)	Non-Progressors (61)
Mean age at presentation ± SD	52.05 ± 9.56	54.54 ± 8.38
Range	32 - 69	32 - 70
Mean duration of exposure up to 1970 ± SD	18.03 ± 9.99	22.59 ± 12.29
Range	2 - 47	1 - 48
Mean time from first exposure to follow-up ± SD	33.19 ± 11.26	38.63 ± 10.73
Range	17 - 56	19 - 61
Mean time from last exposure ± SD	14.75 ± 11.18	14.75 ± 10.76
Range	7 - 52	7 - 50
Mean length of follow-up ± SD	7.97 ± 2.01	7.18 ± 1.99
Range	4 - 11	4 - 11
Percentage with finger clubbing at presentation	43%	21%
Percentage smoking at presentation	73%	66%
Percentage with antinuclear antibody at presentation	25%	23.7%

TABLE 21a

Comparison of Cases Detected by Routine Surveillance with those Detected by Other Methods

	Routine Surveillance (25)	Others (73)	Probability Value
Mean age at presentation	49.24	55.06	*0.002
Range	32 - 62	32 - 70	
Mean duration of exposure up to 1970 (yrs)	17.28	22.09	*NS
Range	10 - 34	1 - 48	
Mean time from first exposure to follow-up (yrs)	26.42	40.00	*0.001
Range	19 - 43	17 - 61	
Mean length of follow-up (yrs)	7.6	7.49	NS
Range	5 - 11	4 - 11	
Deterioration in breathlessness score at follow-up	57%	54%	NS
Percentage with finger clubbing at presentation	48%	33%	NS
Percentage smoking at presentation	72%	54%	NS
Positive ANA at presentation	24%	24.2%	NS
Progressors	56%	31.5%	NS

*Mann-Whitney U Test

TABLE 21b

Comparison of Radiographic Profusion Category at Presentation

Radiographic Profusion	Routine Surveillance (25)		Others	
	No.	% age	No.	% age
0	6	24%	27	37%
1	14	56%	31	43%
2+3	5	20%	15	20%

TABLE 21c

Comparison of Breathlessness Score at Presentation

Breathlessness Score	0		1		2		3		4	
	No.	% age	No.	% age	No.	% age	No.	% age	No.	%age
Routine Surveillance (24)	9	37.5%	7	29%	5	21%	2	8.3%	1	4.2%
Others (71)	12	16.9%	27	38%	19	26.8%	13	18.3%	0	

FIG. 27

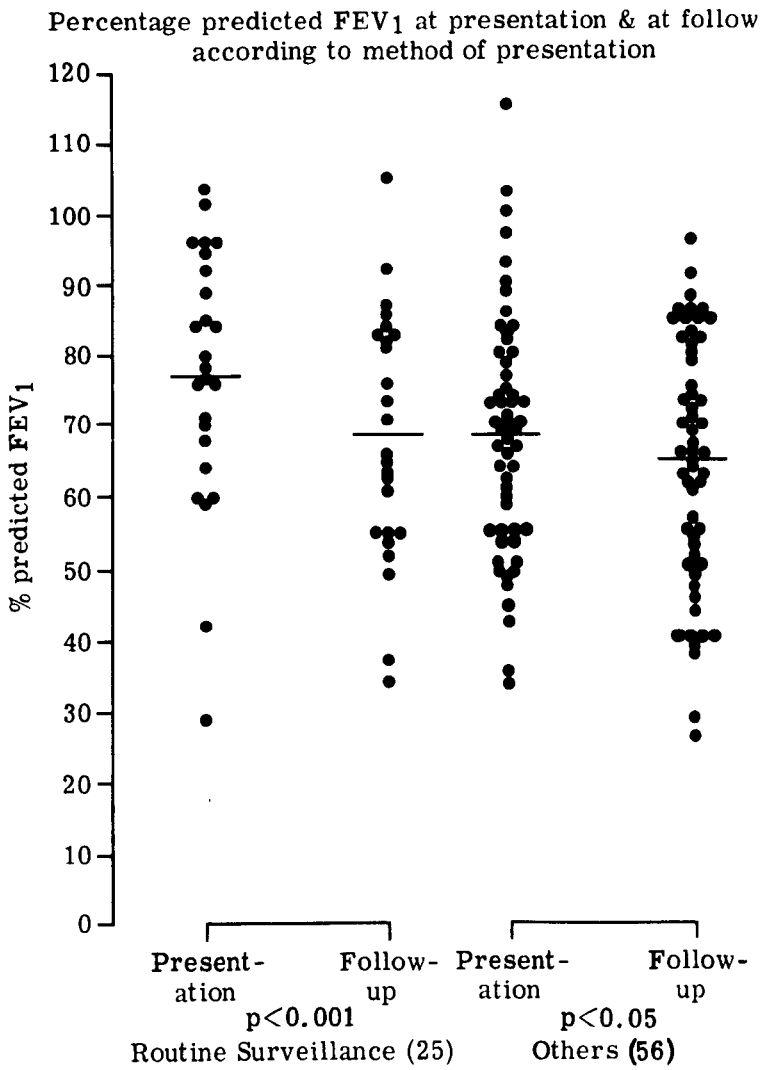

Percentage predicted FEV1 at presentation & at follow-up
according to method of presentation
% predicted FEV1
120
110
100
90
80
70
60
50
40
30
20
10
0
Present-ation
Follow-up
Present-ation
Follow-up
p<0.001
p<0.05
Routine Surveillance (25)
Others (56)

FIG. 28

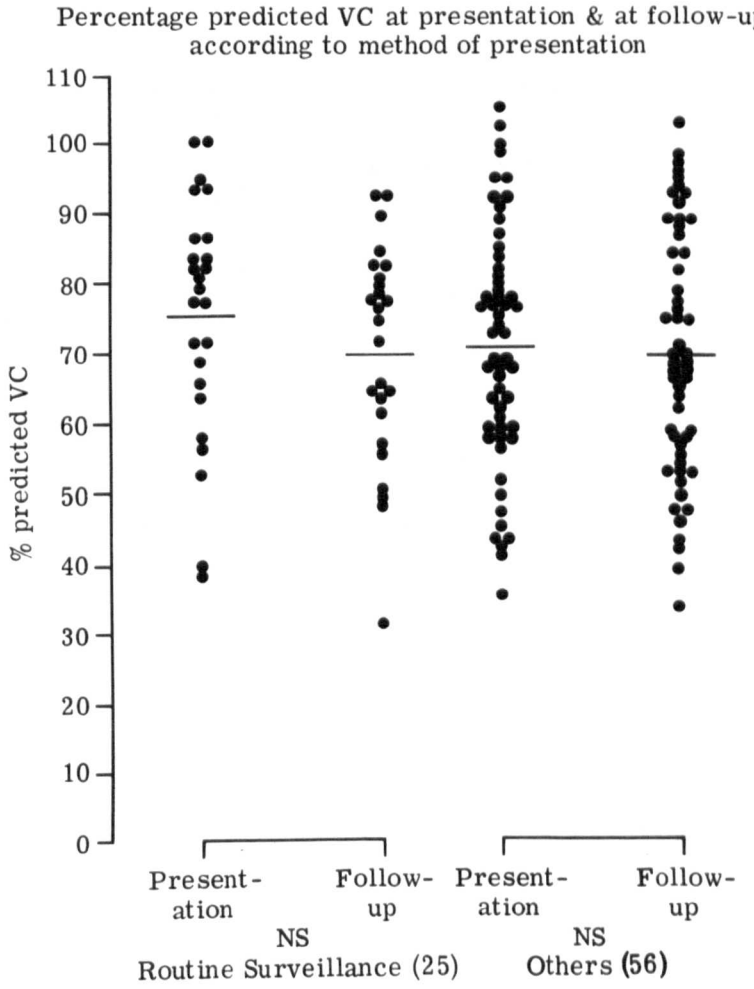

Percentage predicted VC at presentation & at follow-up
according to method of presentation
% predicted VC
110
100
90
80
70
60
50
40
30
20
10
0
Present-
ation
Follow-
up
NS
Routine Surveillance (25)
Present-
ation
Follow-
up
NS
Others (56)

FIG. 29

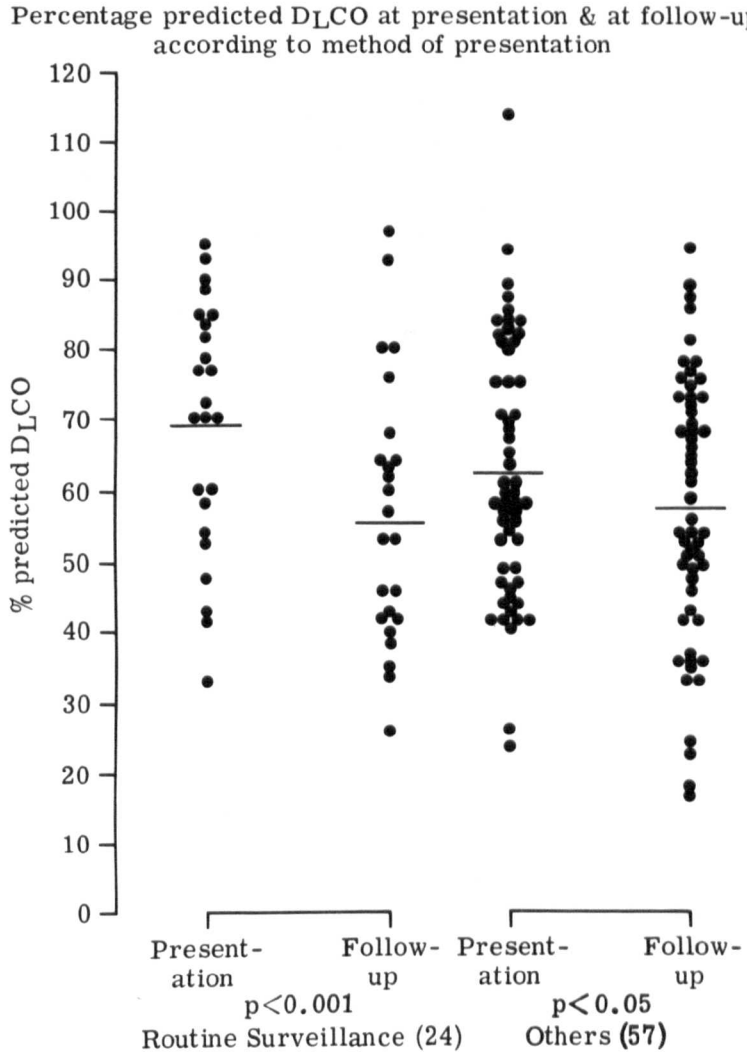

Percentage predicted DLCO at presentation & at follow-up
according to method of presentation
% predicted DLCO
120
110
100
90
80
70
60
50
40
30
20
10
0
Present-ation
Follow-up
Present-ation
Follow-up
p<0.001
p<0.05
Routine Surveillance (24)
Others (57)

TABLE 22

Progression in Relation to Length of Follow-Up Excluding Cases Detected by Routine Surveillance

Follow-Up (yrs)	4	5	6	7	8	9	10	11	TOTAL
Cases	4	13	9	16	8	4	12	7	23
Progressors	1	3	2	6	2	1	4	4	73
% Progressing	25	23	22	37	25	25	33	57	31·5

TABLE 23

Progression in Relation to Radiographic Category at Presentation

Excluding Routine Surveillance Cases

Small opacity Score	0	1	2+3	TOTAL
Cases	27	31	15	73
Progressors	4	13	6	23
% Progressing	15%	42%	40%	31.5%

Finger clubbing in asbestosis

Finger clubbing in asbestosis

Forty three percent of the 167 cases had finger clubbing at presentation. Table 24 shows the proportion of cases with finger clubbing in each radiographic category.

Table 25 shows the same data for the 155 male cases. The proportion with finger clubbing rises with increasing radiographic profusion score and there is a significant linear correlation between the proportion with finger clubbing and increasing radiographic profusion of small opacities expressed on the 12 point scale of the ILO/U-C classification (r 0.3576, $p < 0.01$).

Table 26 compares the age and exposure characteristics of the clubbed and non-clubbed male cases at presentation. The two groups are comparable in terms of age and time from first exposure to asbestos but the group with finger clubbing have had a shorter duration of exposure to asbestos. A weak negative correlation was found between finger clubbing and duration of exposure (r-0.2217, $P < 0.05$).

Table 27 compares lung function in the two groups. The percentage of predicted FEV_1 and VC are comparable in the two groups but the percentage of predicted D_LCO is considerably lower in the group with finger clubbing.

Figure 30 compares the mortality experience of the two groups. Sixty one male deaths are included in this analysis and mortality in the two groups has been compared using the Log Rank test (Peto et al 1977). The group with finger clubbing has a significantly increased mortality by comparison with the non clubbed cases and the increased risk appears to persist throughout the period of observation.

Table 28 examines the association between finger clubbing at presentation and subsequent progression of small intrapulmonary opacities. Progression is more likely to occur in those with finger clubbing at presentation ($p < 0.01$) but its sensitivity as a predictor of progression (the proportion of those who subsequently progress who are clubbed at presentation) is only 54%. Its specificity (the proportion of those who do not progress and who are not clubbed at presentation) is slightly better at 79%.

Table 29 shows the degree of agreement between the observers at presentation and follow up over the presence or absence of finger clubbing.

Two progressing cases were considered to have finger clubbing at follow up but not at presentation and a further three progressors were considered to show finger clubbing at presentation but not at follow up. Two non-progressors were recorded as clubbed only at follow up and five were

regarded as clubbed only at presentation. Some of these differences are probably due to observer variation but it is of interest that of the four cases where finger clubbing apparently developed three had profusion scores for small opacities of 0/0 and the other case had a profusion score of 0/1 at presentation. One man was a 32 year old asbestos sprayer whose case was diagnosed at the result of a routine chest radiograph at work. A second case was also under regular surveillance at work but was diagnosed as having asbestosis following a hospital admission with a benign pleural effusion having previously had normal chest radiographs at work. It is probable that both these cases were seen very early in the course of their disease and before finger clubbing had developed. The low profusion scores in the other two cases, 0/0 and 0/1 make it at least possible that they were also early cases.

These results suggest that if finger clubbing is going to develop in asbestosis it does so early and usually before the disease comes to clinical attention. Further support for this view comes from consideration of the routine surveillance cases (Table 21). These cases are younger at presentation, have had less exposure and have had considerably less time from first exposure than the cases not detected in this way. They were detected as a result of periodic examinations at work and so there is good reason to think that they are at an earlier period in the course of the disease. Despite this 48% of the routine surveillance cases had finger clubbing, a figure

similar to that for the whole group at presentation and rather higher than the 34% recorded for the whole population seen at follow up. The higher proportion of cases with finger clubbing in the routine surveillance group compared with the other cases seen at follow up probably arises because the group is younger at presentation and has not yet experienced the full impact of the excess mortality seen in this disease.

SUMMARY

(1) Forty-three percent of the cases had finger clubbing at presentation.

(2) Finger clubbing is proportionately more frequent as the profusion score for small opacities increases.

(3) The group with finger clubbing is similar to the group without it in terms of age at presentation and time from first exposure to asbestos but the group with finger clubbing has a shorter duration of exposure.

(4) Finger clubbing is associated with a lower percentage of predicted D_LCO but there is no difference between the groups in terms of percentage of predicted VC and FEV_1.

(5) Finger clubbing occurs early in the course of the disease and usually in the pre-clinical stages.

(6) Finger clubbing occurs in a group with:-

(a) an increased mortality in comparison with cases without finger clubbing.

(b) an increased likelihood of progression of intrapulmonary disease.

It is a marker for a group with a relatively more severe disease.

TABLE 24

Finger Clubbing by Radiographic Category. All Cases.

Radiographic Category	0	1	2	3
No. with finger clubbing	9	37	21	5
TOTAL	41	89	32	5
% with clubbing	21.9%	41.6%	65.6%	100%

TABLE 25

Finger Clubbing by Radiographic Category. Male Cases

Radiographic Category	0	1	2	3
No. with finger clubbing	9	34	19	5
TOTAL	36	84	30	5
% with clubbing	25%	40.5%	63.3%	100%

TABLE 26

AGE, DURATION OF EXPOSURE AND TIME FROM FIRST EXPOSURE AT DIAGNOSIS IN 155 MEN WITH ASBESTOSIS

	AGE		DURATION OF EXPOSURE		TIME FROM FIRST EXPOSURE	
	Mean	Range	Mean	Range	Mean	Range
Clubbed (67)	55.4	(40-73)	18.1	(1-46)	27.2	(9-54)
Not clubbed (88)	54.7	(32-75)	22.8	(2-48)	30.1	(10-50)
p	NS		0.02		NS	

Mann-Whitney U Test

TABLE 27

% Predicted DLCO, VC and FEV1 at diagnosis in 155 men with Asbestosis

	% pred. DLCO	% pred. VC	% pred. FEV_1
	Mean ± SD	Mean ± SD	Mean ± SD
Clubbed (67)	54.5 ± 18.4	68.7 ± 16.4	69.4 ± 18.1
Not clubbed (88)	63.2 ± 18.8	72.4 ± 17.2	69.3 ± 18.1
p	<0.01	NS	NS

t test

FIG. 30

SURVIVAL AFTER DIAGNOSIS IN MEN WITH ASBESTOSIS
IN RELATION TO FINGER CLUBBING

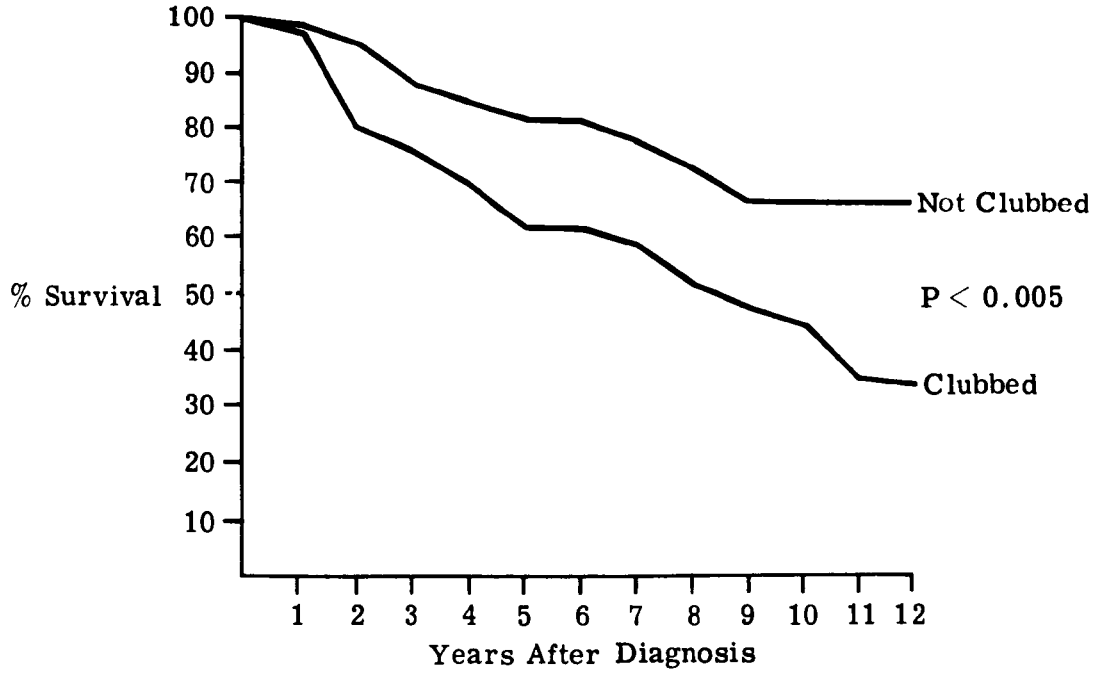


TABLE 28

Progression in Relation to Finger Clubbing

	Finger Clubbing	No Finger Clubbing	TOTAL
Progressors	20	17	37
Non-Progressors	13	48	61
TOTAL	33	65	98

x^2 9.63 $p < 0.01$

TABLE 29

Comparison of Finger Clubbing at Presentation and Follow-Up

Finger clubbing at presentation and at follow-up	24
No finger clubbing at either assessment	51
Finger clubbing at presentation but not at follow-up	8
Finger clubbing at follow-up but not at presentation	4
TOTAL	87

Immunology

Antinuclear Antibody (ANA)

Antinuclear antibody at presentation

At presentation 46 of 162 cases (28.4%) had an unequivocally positive ANA. Table 30 shows the number of positives in each radiographic profusion category. A clear difference emerges between category 0 (12.8%) and the other categories (33.7% and 32.4%). There was no relationship to age at presentation or to duration of exposure to asbestos. (Table 31 and Table 32). When the cases who survived to follow up are set out according to whether or not they subsequently progressed no difference is seen in the frequency of ANA at presentation between the two groups (Table 33).

Antinuclear antibody at follow up

In the survivors seen at follow up the prevalence of ANA had risen from 24.2% to 35.4%. This increase occurred in both progressing and non-progressing groups but was most marked in the progressors. The difference was not statistically significant (Table 34).

The relationship between positive ANA and clear cut evidence of small intrapulmonary opacities seen at presentation was not observed at follow up (Table 35).

Table 36 shows the distribution of positive ANA by age and contrary to the findings at presentation there now appears to be an increase with age. At presentation 30.4% of the cases aged 59 or less were positive and 25.7% of those who were 60 or over. At follow up 20.5% of those aged 59 or less were positive and 48.8% of those aged 60 or more.

No case with a positive ANA at presentation was negative at follow up.

SUMMARY

(1) 28.4% of cases had a positive ANA at presentation and this was related to the presence of small opacities on the chest radiograph but not to age or duration of exposure to asbestos.

(2) Positive ANA does not predict progression of intrapulmonary disease.

(3) The prevalence of ANA inceased during the follow up period to 35.4%. The increase occurred in both progressors and non-progressors and whilst the increase was most marked in progressors the difference was not statistically significant.

(4) At follow up there was a higher prevalence of ANA in those aged 60 and over.

TABLE 30

Frequency of Antinuclear Antibody According to Radiographic Category for Profusion of small Opacities at Presentation

Radiographic Category	0	1	2+3	ALL
No with +ve ANA	5	29	12	46
Total Cases	39	86	37	162
% with +ve ANA	12.8	33.7	32.4	28.4

TABLE 31

Frequency of Antinuclear Antibody according to Age at Presentation

Age	Cases	ANA +ve	% age ANA +ve
30 - 34	4	2	50
35 - 39	1	0	0
40 - 44	12	5	41.6
45 - 49	18	3	16.7
50 - 54	29	9	31.0
55 - 59	28	9	32.1
60 - 64	35	10	28.6
64 - 69	23	5	21.7
70+	12	3	25
TOTAL	162	46	28.4

TABLE 32

Frequency of Antinuclear Antibody According to Duration of Exposure to Asbestos in years at Presentation

Duration of Exposure to Asbestos at Presentation	Cases	ANA +ve	% ANA +ve
0 - 5	22	9	41
6 - 10	15	2	13.3
11 - 15	23	8	34.7
16 - 20	35	9	25.7
21 - 25	24	9	37.5
26 - 30	12	2	16.6
31 - 35	15	3	20
36 - 40	9	1	11.1
41 - 45	4	2	50
46 - 50	2	1	50
51 - 55	1	0	0
TOTAL	162	46	28.4

TABLE 33

Distribution of Antinuclear Antibody at Presentation according to whether or not subsequent radiographic progression occurred

	Radiographic Progression	No radiographic Progression	TOTAL
+ve ANA	9	14	23
Total Cases	36	59	95
% with +ve ANA	25	23.7	24.2

TABLE 34

Distribution of Antinuclear Antibody at Follow-Up in those with and without evidence of radiographic progression

	Radiographic Progression	No radiographic Progression	TOTAL
+ve ANA	15	14	29
Total Cases	31	51	82
% with +ve ANA	48.4	27.5	35.4

X^2 2.83 NS

TABLE 35

Distribution of Antinuclear Antibody at Follow-Up according to Radiographic Category at Follow-Up

Radiographic Category	0	1	2	3	TOTAL
No. with +ve ANA	5	9	12	3	29
Total Cases	14	34	23	11	82
% with +ve ANA	35.7	26.5	52.2	27.2	35.4

TABLE 36

Frequency of Antinuclear Antibody according to Age at Follow-Up

Age	Cases	ANA +ve	% age ANA +ve
40 - 44	2	2	100
45 - 49	5	1	20
50 - 54	10	3	30
55 - 59	22	2	9.1
60 - 64	15	7	46.7
65 - 69	12	5	41.7
70 - 74	12	7	58.3
75+	4	2	50.0
	82	29	

Rheumatoid Factor

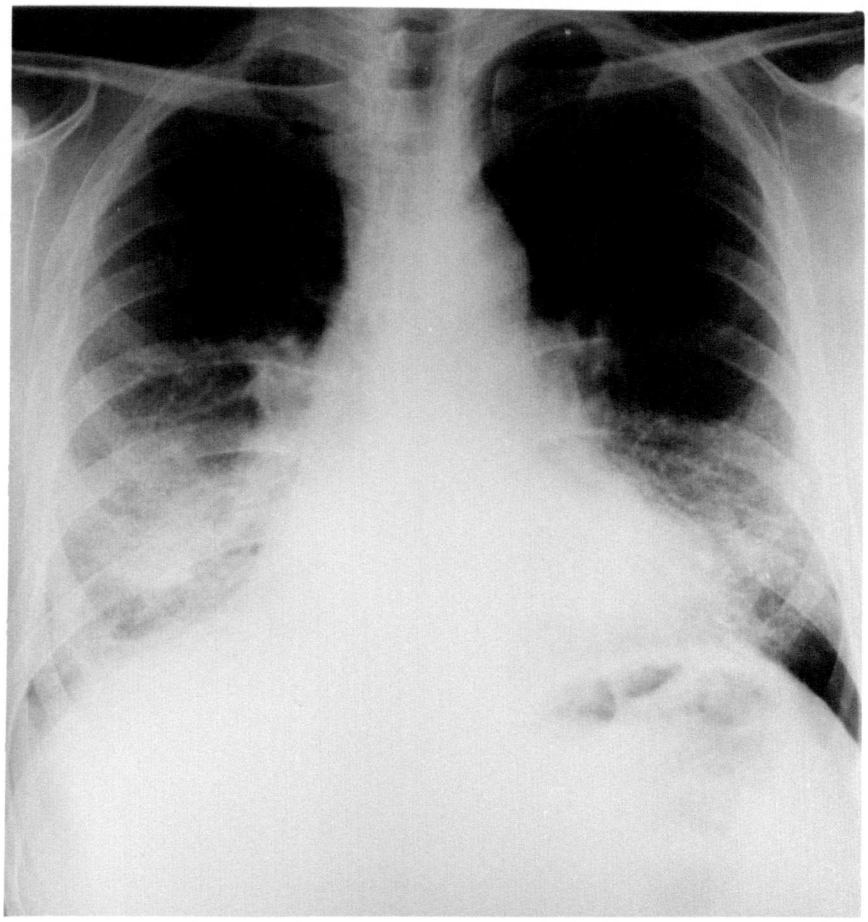
Rheumatoid factor ≥ 1/32 at presentation

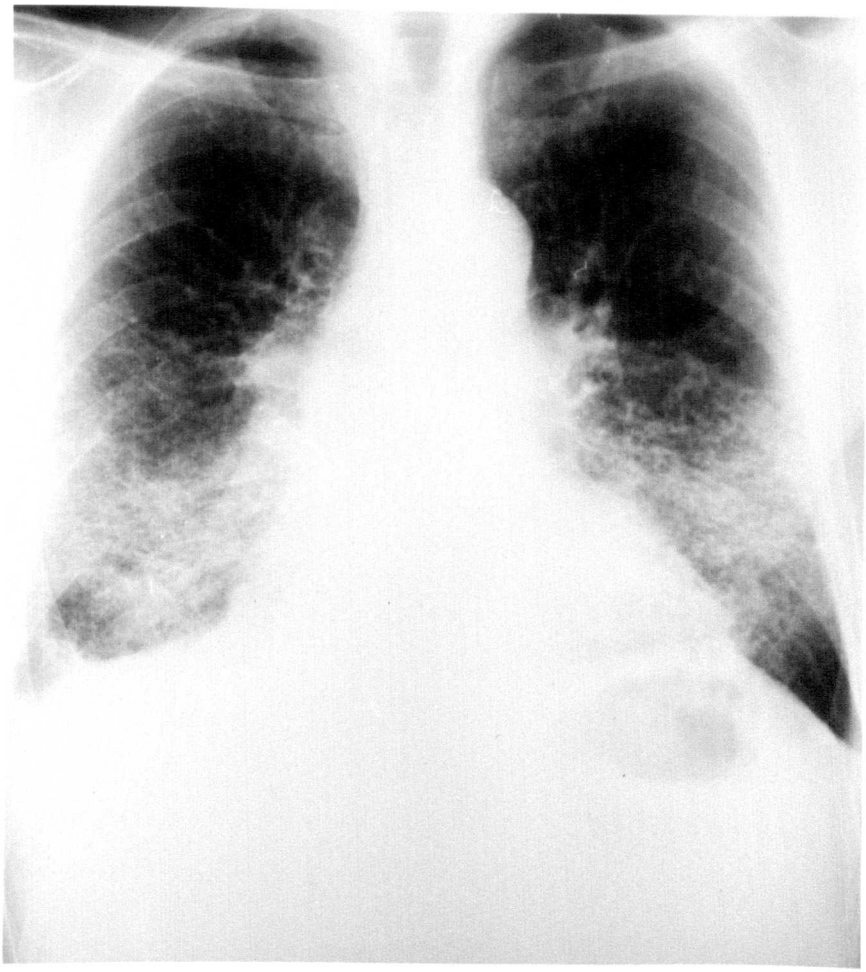
No women had a positive rheumatoid factor at presentation. Eleven of the 150 men tested were positive (7.3%). Eight of these cases survived to follow up and a complete follow up was obtained in seven. The eighth case was known to be severely incapacitated with sero-positive rheumatoid arthritis. Four of these cases had titres of less than 1/32 at follow up. Two of these cases had complained of mild joint symptoms at presentation (titres 1/32 and 1/256). The other two cases had no joint symptoms (titres 1/32 and 1/512). One of these four cases, a man with mild joint symptoms and a titre of 1/32, subsequently showed progression of intrapulmonary fibrosis but had no further joint trouble.

The three remaining cases who were tested twice in this laboratory were positive on both occasions. One case had rheumatoid arthritis and radiographic evidence of severe intrapulmonary fibrosis (Plate 6) but did not progress radiographically or show deterioration in lung function over a nine year follow up period. The other two cases showed radiographic evidence of deterioration but had no joint symptoms. The final case in whom a follow up serum sample was not obtained was known to have sero-positive rheumatoid arthritis and had radiographic evidence of progression.

PLATE 6a Asbestosis in a man with rheumatoid arthritis.

PLATE 6b Chest radiograph at follow up 9 years later. Radiographic progression was not considered to have occurred and there was no deterioration in lung function tests.





Rheumatoid factor $\geq$ 1/32 at follow up

At follow up 11 of the 82 (13.4%) sera tested in this laboratory were $\geq$ 1/32. Table 37 shows the relationship between progressor status at follow up and a titre of $\geq$1/32. Twenty-seven percent of the progressors had a positive titre as against 5.9% of the non-progressors. Two of the three non-progressors with a positive rheumatoid factor had rheumatoid arthritis. Two of the eight positive progressors had rheumatoid disease which was severe in both cases. One of these cases (Plate 7) had shown marked radiographic deterioration with very extensive disease throughout both lung fields. A third case had a history more in keeping with osteoarthritis. The remaining five cases had no joint symptoms.

Table 38 shows the relationship between positive rheumatoid factor at presentation and profusion score for small opacities at follow up. The proportion of cases with titres $\geq$ 1/32 rises with increasing profusion score.

Table 39 gives some details of the cases with titres $\geq$ 1/32 at follow up. Their mean age at presentation and at follow up and their duration of exposure to asbestos is not appreciably different to those for the whole group seen at follow up.

SUMMARY

(1) Rheumatoid factor at a titre of 1/32 or greater was present in 11 of 150 (7.3%) of male cases at presentation. These cases were not especially likely to have progressive intrapulmonary fibrosis.

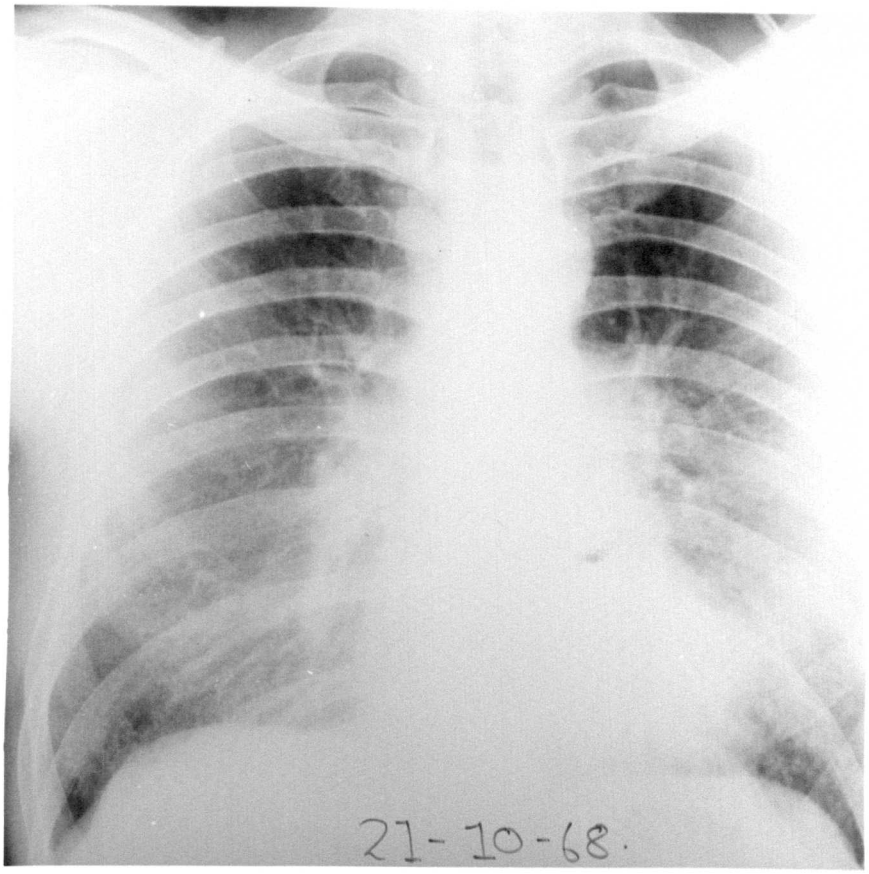
(2) At follow up rheumatoid factor at a titre of 1/32 or greater occurred more commonly in those who had been observed to progress and the titres were often high.

(3) At follow up positive rheumatoid factor occurs with increasing frequency in cases with higher profusion scores.

(4) There is no evidence that cases developing positive rheumatoid factors are either younger or have had less exposure to asbestos than those who do not have a raised titre.

PLATE 7a Asbestosis in a man with 20 years asbestos exposure as a lagger. No evidence of rheumatoid arthritis at presentation. Differential agglutination test for rheumatoid factor was negative.

PLATE 7b Chest radiograph at follow up 11 years later showing evidence of extensive intrapulmonary fibrosis. The man also had severe rheumatoid arthritis and a strongly positive RAHA titre.


21-10-68.

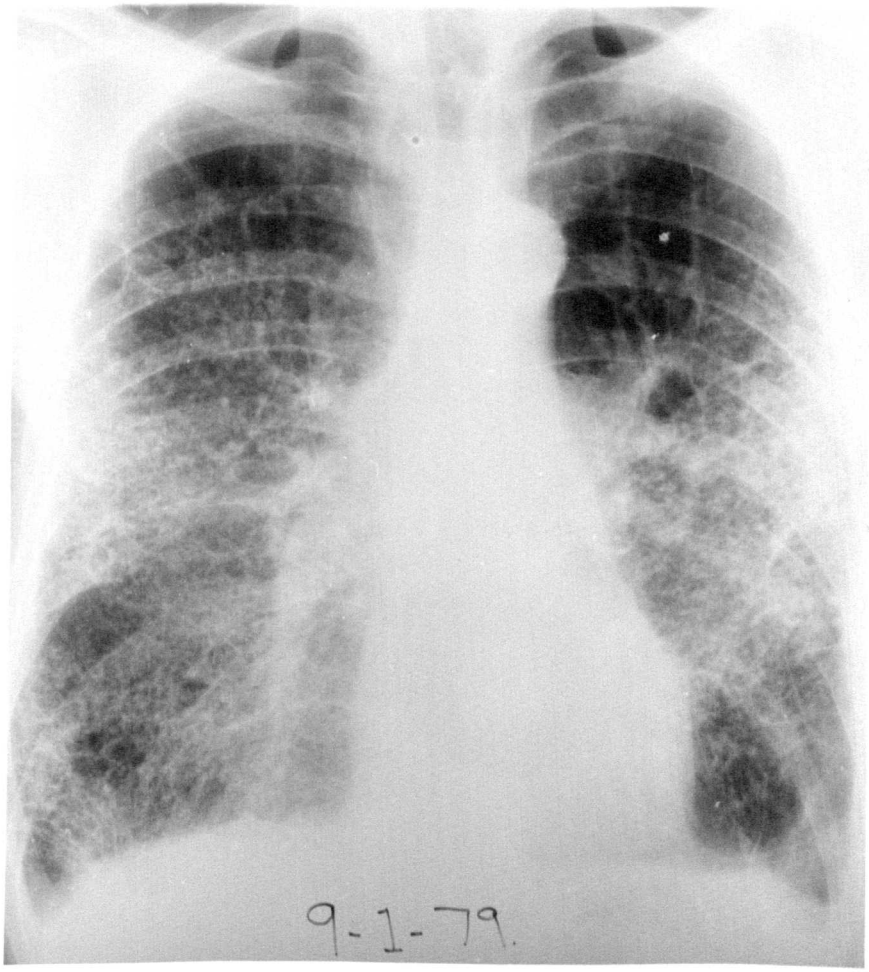

9-1-79.

TABLE 37

Relationship between Radiographic Progressor Status at Follow-Up and Rheumatoid Factor equal to or greater than 1 in 32†

	RF ⩾ 1/32	RF < 1/32	TOTAL
Progressor	8	22	30
Non-Progressor	3	49	52
TOTAL	11	71	82

X^2 5.47 $p<0.02$

TABLE 38

Relationship between Radiographic Category at Follow-Up and Rheumatoid Factor[+] equal to or greater than 1 in 32

Radiographic Category	0	1	2	3	TOTAL
RF $\geqslant$ 1/32	0	3	4	5	11
No. tested	14	34	23	11	82
% +ve	0	8.8	17.4	45.5	13.4

[+]Rheumatoid Factor assayed by RAHA test of follow-up. This test is ten times more sensitive than the DAT and the result has been devided by ten to allow reasonable comparability.

TABLE 39

Details of cases with Rheumatoid Factor Titre equal to or greater than 1 in 32*

Age at Presentation	Age at Follow-Up	Duration of Exposure to Asbestos (yrs)	Finger Clubbing	Joint Disease	Rheumatoid Factor Titre at Presentation	Rheumatoid Factor Titre at Follow-Up+
PROGRESSORS						
42	52	20	C	RA	-	1024
64	73	23	NC	OA	Not Known	512
47	56	6	NC	-	32	1024
67	76	35	NC	RA	-	1024
50	57	16	NC	-	-	64
51	57	23	NC	-	512	1024
47	53	8	C	-	-	1024
50	55	10	NC	-	-	1024
52	56	22	C	RA	512	Not Known
NON-PROGRESSORS						
45	55	19	C	RA	32	1024
58	62	32	NC	RA	-	128
62	67	10	C	-	-	512
MEAN 52.9	59.9	18.67				

*Known to have severe sero-positive rheumatoid arthritis

+Rheumatoid Factor assayed by RAHA test of follow-up. This test is ten times more sensitive than the DAT and the result has been divided by ten to allow reasonable comparability.

DISCUSSION

In considering this data and drawing conclusions from it two points should be borne in mind. Firstly, the results describe the outcome in cases of asbestosis diagnosed by the London Pneumoconiosis Medical Panel between 1968 and 1974. The criteria used by them in making the diagnosis will be reflected in the results. If the criteria change the degree to which it is possible to generalise from these results will be diminished. The most recent criteria for diagnosis set out in"Pneumoconiosis and related occupational diseases" (HMSO 1979) are in the author's view more stringent than those in use between 1968 and 1974 and may result in fewer cases being diagnosed with a category 0 radiograph.

Secondly and more importantly Smither (1965) reporting the experience of asbestosis in one London factory has shown some interesting secular trends over a thirty year period. The mean duration of exposure in cases of asbestosis diagnosed between 1930 and 1934 was 7 years but this had risen to 17.5 years in those diagnosed between 1960-64. The degree of impairment of gas transfer at diagnosis appears to be less in his more recently diagnosed cases. The pattern of mortality has also changed. Death is occurring later but is more frequently due to lung cancer. These changes are almost certainly a consequence of diminished intensity of exposure to asbestos with improving hygiene. As hygiene standards have continued to improve it is possible that further changes in the pattern of the disease will occur.

Clinical Features

A number of the descriptive features of this group of cases at presentation merit comment. They are:-

(a) Exposure history
(b) Grade of breathlessness
(c) Smoking history
(d) Associated disorders
(e) Finger clubbing
(f) Profusion score for small opacities
(g) The significance of a category 0 profusion score

(a) Exposure history

The mean duration of exposure to asbestos in the male cases was 20.7 years and although some cases had only short exposures the disease was only recognised and probably only developed many years later. The shortest time from first exposure to diagnosis was 9 years and the man had been working in the industry throughout that period.

The cases identified at follow up who presented as a result of periodic examination at work shed some light on the length of exposure required to cause asbestosis in the conditions that existed in the years immediately preceding the 1969 Asbestos Regulations. The majority of these cases

were factory workers but a number were insulation workers and their mean duration of exposure was 17.28 years (range 10-34) (See Table 21). This is a shorter exposure than that for the whole group and probably reflects earlier diagnosis rather than heavier exposure. It is of course possible that with the passage of time the less exposed contempories of the routine surveillance cases will go on to develop disease but on the basis of the evidence so far it looks as if asbestosis is unlikely to develop with less than 10 years exposure to asbestos under the conditions that existed in the late 1950's and the 1960's.

(b) Grade of breathlessness

Although over 80% of the cases reported some degree of breathlessness this was often surprisingly slight and less than 18% of the cases were breathless at rest or on level ground. It would be of value to know how often breathlessness was responsible for men losing or changing their jobs but unfortunately this information is not available.

(c) Smoking history

Sixty-five percent of the male cases were smoking at the time of diagnosis and a slightly higher figure would have been expected for men of this age (Lee and Wilson 1976). However only 3% had never smoked compared with an expected

10-12%. This is of interest because some (Berry et al 1979, and McMillan et al 1980) but not all studies have suggested that asbestosis is commoner in smokers. The relative lack of life long non-smokers is in keeping with the possibility that cigarette smoking predisposes to asbestosis but beyond this no evidence emerged to suggest that cigarette smoking influenced progression of asbestosis. The high proportion of cigarette smokers prevented any analysis of smoking and mortality.

Spencer Jones (1977) has suggested that cigarette abandonment is often one of the first signs of respiratory disease and it is interesting that of the cases seen at follow up 72% of those detected by periodic examination were smoking at diagnosis. This figure is slightly higher than expected. However only 54% of those detected in other ways were smoking against an expected of 64-68%. This finding is in keeping with the suggestion that the cases detected by periodic examination are at an earlier stage of the disease.

(d) Associated disorders

A number of cases were seen at follow up where pulmonary fibrosis could have been due to causes other than asbestos exposure. These cases are important because in two instances if the differential diagnosis were the correct one then the condition might have improved with

appropriate management whereas asbestosis is generally considered to be unresponsive to treatment with corticosteriods (Elder 1967, Leathart 1972).

One man with a history of heavy asbestos exposure who developed progressive disease had kept both pigeons and budgerigars. His chest radiograph (Plate 5) showed intrapulmonary shadowing which was coarser and more extensive than that usually seen in asbestosis. At follow up precipitins were present in his serum to both pigeon and budgerigar serum although the exposure to both species had ceased three years earlier. It has been claimed that almost all those with precipitins to budgerigar serum have evidence of disease (Faux et al 1971) whereas precipitins to pigeon serum can occur simply as a consequence of exposure (Barboriak et al 1964, Elgefors et al 1971). Thus there is a strong possibility that this man's disease might in part have been due to avian hypersensitivity and that earlier recognition could have resulted in less pulmonary damage.

In the second case asbestosis was certified in the presence of chronic active hepatitis. This disease can be associated with pulmonary fibrosis and the combination is sometimes susceptible to treatment with corticosteroids (Turner-Warwick 1968). Although asbestos exposure had undoubtedly occurred during this man's work in the construction industry it was difficult to know how heavy this had been. In such cases it seems wise to consider

alternative possibilities and this man was in fact treated with corticosteriods and azathioprine without improvement in either his lung or liver condition.

Basal fibrosis and apical bullae have been described in Von Recklinghausen's neurofibromatosis (Massaro and Katz, 1966). One case was seen with the stigmata of this disease and a compatible chest radiograph (plate 4). The case did not progress but little is known of the natural history of the pulmonary manifestations of Von Recklinghausen's neurofibromatosis. The man had been heavily exposed to asbestos but its relevance in the aetiology of his pulmonary fibrosis is uncertain.

A number of cases also had rheumatoid arthritis. Pulmonary fibrosis may complicate this disease and the association has been reviewed by Popper et al (1972). This association will be discussed in the section dealing with the immunological findings.

(e) Finger Clubbing

Finger clubbing was found in 42% of the cases. The data suggests that it occurs early in the clinical course of the disease. Wyers (1946) formed the same opinion in a review of 29 cases of asbestosis. It is associated with more severe disease and a worse prognosis both in terms of progressive pulmonary fibrosis and increased mortality.

Parkes (1974) formed the impression from clinical observation that cases with increasing finger clubbing or nailbed fluctuation often had actively advancing pulmonary fibrosis. Finger clubbing occurs more commonly in cryptogenic fibrosing alveolitis. In a series recently reported from the Brompton Hospital (Turner-Warwick et al 1980a) it was found in 66% and although its prognostic implications were not fully assessed it is of interest that 19 of the 20 cases that subseqently died of lung cancer had finger clubbing at presentation (Turner-Warwick et al 1980b).

A number of workers (Harries 1971 and Ferris in work quoted by Selikoff and Lee 1978) have shown an increasing prevalence of finger clubbing with increasing asbestos exposure in groups of heavily exposed insulation workers. The data does not make clear whether this is an independent effect of asbestos exposure or an association with asbestosis.

Wallace and Langlands (1971)in a case control study of 50 Belfast asbestos insulation workers found that their hyponychial angles were significantly greater than those of controls but again it is not possible to determine whether this was the result of asbestos exposure per se or of an association with asbestosis. Fourteen of the cases had radiographic evidence of intrapulmonary fibrosis and a further six cases had evidence of possible asbestosis.

The data in this thesis shows an increasing prevalence of finger clubbing with increasing profusion of small intrapulmonary opacities and a negative correlation with exposure suggesting that finger clubbing is independent of exposure and related to the presence of intrapulmonary fibrosis. Furthermore it suggests that finger clubbing is developing in subjects who are more vulnerable to the effects of asbestos exposure. However it occurs too late to be of value in preventative medicine.

Regan et al (1967) compared the subjective assessment of finger clubbing made by 13 chest physicians with objective measurements in 50 asbestos workers. They suggested that the hyponychial angle might be used as a continuous variable for correlation with other indices of abnormality. A gradient of increasing radiographic and lung function abnormality through normal, doubtful normal, doubtful clubbed and clubbed cases was demonstrated but the major differences appeared to lie between the clubbed cases and the rest. Williams and Hugh-Jones (1960b) showed a correlation between diffusing capacity and finger clubbing recorded as absent, slight or marked in their study of lung function changes in asbestosis.

We did not measure the hyponychial angle or grade finger clubbing and whilst it would be of interest to see whether more refined measurements could predict outcome more satisfactorily the technique required to measure this angle

involves making casts of the finger so is unlikely to become available routinely. Despite slight variations in the classification of finger clubbing by the observers at presentation and at follow up the correlation between progression and finger clubbing was equally well described by both observers suggesting that clinical assessment is reasonably reliable in this situation.

The mechanisms underlying finger clubbing in asbestosis and the other conditions in which it occurs are unknown (Shneerson 1981) but it is of interest that Kitis et al (1979) found that finger clubbing measured objectively in Crohn's disease and ulcerative colitis correlated with both disease activity and the extent of fibrosis in resected specimens. These observations are in broad agreement with those made here in asbestosis.

(f) Profusion score for small opacities

The median profusion score for male cases at presentation was 1/1 for each of the three readers. One of the readers (MTW) has recently read the chest radiographs at presentation of 147 cases of cryptogenic fibrosing alveolitis using the 1971 ULO-U/C classification and the median profusion score in that disease was 2/2 (Turner-Warwick 1980a). The mean percentage of predicted FEV_1 was similar in both groups but the mean percentage predicted vital capacity was lower in the fibrosing alveolitis cases. Transfer factor measurements were not available for the fibrosing alveolitis cases.

These observations and the higher incidence of finger clubbing in cryptogenic fibrosing alveolitis suggest that although there are similarities with asbestosis it is in general a more severe disease. This is further reflected in the higher mortality ratios for all causes of death and for lung cancer in cryptogenic fibrosing alveolitis (Turner-Warwick et al 1980a and b).

(g) The significance of a category 0 profusion score

Forty-one cases (5 women and 36 men) were certified as having asbestosis with a median profusion score for small opacities of 0/0 or 0/1. These cases are of interest because in spite of similar age and exposure characteristics to the cases with higher profusion scores they appear to have a better prognosis both in terms of mortality and progression of intrapulmonary fibrosis.

There was no overall excess mortality in the male category 0 cases either at 5 or 10 years in marked contrast to those with higher profusion scores but the mortality ratios were raised for lung cancer and respiratory diseases which were the main causes of excess mortality in the whole study group. These mortality ratios have to be interpreted with caution because they are based on very small numbers of deaths in a highly selected population and the presence of respiratory symptoms is likely to be one of the selective factors which were operating. The low mortality ratio for

other causes might suggest that the category 0 cases are a particularly fit group who had they not been exposed on average for 21 years to asbestos might have had a lower overall mortality ratio than the general population.

The percentage of category 0 cases showing radiographic progression was only 21% compared with 47% in category 1 and 45% in category 2 and 3, and this occurred despite the fact that relatively more category 0 cases survived to follow up. No features were found which helped to discriminate between category 0 progressors and non-progressors at presentation but a number of interesting differences emerged. The 7 progressors had a mean age of 44.6 years (range 32-62) and only one case was over 50. Their mean duration of exposure was 14.3 years (range 13-17) and six of the seven were periodically examined at work and although presentation was not directly attributable to such an examination in every case it seems likely that these are cases diagnosed early in the course of their disease. One of the cases observed to develop finger clubbing was in this group. The non-progressors had a mean age of 55.1 (range 32-68) and a mean duration of exposure of 25.4 years (range 1-48). Only three of these cases were detected by routine surveillance.

A further marked difference occurred in the prevalence of antinuclear antibody at presentation. The prevalence was slightly raised in the category 0 cases (12.8%) but markedly raised in categories 1 (33.7%) and 2 and 3 (32.4%).

Thus there are clear contrasts between category 0 cases and the rest. Furthermore in the cases of mortality, morbidity and the prevalence of antinuclear antibody there were no trends towards increase with rising profusion score merely a stepwise change between category 0 and category 1.

This raises questions about the nature of category 0 cases and whether they are suffering from asbestosis at all. Seven cases deteriorated and it seems likely that their diagnosis is correct but what of the rest? Epler et al (1978) found that 6 of their 58 cases of histologically proven asbestosis had no evidence of intrapulmonary fibrosis when the chest radiographs at the time of biopsy were read on the 1971 ILO-U/C classification. This suggests that asbestosis can occur in the presence of a normal radiograph but as they give no criteria for the clinical diagnosis of asbestosis it is not possible to extrapolate from their findings to this data. Our mortality data is scanty and conflicting. It could reflect an asbestos related effect in a population with a survivor bias or it may merely be describing the mortality of a selected group of asbestos workers without asbestosis.

Whether all these cases have asbestosis or not cannot be answered from this data but they form an important group of certified asbestotics because of their favourable prognosis.

Mortality

(a) Description of mortality

The proportions of deaths occurring due to particular causes (Table 7) are similar to those found by McVittie (1965) and Berry (1981) in studies of cases certified by the Pneumoconiosis Medical Panels. However some of the diseases which have been reported to occur more frequently in asbestos exposed populations did not occur to excess in this study.

An excess mortality from gastrointestinal cancer has been reported in some asbestos exposed cohort studies. In the United Kingdom, Newhouse found an excess of alimentary tract cancer in both male and female workers employed after April 1st, 1933, the date of implementation of the 1931 Asbestos Regulations, in an East London asbestos factory (Newhouse 1969, Newhouse et al 1972, Newhouse and Berry 1979). Peto et al (1977) studying asbestos factory workers first employed in or after 1933 in south-east Lancashire found no excess mortality from gut cancers although mortality from cancers of the lung and pleura was increased. Amongst Belfast insulation workers Elmes and Simpson (1971) found an increased mortality from gastrointestinal cancer but its importance seems to have been declining in their cohort since 1960 (Elmes and Simpson 1977). Similar conflicting findings have been reported from North America. McDonald et al (1980) found no excess mortality in Candadian miners

and millers while Selikoff (1976) showed a marked excess of gastrointestinal cancer in insulation workers. No satisfactory explanation of these differences have emerged but variations in levels of exposure, fibre type and possibly other factors in the working environment may be important.

In this study of heavily exposed individuals no excess mortality from alimentary cancer was detected despite the fact that many of the cases had worked in the factory studied by Newhouse. It is possible that this may be due to differences in susceptibility, there being some who develop pulmonary fibrosis and others who are relatively resistant to the pulmonary complications of asbestos exposure but who tend to develop gastrointestinal cancer. This cannot be the entire explanation because whereas all mortality studies of asbestos workers have shown evidence of the pulmonary consequences of asbestos exposure many show no excess mortality from gut cancer. Perhaps alimentary cancer develops only after very heavy exposures and those who develop asbestosis do so and leave the industry before reaching the dose of asbestos required to induce gastrointestinal cancer.

Stell and McGill (1973) in a case control study found an excess of laryngeal carcinoma in cases with a history of asbestos exposure. Despite the long (average 27 years) and heavy exposure of many of their cases only one had asbestosis. No case of laryngeal cancer was found in this study but it is a relatively rare condition with an incidence of only 1 in 50,000 per annum and a study of this size could easily

fail to detect an increased incidence. It should be noted that not all workers have found an excess mortality from this disease in asbestos workers (McDonald et al 1980).

Seven of the 66 deaths were due to mesothelioma. Four were thought to have originated in the peritoneum and three in the pleura. The similar proportions arising in each site is in contradistinction to two recent large British series of mesothelioma. Greenberg and Lloyd Davies (1974) noted that 12% of mesotheliomas reported to the Mesothelioma Register in 1967-68 were peritoneal in origin and Elmes and Simpson (1976) found a similar proportion among 327 cases accepted by a panel of pathologists. However Newhouse and Berry (1976, 1979) have reported similar proportions of pleural and peritoneal tumours in their studies of East London asbestos workers and Newhouse (1972) has suggested that the increased incidence of peritoneal tumours may be due to heavier exposure. It is widely held that peritoneal mesothelioma tends to occur in association with asbestosis whereas pleural mesothelioma is only infrequently associated with intrapulmonary fibrosis. Whitwell et al (1977) found that the asbestos fibre burden in the lungs of pleural mesothelioma cases was generally much less than that seen in cases of asbestosis suggesting that asbestos exposures insufficient to cause fibrosis may result in pleural mesothelioma. Similar date on fibre counts are not available for peritoneal mesothelioma.

Among the seven cases reported here there were no obvious differences in the asbestos exposures of the pleural and peritoneal cases but all had had heavy exposure and developed clinical and radiographic evidence of pulmonary fibrosis.

In this study the mortality ratios for all causes of death are high at both the 5 and 10 year points (Tables 9 and 10) but the mortality ratio for the second 5 year period is not significantly elevated. Eighteen deaths occurred in 410 man years of observation with a mortality ratio of 1.51. If this figure represents a stable estimate of mortality then it would appear that the excess mortality in asbestosis diminishes with time. Relative to expectation mortality diminishes with increasing age suggesting a possible survivor effect (Table 11).

(b) Factors predicting mortality

The influence of cigarette smoking on the mortality experience of this group is difficult to determine because of the very high proportion of smokers. Only one male death occurred in a non-smoker and all the lung cancer deaths occurred in cigarette smokers. Berry (1981) in his larger mortality study of Panel certified cases noted three lung cancer deaths in non-smokers.

Neither the presence of antinuclear antibody or a differential agglutination titre of 1 in 32 or greater

predicted outcome. Similar observations have been made in cryptogenic fibrosing alveolitis by Stack et al (1972) and Turner-Warwick et al (1980a).

A discriminant analysis was carried out to try and identify factors which might be of value in predicting mortality. Both the positive and negative findings require comment. Predictably death was more likely in older subjects but when allowance was made for age death was not related to either of the measures of asbestos exposure. Cohort studies of asbestos workers have almost invariably shown increasing mortality with increasing exposure (McDonald et al 1971, 1980, Enterline et al 1973). The failure to demonstrate such an effect in this study may be due to the crude measures of dose employed but a more likely explanation is that given sufficient asbestos exposure to develop disease then mortality becomes dependent on the consequences of the disease process.

The severity of the disease as measures by the profusion of small intrapulmonary opacities on the chest radiograph did not predict outcome. Similar observations were made by Turner-Warwick et al (1980c) in untreated cases of cryptogenic fibrosing alveolitis and by Stack et al (1972) in both treated and untreated cases. Wright et al (1981) found that the risk of death from lung cancer in cryptogenic fibrosing alveolitis was independent of radiographic profusion score. No significant correlations were found between the profusion score for small opacities and the percentage of predicted

FEV_1, VC or D_LCO suggesting that profusion score was a poor guide to the degree of physiological impairment seen in this study.

Finger clubbing was associated with a poorer prognosis. This effect may be partly explained by the lower D_LCO seen in cases with finger clubbing (Table 27) but there is evidence discussed earlier that finger clubbing occurs in cases that are more susceptible to the damaging effects of asbestos inhalation.

Of the lung function tests examined the percentage of predicted FEV_1 ($PPFEV_1$) was the most useful predictor of death. At first sight this is a surprising observation. FEV_1 is reduced in restrictive disease but to a similar or lesser extent than vital capacity. In this study there was no significant difference between VC in the survivors and the non-survivors (Table 12) so it is unlikely that $PPFEV_1$ is simply reflecting the severity of the restrictive defect. There are at least two other possible explanations. Firstly the majority of the men studied were or had been cigarette smokers. This habit is associated with both lung cancer (Doll and Bradford Hill 1964) and airflow limitation (Fletcher et al 1976) and the predictive value of $PPFEV_1$ could be a reflection of these associations. Secondly many workers (Jodoin et al 1971, Muldoon and Turner-Warwick 1972, Fournier-Massey and Becklake 1975 and Weill et al 1975) have found evidence of airway disease in asbestos workers and

furthermore there is evidence that this is related to asbestos exposure as well as cigarette smoking. Thus there are a number of reasons why $PPFEV_1$ might predict mortality but their relative importance cannot be assessed in this study.

(c) Histology of bronchial carcinoma in asbestosis

Adenocarcinoma was the commonest histological type in this study. Whitwell et al (1974) in a larger study of the cell type in lung cancer occurring in Panel certified cases of asbestosis made the same observation and other workers (Heuper 1966, Hourihane and McCaughey 1966) have also commented on the frequency of adenocarcinoma in asbestosis. Kannerstein and Churg (1972) however did not find an excess of adenocarcinoma in a case control study of lung cancer associated with asbestos exposure but many of their cases did not have asbestosis.

Whether the frequency of adenocarcinoma is truly increased in asbestosis is difficult to know because of the lack of any comparable series of non-asbestos exposed lung cancer cases. The frequency of adenocarcinoma in different series depends upon whether the histological specimen was obtained at bronchial biopsy, operation or post-mortem. Even post-mortem series are not strictly comparable because of the higher rate of autopsy in asbestosis than in the

general population. In men without asbestosis Whitwell et al (1974) found the proportion with adenocarcinoma rose from 2% in bronchial biopsies to 27% at post mortem. He thought the true incidence probably lay between 15 and 20%.

So the evidence of this study and that of Whitwell suggests that adenocarcinoma complicates asbestosis more frequently than other histological types of lung cancer. If this is so it might be expected that those with the more severe asbestosis will be more likely to develop adenocarcinoma and there is some evidence in Table 14 to suggest that this cell type is more frequent in those with higher profusion scores. Whitwell found adenocarcinoma more frequently in cases with histologically more advanced fibrosis. Wagner et al (1974) in asbestos inhalation studies with rats found that adenomata and adenocarcinoma occurred more frequently in areas of fibrosis.

Lung cancers complicating asbestosis are said to be commoner in the lower lobes in contrast to the usual preponderance of upper lobe tumours (Hueper 1966, Kannerstein and Churg 1972, Whitwell et al 1974) and they are frequently peripheral. Further evidence on these points is not available from this study.

Although there is reason to suppose that adenocarcinoma is more frequent in asbestosis it does not account for the excess of lung cancers observed and there is probably an

increase in all cell types but with a greater rise in the incidence of adenocarcinoma. This is in contrast to the situation with uranium (Archer et al 1974) and chloromethyl ether (Weiss et al 1979) where large increases in one cell type, oat cell carcinoma, are seen.

Progression of intrapulmonary fibrosis

It is generally held that asbestosis is a progressive disease (Morgan and Seaton, (1975), Parkes (1974), Selikoff and Lee (1978)) although Parkes comments that in some cases the disease is apparently arrested. The effect of ceasing exposure on the course of the disease is unknown. Stone (1940) noted radiographic progression in 2 of 13 advanced cases of asbestosis over a 2-3 year follow up after exposure had ceased but did not detect progression in any early cases after ceasing exposure. Smith (1955) stated that progression ceased when exposure stopped but offered no evidence to support his view. Leathart (1960) found that cases of asbestosis attending hospital deteriorated clinically after ceasing exposure and in lung function (Leathart 1960, 1968). The clinical deterioration in his cases was not always associated with radiographic deterioration. There is now good evidence that small irregular intrapulmonary opacities on the chest radiograph, and by implication asbestosis, can arise after exposure has ceased. (Becklake et al 1979, Rossiter et al 1980). Gregor et al (1979) in a study which included many of the patients reported here found that the rate of progression was relatively slow but the numbers showing progression increased with time so that 30% showed evidence of radiographic progression after six years.

In this study only 38% were considered to show radiographic progression over a mean follow up period of

Insert after paragraph 3.

Two studies from the United Kingdom have examined the effects of smoking on the development, but not the progression, of asbestos related disease.

McMillan et al (1980) examined the attack rates for asbestos related readiographic abnormalities according to smoking habit when their population was first examined radiographically in 1966. Men were divided into lifelong nonsmokers, exsmokers and smokers. Smokers and exsmokers were significantly more likely to develop asbestos related abnormalities and all those with intrapulmonary fibrosis were or had been smokers. There were no consistent differences between smokers and exsmokers.

Berry et al (1977) used information on current smoking habits in their study of asbestos textile workers. They found more signs of asbestosis in the heavier (5 or more cigarettes a day) and exsmokers than in the light and nonsmokers. The differences was also significant for small opacities on the chest radiograph but not for possible or certified asbestosis.

It appears possible that cigarette smoking may predispose to the development of asbestosis. If this is so than it may also have an effect on progression. It is possible that more detailed analysis of smoking might have shed further light on the factors influencing progression. Such analyses were not carried out because of doubts about the reliability of smoking histories obtained when men were applying for industrial compensation. Furthermore as many cases were not observed to progress despite continued smoking the crucial analyses are likely to be those which examine smoking prior to attack and the effects of smoking during the active phase of the disease. This requires knowledge of the time when disease actually developed and not simply when it was identified which is the only information that is available for most of the cases.

Among cases detected by routine surveillance where there is reason to think that disease was detected early 11 of the 14 progressing cases were smokers and 6 of the 9 nonprogressors smoked. All the cases had been smokers. There is no clear evidence that smoking influences progression.

7.5 years. Sixty-two percent did not progress. Whether or not the 66 deaths had progressive pulmonary fibrosis is not known but even if they were all progressing over one-third (61/167) of the 167 cases did not progress.

There was no evidence that the presence of antinuclear antibody or rheumatoid factor predicted progression.

As nearly all the cases were or had been cigarette smokers no comparisons were possible between non-smokers and smokers but it was possible to compare those who gave up smoking at or before certification with those who continued. No significant differences were found in the rates of progression.

A discriminant analysis was used to try and detect factors which predicted progression. Only one discriminator, finger clubbing, was found. As in the case of mortality the indices of exposure to asbestos were not useful discriminators suggesting that given an exposure sufficient to cause asbestosis further progression was independent of dose. A number of studies (Rossiter et al 1980, Jones et al 1980) suggest that progression is related to dose but in the author's view these studies do not differentiate between progression, that is to say worsening of established abnormality and attack, the appearance of abnormality for the first time. Most of the abnormality in these studies was due to attack and the exposure response relationships

observed serve only to re-emphasise the known association between asbestos exposure and small irregular opacities on the chest radiograph. They provide no evidence that progression of established disease is dose related.

Increasing profusion score for small opacities above category 0 was not related to progression and it seems unlikely that radiographic progression was underestimated in those with higher profusion scores at presentation (Table 19). Lung function tests at certification did not predict progression.

In this study there was no trend towards increased progression rates with increasing length of follow up. This is important because if correct it suggests that in many cases the disease becomes inactive. Furthermore as this study could only detect cases where activity had ceased before certification it may have underestimated the proportion of cases in which the fibrotic process becomes arrested. Some support for the idea of a non-progressive stage comes from the work of Britton et al (1977) who postulated such a possibility on the basis of serial lung function tests in asbestosis.

Many of the non-progressing cases had marked abnormalities on the chest radiograph and on lung function testing. Clearly there must have been a time when the disease was active and this must have been before certification

in non-progressive cases. This suggests that there may be an early active stage in the disease. An attempt was made to investigate this possibility by comparing cases detected by periodic examination at work with those detected in other ways. Tables 21a, b and c compare the two groups. The routine surveillance cases are younger, have had a shorter exposure to asbestos and have had less time from first exposure than cases coming to attention by other means. It is likely that as they were often exposed more recently than the other cases the intensity of their exposure was also less severe. As a group they were less breathless at presentation than the others but had a similar distribution of radiographic profusion scores. The comparison of lung function between the two groups is particularly interesting (Figs 27-29). Although falls in mean lung function occurred in both groups the routine surveillance group began with better lung function and then underwent the greater decline before levelling out with similar mean values to the other group. These observations are compatible with the notion of any early active phase. Further support comes from the observations of Wegelius (1947) on radiographic change in Finnish asbestos workers. Over a period of two years he observed 27 of 36 cases with what he described as ante-primary absestosis* progress to Stage 1. Only 6 of 42 cases with stage 1 or greater disease progressed in the same period.

* Ante-primary stage of asbestosis: still fairly uncharacteristic strengthening of the lung picture mainly in the middle and basalfields, fine x-ray shadows and quite slight indications of small nodules in the costrophrenic or cardiophrenic angles.

When the rate of progression is examined after removal of the routine surveillance cases (Table 22) there was not even a hint of increasing progression with longer follow up.

When the changes in lung function in the progressors and non-progressors (Tables 24-26) irrespective of method of detection were examined the mean percentage of predicted FEV_1 and VC were both found to be higher at presentation in the progressors in keeping with the ideas discussed above. However the percentage of predicted D_LCO in the progressors at presentation was already at the level of the non-progressors and fell further. At first sight this is out of keeping with the idea of early progression but it probably reflects the association between finger clubbing and progressive disease. As has been demonstrated cases with finger clubbing tend to have lower transfer factors than thosewithout finger clubbing.

Thus the evidence discussed here suggests that there is an early active period of fibrosis followed in many cases by a quiescent period. Some cases may follow a more aggressive course and finger clubbing is of some value in identifying these cases at presentation.

The proportion of cases falling into the different categories cannot be accurately assessed from this study but it can be stated that over 60% of the cases seen at follow up had not progressed. Furthermore it is possible that many of the progressors had entered a quiescent stage and there is

some anecdotal evidence that this was so in two cases.

Nothing is known of the rate of progression in the deaths but in view of the associations between finger clubbing and progression of intrapulmonary fibrosis and finger clubbing and mortality it is reasonable to suppose that it might have been greater than in the survivor population studied.

If there really is an early active phase its length cannot be ascertained from this data but in view of the 44% of routine surveillance cases that did not progress one might surmise that at least in some cases it is quite short. Finally there is no way of knowing from the evidence here whether non-progressive asbestosis can become reactivated.

Immunology

(1) Antinuclear antibody (ANA)

A raised prevalence of ANA in asbestosis was first reported by Turner-Warwick and Parkes (1970). The prevalence of ANA in the cases reported here was 28.4%, a figure similar to that of Turner-Warwick and Parkes and greatly in excess of that found in normal population. Turner-Warwick and Haslam (1971) detected ANA in only 2 of 75 (2.6%) asbestos exposed but non-diseased individuals matched for age, sex and duration of exposure with 75 cases of asbestosis. The prevalence of ANA among the cases was 25%. Haslam (1976) found ANA in 10 of 107(9%) normal males over the age of 40. All the data referred to above including the data in this thesis was collected in the same laboratory using the same techniques. Beck (1963) found raised titres of ANA ($\geqslant$1/16) in 2.2% of 220 male hospital inpatients having blood cross-matched prior to surgery.

Thus it is clear that the prevalence of ANA is markedly raised in asbestosis at the time of diagnosis. The prevalence is similar in cases detected both by routine surveillance and by other methods (Table 21a) suggesting that ANA appears early in the course of the disease. When the prevalence of ANA is examined in relation to the profusion of small opacities (Table 30) a marked contrast is seen

between category 0 and the higher categories. The prevalence in category 0 is 12.8%, a figure only slightly higher than that expected in a normal population, suggesting the development of ANA is associated with clear cut radiographic evidence of pulmonary fibrosis.

In this study there was no association between the prevalence of ANA and duration of exposure to asbestos. This is in keeping with the findings in asbestos exposed populations where the prevalence of ANA is similar to that in normal populations. (Turner-Warwick 1973).

At follow up the prevalence of ANA had risen to 35.4% but the association of ANA with radiographic evidence of disease was no longer apparent (Table 35). A marked increase in prevalence was seen in cases aged 60 or more at follow up. Some increase was also seen in the cases who showed radiographic progression but the increase was not statistically significant.

It has been suggested that ANA may act as an accelerator of fibrosis (Turner-Warwick 1974, 1978). This seems unlikely in asbestosis because the proportion of cases with ANA at presentation is closely similar in both the progressors and the non-progressors (Table 33).

Thus ANA appears to be an epiphenomenon associated with the development of radiographic evidence of asbestosis.

It is of no value either in assessing the seventy or in predicting the future course of the disease.

(2) Rheumatoid Factor (RF)

Increased prevalence and titres of RF in asbestos workers were first observed by Pernis et al (1965). In their study the increase occurred in those with radiographic abnormality. This finding was confirmed by Turner-Warwick and Parkes (1970) and a subsequent case-control study by Turner-Warwick and Haslam (1971) showed that the effect was confined to cases with asbestosis. Only one of seventy-five asbestos exposed controls matched for age, sex and exposure to asbestos had a titre equal to or greater than 1 in 32 compared with 12 of the 75 cases. In this study 7.3% of the male cases had RF present in titres equal to or greater than 1 in 32. This is marginally higher than the prevalences of up to 6.2% found by Ball and Lawrence (1961) in surveys of the general male populations aged 55-64.

No relationships could be detected between RF (titres $\geq$ 1 in 32) at presentation and the severity of intrapulmonary fibrosis, the subsequent progression of intrapulmonary fibrosis or mortality. However at follow up some interesting associations emerged.

Firstly, the presence of RF ($\geq$ 1 in 32) at follow up was significantly associated with progressor status (Table 37)

and secondly the prevalence of RF rose with increasing radiographic profusion score suggesting that RF might be arising in cases with more aggressive disease. As with ANA the evidence does not suggest a role for RF as an accelerator of fibrosis. Rather it appears to be an epiphenomenon occurring in some cases of progressive disease. In contrast to ANA it tends to appear while the disease is under observation and to be associated with progression, but on the basis of the evidence here it cannot be used to predict progression.

A relationship between unusual radiographic appearances in coal workers pneumoconiosis and rheumatoid disease was noted by Caplan (1953). He described well defined round opacities in the lungs of coalworkers with rheumatoid arthritis. These shadows could appear before rheumatoid arthritis had developed and they were sometimes found in coalworkers with little or no evidence of simple coalworkers pneumoconiosis. In a review of rheumatoid pneumoconiosis in coalworkers Lindars and Davies (1967) suggested that in the presence of a heightened tendency to auto-immune disorders nodular lesions might occur with a lower dose of dust. The tendency to auto-immune disease might modify the response to inhaled dust.

Caplan's syndrome has now been reported following exposures other than to coal mine dust and these include asbestos. (Richards and Barrett (1958), Tellesson (1961), Morgan (1964), Mattson (1971)). The association of

asbestos exposure and rheumatoid disease reported in these cases may be a chance occurrence. Indeed the case reported by Tellesson has subsequently come to postmortem and been reported again (Greaves 1979). With hindsight it was thought unlikely that asbestos exposure had been important in causing disease in that case. None of our cases, even those with rheumatoid arthritis and or rheumatoid factor had Caplan nodules either at presentation or at follow up.

The suggestion by Lindars and Davies (1967) that a heightened tendence to auto-immune disorders might result in disease after smaller exposures still needs to be considered. If the presence of rheumatoid arthritis can be regarded as evidence of a heightened tendency to auto-immune disease then there is no evidence here (Table 39) that such subjects develop asbestosis with shorter exposures nor is it reasonable to assume that the presence of rheumatoid arthritis makes progression more likely although it is a possibility. Three of the five cases with rheumatoid arthritis progressed.

However, the presence of five cases of rheumatoid arthritis among the 98 cases seen at follow up is high and might represent selection into the asbestotic group of subjects with the 'rheumatoid diathesis'. If this is so the effect appears to be a small one. Alternatively, it might be argued that cases of rheumatoid arthritis complicated by pulmonary fibrosis and with a history of asbestos exposure are being misdiagnosed as asbestosis.

This may be so but the cases seen here all had long and heavy exposures to asbestos sufficient to account for their pulmonary fibrosis.

The possibility that a 'rheumatoid diathesis' might increase susceptibility to asbestosis has been investigated by White et al (1974) using a symptom questionnaire in an age stratified random sample of 1069 asbestos workers. The authors acknowledged that the method of detecting symptoms of rheumatoid arthritis was crude and that this might result in failure to detect small effects. A further difficulty arises because workers with symptoms of rheumatoid arthritis may have to change their job and so be selected out of the study population. Whether and to what extent these factors operated is not known but the study showed no relationship between radiological response to chrysotile and rheumatic symptoms.

Thus on present evidence it seems unlikely to the author that the 'rheumatoid diathesis', if such a thing exists, increases susceptibility to asbestosis. Nor does rheumatoid arthritis when present necessarily lead to a more vigorous fibrotic response.

Implications for the pathogenesis of asbestosis

Any hypothesis which tries to account for the pulmonary fibrosis which can occur with asbestos exposure has to explain the following four clinical observations:-

1. The latent period between first exposure and the development of clinical disease.

The existence of a latent period before the development of clinically apparent asbestosis was first noted by Merewether and Price (1930) and has been a constant feature of the disease. Even in the most heavily exposed workers seen by Merewether and Price clinical disease was not found in those with less than five years from first exposure. It is now certain that radiographic evidence of disease can develop after exposure has ceased (Becklake et al 1979, Rossiter et al 1980) and when the asbestos content of the lung is at least static if not declining.

2. The cessation of the fibrotic process.

The information in this thesis suggests that the fibrotic process ceases in many cases. This needs to be explained. There is usually no difficulty in identifying asbestos bodies and fibres in lungs affected by asbestosis at post mortem and asbestos bodies and fibres have been

recovered from the broncho alveolar lavage fluid of one of the non-progressing cases described in this thesis. It seems unlikely that activity ceases because asbestos is cleared from the lung. Indeed it is uncertain whether any appreciable clearance occurs at all but if it does then the studies of Becklake et al (1979) and Rossiter et al (1980) imply that disease can develop while the asbestos load in the lung is declining. If clearance does occur and is responsible for the cessation of the fibrosing process then one might expect to find that the progressing cases had ceased exposure more recently than the non-progressing cases. This was not so among the cases reported here (Table 20) and the range of times from last exposure was very wide in both groups.

3. The predominantly lower zone distribution of fibrosis.

Asbestosis is predominantly a lower zone disease and only encroaches on the upper parts of the lung in severe cases. Asbestos bodies and fibres are distributed throughout the lungs (Bell and Elmes, 1971 and Sebastien et al 1977) and not preferentially in the lower zones. Why in these circumstances does asbestos give rise to a lower zone fibrosis?

4. The apparent resistance of some individuals to asbestosis

Selikoff et al (1965) found that nearly 90% of insulation workers in whom 30 or more years had elapsed since first

exposure had parenchymal changes detectable on the chest radiograph. Why did 10% of these heavily exposed men apparently have no disease?

It is clear that asbestos is in some way implicated in the development of pulmonary fibrosis. Many cohort studies (Selikoff et al 1965, Berry et al 1979, Weill et al 1973 and Rossiter et al 1972) of asbestos workers have shown a dose-response relationship between asbestos exposure and radiographic and clinical evidence of asbestosis. The study by Rossiter et al (1972) is of particular interest because they studied five measures of exposure, years since first exposure, total years of exposure, total dust exposure, time weighted dust exposure and effort weighted dust exposure. The largest correlation coefficients between radiographic profusion score for small irregular opacities were 0.27 for total dust exposure in the Thetford mining area and 0.27 for years of exposure at Asbestos. Both these correlation coefficients were highly statistically significant but they imply that only 7.3% of the total variation in small irregular opacities was related to the exposure indices used.

Studies of the asbestos content of lungs at post mortem have shown a similar picture. The early studies of Beattie and Knox (1961) and Nagelschmidt (1965) found no relationship between the mineral content of the lung and fibrosis. Ashcroft and Heppleston (1973) have shown dose-response relationships between the fibre content of the lung and

Insert after paragraph 2.

Animal models of asbestosis have been useful in confirming that the inhalation of asbestos can lead to pulmonary fibrosis but the disease in rats continues to progress after ceasing exposure and has not been reported to enter a quiescent phase. (Holt et al 1966, Wagner et al 1974 and Hiett 1978). If the findings in this thesis are correct and the disease frequently enters a nonprogressive stage then the animal model differs in an important respect from human disease.

It is of interest that Wagner et al (1974) found that for a given cumulative airborne dose of fibre much less chrysotile was retained in the rat lung than crocidolite or amosite. Dispite this chrysotile was associated with more fibrosis than the amphiboles. As yet there is little information on the relative fibrogenicity of the different fibres in man although Weill et al (1977) have suggested that crocidolite may be associated with more fibrosis than chrysotile.

Holt, P.J., Mills, J., and Young, D.K. (1966).
Experimental asbestosis in the guinea-pig
Journal of Pathology and Bacteriology 92, 185.

Heitt, D.M. (1978)
Experimental asbestosis: an investigation of functional and pathological disturbances. I Methods, control animals and exposure conditions.
British Journal of Industrial Medicine 35, 129.

Weill, H., Rossiter, C.E., Waggenspack, C., Jones, R.N. and Ziskind, M.M., (1977)
Differences in lung effects resulting from chrysotile and crocidolite exposure.
In: Inhaled Particles IV Ed. Walton, W.H., Pergamon Press, Oxford, pp 789-798.

the degree of fibrosis but they were poor. A rough dose-response relationship was found with mild and moderate fibrosis but it broke down when severe disease was considered. These authors suggested that this might be due to the supervention of other pathologies particularly infection.

The inability of the dose-response relationship to explain much of the variation found is perhaps not surprising as the response measured is dependent on a biological change occurring in the lung. (Unlike coalworkers pneumoconiosis where the radiographic abnormality is due to accumulated dust and where the exposure-response relationship is much better). This inability of exposure to account fully for the observed phenomenon has lead to a search for differences in individual susceptibility. The implication behind much of this work is that immunological differences presumably genetically determined play a part in the response to inhaled asbestos. Whilst such differences may well exist none have yet been identified. Histocompatibility antigens have been studied by a number of groups and the results have been reviewed by Turner-Warwick (1979). No important associations were found. If an important predisposing factor is found it will be interesting to discover how cessation of the fibrotic process comes about.

The effects of asbestos on macrophages have been studied in vivo and Allison (1973) has suggested that

one of the consequences of the interaction between asbestos fibres and macrophages may be the release of a fibrogenic factor. If this happens in man and leads to fibrosis it is difficult to explain the lower zone distribution of fibrosis and the cessation of the fibrotic process given the wide distribution of asbestos throughout the lung and its persistence long after exposure has ceased.

It is difficult to construct a plausible model for the pathogenesis of asbestosis from the information discussed above. If however asbestos plays its part not by causing fibrosis itself but by altering the lung in such a way that fibrosis occurs more readily in response to other injurious agents then a plausible hypothesis which takes account of the clinical observations can be advanced.

It is suggested that asbestos fibres alter the normal response of the epithelial lining of the alveoli and respiratory bronchioles to injury by other agents in such a way that the epithelial lining does not regenerate properly and healing tends to occur by fibrosis. The effects of mild damage to the alveolar capillary membrane may be more severe at the lung bases because of the effects of hydrostatic pressure leading to transudation of fluid. The fibrotic process might be expected to stop once the pulmonary damage was repaired. Blood would be diverted to higher parts of the lung as the disease advanced. This could explain the distribution of the disease and its

tendency to spread up the lung fields. The latent period before disease develops might reflect either the time taken for asbestos to accumulate in sufficient quantity to impair healing or the time required before inhaled fibre starts to exert a deleterious effect. It may be for instance that impaired healing develops quite rapidly after very heavy exposures but only slowly after more modest exposures. The observed dose-response relationships are compatible with this hypothesis. The greater the exposure to asbestos the more likely the development of fibrosis becomes. Thus attack, the development of fibrosis is related to dose. The relationship is weak because it depends on the occurrance of a second insult to the lung. If the second insult never occurs fibrosis will never develop. The severity of the fibrosing process might depend not only on the degree of asbestos exposure but also the nature of the secondary insult. This would serve to further weaken the dose-response relationship and would help to explain the lack of a relationship between asbestos exposure and progression of fibrosis seen in this study and in that of Liddell et al (1977) who distinguished between attack (the development of abnormality) and progression (the worsening of established abnormality).

A two stage animal model of pulmonary fibrosis has been described (Witschi et al 1980) and it seems likely that damage to the type II alveolar lining cell is important in allowing healing to occur by fibrosis. Perhaps asbestos fibres can impair the function of this cell.

If this theory is correct and a second agent is involved in the pathogenesis of asbestosis its nature is quite unknown. Whatever it is it must occur worldwide and be reasonably common. Some form of infective organism might be a suitable candidate, probably one which caused only a mild illness which was not later recalled. If this is so acquired immunity may be a further factor in determining the development and progression of the disease. Finally it may be that a variety of agents are capable of causing the kind of pulmonary damage that results in healing by fibrosis in those with asbestos fibre in their lungs.

CONCLUSIONS

The study population consisted of 167 cases of asbestosis diagnosed by the London Pneumoconiosis Medical Panel between 1968 and the end of 1974. The characteristics of the population are set out in the first section of the results. A summary of the conclusions to each of the four remaining sections of results is given at the end of each section. What follows here is an attempt to summarise the overall study results under five headings:-

(1) Mortality

(2) Progression of pulmonary fibrosis

(3) The predictive value of finger clubbing

(4) The lack of importance of indices of asbestos exposure in predicting mortality or progression of established intrapulmonary fibrosis.

(5) The significance of radiographic category 0.

(1) Mortality

The male cases of asbestosis had a mortality rate of 2 to 3 times higher than the general male population. The excess mortality was accounted for by death due to lung cancer, mesothelioma and other respiratory diseases. It is of note that there was no excess mortality from gastrointestinal cancer.

The female cases had a higher mortality ratio than the men but the number of female cases is too small to allow any useful interpretation.

Three factors were of value in predicting mortality in male cases. They were age at diagnosis (hardly a surprising result), finger clubbing and percentage of predicted FEV_1. The last predictor was surprising and its explanation must remain speculative but it may reflect a number of factors all adversely affecting survival. Firstly, FEV_1 is reduced in restrictive disease but if it was merely reflecting the severity of the restrictive defect, then vital capacity would be expected to be a more powerful predictor. Secondly, FEV_1 is adversely affected by cigarette smoking. The mortality from lung cancer was very high in this group and it may be that reduction in FEV_1 was linked through cigarette smoking with mortality. Finally asbestos exposure itself has been asociated with obstructive airways disease in exposed work forces. Perhaps some combination of these three effects accounts for the predictive value of reduction in percentage of predicted FEV_1.

(2) Progression of Intrapulmonary Fibrosis

This was assessed in the 98 available survivors of the original study population and caution is required in generalising from these observations to the whole study group.

62% of the survivors showed no evidence of radiographic progression. Cases with marked radiographic evidence of fibrosis were seen which did not progress either radiographically or physiologically. Clearly their disease must have been progressive at one time and there was some evidence for an early more active fibrosing stage in the disease.

Progression was not related to the length of follow up. This is in keeping with the idea of an early active phase. The mean length of follow up was around 7.5 years and one would expect to see some deterioration in that time even in a slowly progressive form of fibrosis.

Progression was not related to time from last exposure to asbestos. There is no suggestion that progressive fibrosis occurs until either asbestos is cleared from the lung or until the fibre is in some way rendered harmless.

38% of the survivors showed evidence of radiographic progession and in some cases this was marked (Plate 7a and b).

Finger clubbing at presentation was the only predictor of progression to be identified.

(3) The Predictive Value of Finger Clubbing

When finger clubbing occurs it develops early in the clinical course of asbestosis and usually before certification. It is a predictor of both mortality and progression of pulmonary fibrosis.

There was no evidence that finger clubbing developed in a more heavily asbestos exposed group. It is a marker for a subgroup with a relatively more aggressive form of asbestosis.

(4) The Lack of Importance of Indices of Asbestos Exposure in Predicting Mortality and Progression of Established Intrapulmonary Fibrosis.

In studies of asbestos exposed populations correlations have been found between the presence and profusion of small irregular opacities on the chest radiograph and measures of exposure and also between mortality experience and exposure.

In this study, the measures of exposure were crude. Total duration of exposure and time from first exposure to asbestos were used. No correlations were found between the profusion of small opacities and either measure of dose. Neither measure of dose predicted either mortality or progression of intrapulmonary fibrosis.

It might be argued that the failure to correlate dose with indices of response arose simply because the dose data was so crude. This may be so but alternatively it could be that dose is only important in determining attack, that is to say the development of disease, and that outcome in established asbestosis is dependent on factors other than dose. The predictive value of percentage of predicted FEV_1 in determining mortality and of finger clubbing in determining both mortality and progression tend to support the latter hypothesis.

(5) The Significance of Radiographic Category 0

There was no overall excess mortality among the 36 male cases with category 0 radiographic profusion scores. The mortality from lung cancer and other respiratory disease was raised but the small number of cases make interpretation of the figures difficult. On the one hand these deaths may reflect the effects of asbestos exposure but on the other hand they may reflect the selective process involved in coming before the Pneumoconiosis Medical Panel.

The proportion of category 0 cases showing radiographic progression was much lower than that for categories 1 and 2 + 3 despite the fact that proportionately more category 0 cases survived to progress.

The frequency of positive antinuclear antibody was only marginally elevated in category 0 cases and considerably lower than in the other profusion categories.

The data suggests that the category 0 cases as a group are different from those with small irregular opacities on the chest radiograph. It seems probable that many of these cases do not have asbestosis.

APPENDICES

APPENDIX 1

Details of follow-up of 313 claimants seen between 1968-74

	TOTAL	ALIVE	DEAD	UNTRACED	FOLLOW-UP OBTAINED	NO FOLLOW-UP
Certified cases of asbestosis	167	101	66	0	98	3
Certified cases of mesothelioma*	9	0	9	0	-	-
Cases certified for industrial diseases unrelated to asbestosis	3	2	1	0	2	0
Cases not certified for any industrial disease	134	90	42	2	77	13
	313	193	118	2	177	16

*This does not include cases of asbestosis who subsequently developed mesothelioma

APPENDIX II

ASBESTOSIS RESEARCH

BASIC DATA:

LAB. NO. | | | | | |

Hospital No. | | | | | | | | | |

National Insurance No. | | | | | | | | | |

Date of attendance. | | | | | | | | | |

SURNAME _____

FORENAME _____

SEX Male ☐ Female ☐

AGE | |

DATE of BIRTH | | | | | | |

HEIGHT | | | CMS.

WEIGHT | | | Kg.

NATURE OF JOBS WITH DATES (INCLUDING NON-ASBESTOS INDUSTRY)_____

_____

_____

_____

Duration from 1st exposure to asbestos | | years

Duration of exposure to asbestos | | years

Category of severity of exposure (see definition)

heavy ☐

medium ☐

light ☐

Type of asbestos used:

Crocidolite ☐

Amosite ☐

Crysotile ☐

Pension: Yes ☐ No ☐

If yes year awarded | | | |

ERCISE GRADE (MRC)

	Yes	No
ce you ever troubled by shortness of breath when urrying on the level or walking up a slight hill?	☐	☐
o you get short of breath walking with other people t an ordinary pace on the level?	☐	☐
o you have to stop for breath when walking at your wn pace on the level?	☐	☐
ce you short of breath on washing or dressing?	☐	☐

RONIC COUGH AND SPUTUM

o you have a daily cough for more than months each year? Yes ☐ No ☐

If yes, how long. . . . . .

o you have daily sputum for more than months each year? Yes ☐ No ☐

if yes:

) How long. . . . . .

) What is your usual volume of sputum:

- none ☐
- up to 4 blobs per day ☐
- up to an egg cup full ☐
- up to a tea cup full ☐
- greater than a tea cup ☐

) What is your usual colour of sputum:

- white/grey ☐
- yellow/green ☐

) Do you have difficulty in expectorating: Yes ☐ No ☐

RESENT COUGH AND SPUTUM

lave you had cough within the last week? Yes ☐ No ☐

lave you had sputum within the last week? ☐ ☐

f yes, what volume:

- up to 4 blobs per day ☐
- up to an egg cup full ☐
- up to a tea cup full ☐
- greater than a tea cup ☐

If yes, what colour:

- white/grey ☐

EXERCISE GRADE (PRESTON)

	Duration (years)
Normal exercise tolerance	
Breathless climbing hills or 2 flights of stairs	
Breathless on slight incline or 1 flight of stairs	
Breathless on flat	
Breathless at rest	

Do you regularly feel tired Yes ☐ No ☐

If yes, describe and give duration _____

OTHER ILLNESSES

Do you have:	Yes	No
rheumatoid arthritis	☐	☐
transient polyarthritis	☐	☐
thyroid disease	☐	☐
anaemia	☐	☐
kidney disease	☐	☐
atropy	☐	☐
other diseases	☐	☐

If yes, give details _____

Have you had any chest diseases other than bronchitis?

Yes ☐ No ☐

If yes, details _____

FAMILY HISTORY

Is there a family history of any of the above diseases or asbestosis?

Yes ☐ No ☐

If yes, details _____

TOBACCO SMOKING

Do you smoke? (yes, if regular up to 1 month ago) Yes ☐ No ☐

Have you ever smoked? (No, if one or less cigarettes or less than 1 oz. tobacco per month, for 1 year) Yes ☐ No ☐

If yes to either of above questions:-

	AMOUNT SMOKED	
	NOW	PREVIOUSLY
cigarettes/day		
oz. tobacco/week (hand rubbed)		
oz. tobacco/week (pipe)		
cigars/week (large)		
cigars/week (small)		

Age started regular smoking ☐☐

Age stopped regular smoking ☐☐

If stopped or reduced, give reasons _____

PHYSICAL SIGNS

	Yes	No
Clinical finger clubbing	☐	☐
Cyanosis	☐	☐
Rales	☐	☐

If yes:		Yes	No
Right lung -	basal	☐	☐
	persistant (after coughing)	☐	☐
	other regions	☐	☐
	persistant	☐	☐
Left lung -	basal	☐	☐
	persistant (after coughing)	☐	☐
	other regions	☐	☐
	persistant	☐	☐

	Yes	No
Wheeze on auscultation	☐	☐
Persistant	☐	☐

Pulse rate - per minute ☐☐

Blood pressure ☐☐☐☐☐☐

Arthritis Yes ☐ No ☐

If yes joints involved _____

Soft tissue swelling or effusions Yes ☐ No ☐

Other physical findings

If yes _____

APPENDIX III

	HOSPITAL NUMBER		1-6
	READER		7
	DATE OF FILM		8-9
FILM QUALITY	Grade 1, 2, 3 or 4		10
	If not 1, Black, White, Grey, Movement		11
	Cut Bases	R L	12-13
	Parenchymal details clearly visible		14
	Pleural details clearly visible		15
COSTOPHRENIC ANGLES	Below standard	R L	16-18
PLEURAL THICKENING	None		19
	Diffuse	R L	20-21
	Plaques	R L	22-23
	Width (A,B or C)	R L	24-25
	Extent (0,1 or 2)	R L	26-27
PLEURAL CALCIFICATION	None		28
	Diaphragm	R L	29-30
	Wall	R L	31-32
	Other Sites	R L	33-34
	Grade (1,2 or 3)	R L	35-36
ILL-DEFINED DIAPHRAGM	Below standard	R L	37-39
ILL-DEFINED CARDIAC OUTLINE	(1,2 or 3) Below standard		40-41
SMALL ROUND OPACITIES	None		42
	Type (P,Q or R)		43
	Profusion		44-45
	Zones	R L	46-47
		R L	48-49
		R L	50-51
SMALL IRREGULAR OPACITIES	None		52
	Type (S,T or U)		53
	Profusion		54-55
	Zones	R L	56-57
		R L	58-59
		R L	60-61
LARGE OPACITIES	None		62
	Type (well-defined or Ill-defined)		63
	Size (A,B or C)		64
SYMBOLS	Up to 3 from : AX EU CA CN CO CP		66-68
	CV DI EF EM ES ET FR HI HO K		69-71
	OD ODA POR PCL PX RL TB		72-74
CARD NO			75-80

HOSPITAL NUMBER	☐☐☐☐☐☐	1-6
YEAR OF FIRST FILM	☐☐	7-8
YEAR OF LAST FILM	☐☐	9-10
READER	☐	11

COMPARABILITY		☐			12
SECOND FILM BLACKER OR WHITER		☐			13
COSTOPHRENIC ANGLES	No change	☐	R ☐☐	L	14-16
PLEURAL THICKENING	No change	☐			17
	Diffuse	R ☐☐	L		18-19
	Plaques	R ☐☐	L		20-21
	Diaph. plaques	R ☐☐	L		22-23
PLEURAL CALCIFICATION	No change	☐			24
	Wall	R ☐☐	L		25-26
	Diaphragm	R ☐☐	L		27-28
	Other sites	R ☐☐	L		29-30
DIAPHRAGM LEVEL	No change	☐			31
	Up or down	R ☐☐	L		32-33
	Distance	R ☐☐	L		34-35
SMALL OPACITIES	No change	☐			36
	Inc. prof	R ☐☐	L		37-38
	Inc. zones	R ☐☐	L		39-40
	Comments	☐			41

CARD NUMBER	☐☐	79-80

APPENDIX V

Analysis of Inter and Intra Observer Variation in the Assessment of Small Intra Pulmonary Opacities

A subset of 34 radiographs drawn from the 313 presenting films plus the 27 normal films added to that series were assessed on three occasions by each reader. They were read firstly for use as trigger films (T), secondly during the reading of the radiographs at presentation (R1) and thirdly during the reading of the follow up films (R2). The three readers, MTW, IHK and JCG all worked independently.

These three sets of readings have been used to assess intra-observer variation. They also provide information about inter-observer variation. Further assessment of inter-observer variation has been made by comparing the profusion scores given by each reader in the presenting and follow up radiograph series.

For the purpose of calculating the coefficient of concordance (W) and in the analysis of variance the twelve point scale of the ILO/UC classification has been quantified as follows:- 0/- = 1, 0/0 = 2, ... 3/2 = 10, 3/3 = 11, 3/4 = 12.

Intra-Observer Variation

This has been examined using two statistical approaches.

(1) Kendalls coefficient of concordance (W)

(2) Analysis of variance.

(1) Kendall's Coefficient of Concordance (W)

With this test it is possible to assess whether the readers rank the profusion of small intra pulmonary opacities in more or less the same order. The test is robust even in the presence of many tied appraisals. W varies from -1 to +1.

The following coefficients of concordance were obtained:-

Within	MTW	T/R1/R2	0.8145
Within	IHK	T/R1/R2	0.8251
Within	JCG	T/R1/R2	0.8465

These values show good positive concordance and suggest that each reader is highly consistent in ranking the profusion of small intra pulmonary opacities. However a high degree of concordance does not necessarily mean that the score given to a particular radiograph is the same or similar on each occasion. It merely indicates that the assessment of abnormality has not changed relative to the other radiographs in the series.

(2) Analysis of Variance (Table 1)

Despite the fact that the distribution of radiographic readings was not very normal, it was considered that the analysis of variance procedure was sufficiently robust to use in determining the sources of variation within this data.

A small but significant percentage of the total variation was found to be due to between set differences. The mean scores

pooling all three readers for each set were :-

T	4.07
R1	3.83
R2	4.17

The difference between the mean scores for R1 and R2 was significant at the 1% level, showing that the R2 set of radiographs was read more severely in the follow up series than in the presenting series.

Inter-Observer Variation

This has been examined in three ways:-

(1) By examining the distribution of radiographic scores for each reader.

(2) By calculating correlation coefficients between the three possible pairs of readers.

(3) By examining the between reader and the reader/patient interaction in the analysis of variance.

(1) Distribution of radiographic category

Figure 1 shows the distribution of categories for each reader for the 167 cases of asbestosis at diagnosis. Figure 2 shows the distribution of categories in the 98 cases seen at follow up. The distribution of categories are similar in the cases at diagnosis but at follow up, MTW read rather fewer radiographs in categories 0/0, 0/1 and 1/0 than the other readers.

(2) Correlation coefficients

At presentation	MTW v. IHK	0.768
	MTW v. JCG	0.674
	IHK v. JCG	0.640
At follow up	MTW v. IHK	0.829
	MTW v. JCG	0.763
	IHK v. JCG	0.791

These correlations are all highly significant ($p < 0.001$). It is noticeable that the correlations between MTW and IHK are higher on both occasions than those with either reader and JCG.

(3) Analysis of variance

Only 0.4% of the total variation was due to between reader differences, but this did reach statistical significance ($p < 0.05$). However, there was a highly significant reader/patient interaction ($p < 0.001$). The individual reader/set totals ranged between 124 and 139 with the exception of MTW/R2 which was 150, a statistically insignificant difference. This implies that there are differences in the way the readers assess some radiographs even though each reader/set total is similar. Given the lower correlation coefficients between JCG/MTW and JCG/IHK this suggests that JCG reads differently, but not simply higher or lower, than the other two readers.

Conclusions

(1) The readers were highly consistent within themselves in the way they graded the profusion of small opacities but there was a tendency to give higher scores for profusion when the radiographs were read as part of the follow up series.

(2) There was a good correlation between the readers in the assessment of the profusion of small opacities both in the presenting and the follow up radiographs.

(3) There was some evidence that one reader (JCG) read differently to the others. In spite of this, the overall intra and inter observer variation was small.

TABLE 1

Analysis of Variance

% of total Variation	Source of Variation	Significance level of F ratio
77.1	Between patients	$p<0.001$
0.4	Between readers	$p<0.05$
0.5	Between T/R1/R2 sets	$p<0.01$
0.4	Interaction Reader/Set	NS
11.0	Interaction Reader/Patients	$p<0.001$
3.9	Interaction Set/Patient	NS
6.7	Residual variation	

FIGURE 1

DISTRIBUTION OF RADIOGRAPHIC CATEGORY FOR EACH READER. 167 CASES OF ASBESTOSIS AT PRESENTATION

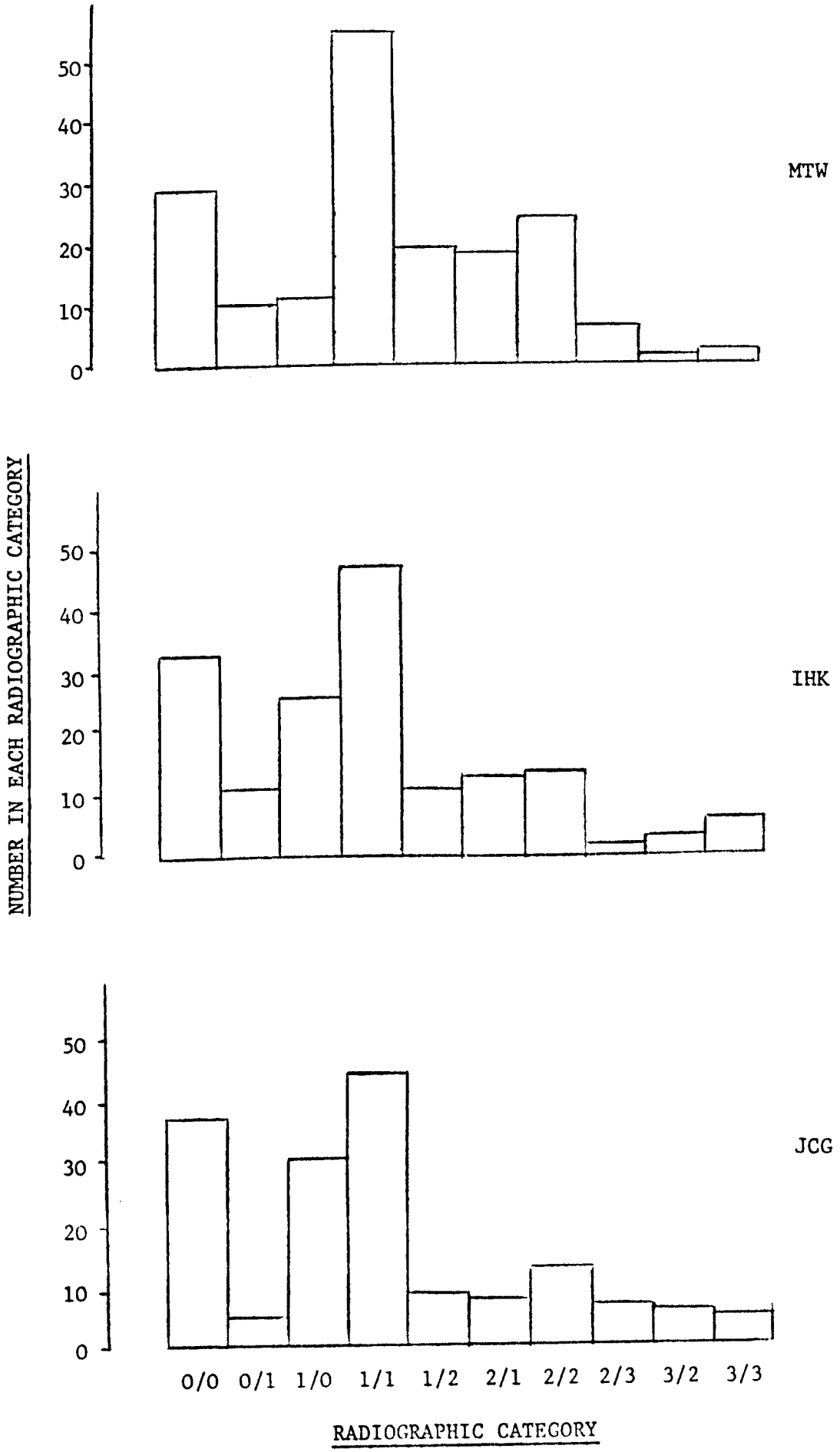
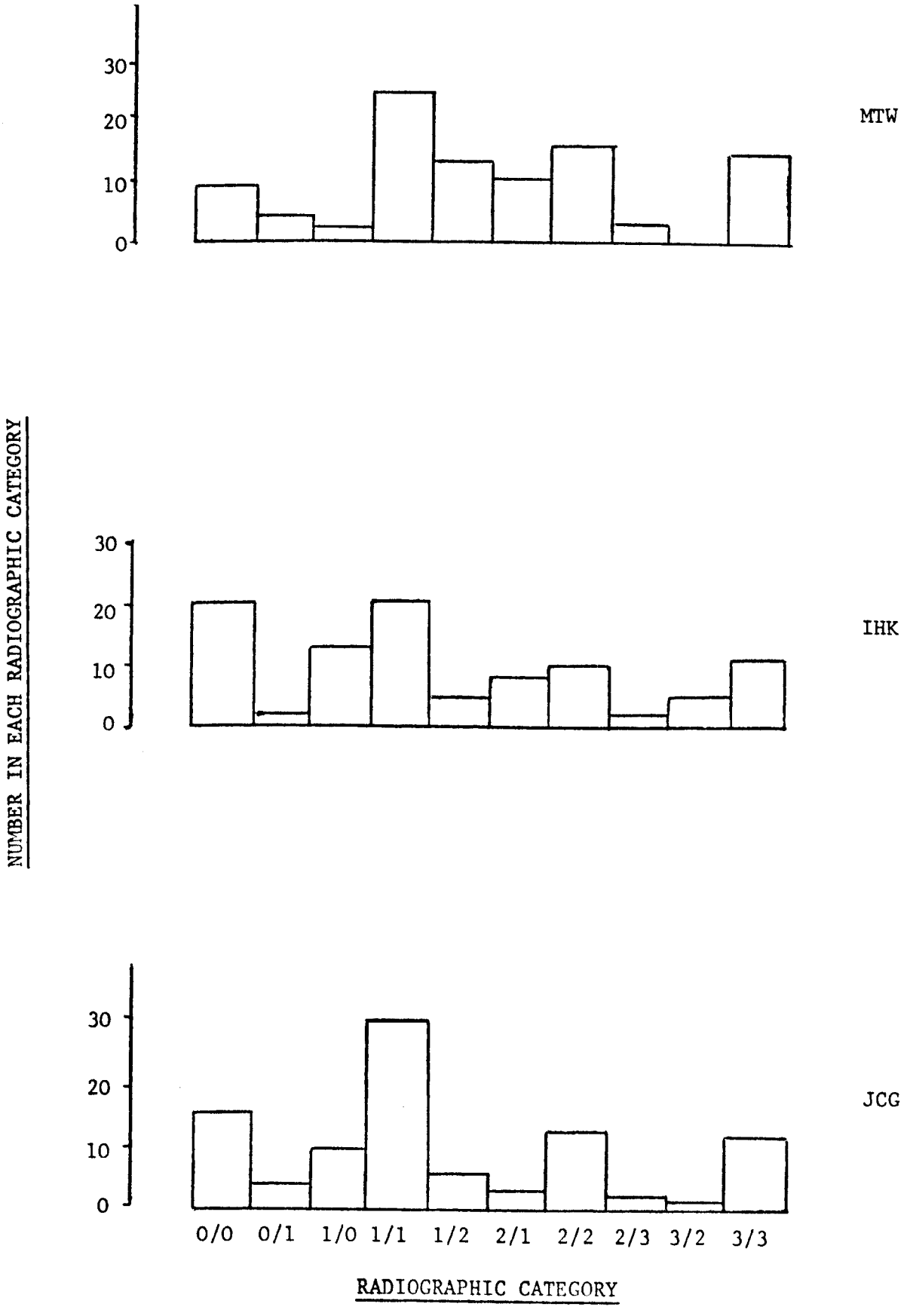


FIGURE 2

DISTRIBUTION OF RADIOGRAPHIC CATEGORY FOR EACH READER. 98 CASES OF ASBESTOSIS AT FOLLOW-UP



APPENDIX VI

SCORES FOR RADIOGRAPHIC PROGRESSION OF SMALL INTRAPULMONARY OPACITIES

One hundred and one cases of asbestosis were available for follow-up and 98 cases pairs of films were available for comparison.

In 44 cases no reader noted evidence of progression.

Some degree of deterioration was recorded in 54 cases and the scores are given in the table.

Points for Progression	Number of Cases
6	17
5	7
4	5
3	8
2	6
1	11
TOTAL	54

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