EFFECTS OF PLATELET ACTIVATING FACTOR ON VARIOUS PHYSIOLOGICAL PARAMETERS OF NEUTROPHILS, ALVEOLAR MACROPHAGES, AND ALVEOLAR TYPE II CELLS

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INTRODUCTION

Platelet activating factor (PAF) is a glycerophospholipid (1-0-alkyl-2-acetyl-sn-glycerol-3-phosphoryl choline) which has been shown to mediate a broad range of biological activities.[1-3] Its pulmonary actions include contraction of pulmonary tissue,[4] secretion of leukotrienes from leukocytes,[5] airway constriction,[6] pulmonary edema,[7] and enhanced migration of neutrophils into the airspaces of the lungs.[8,9]

PAF can be released from several different cell types, such as, basophils, neutrophils and alveolar macrophages, in response to a variety of particulates or membrane stimulants which include zymosan, calcium ionophore, phorbol esters, chemotactic agents, and endotoxin.[10-13] Therefore, PAF may play an important role in the development of pneumoconioses by mediating pulmonary responses of lung cells to a variety of occupational dusts. To investigate this possibility, we determined the effects of PAF on several physiological parameters of neutrophils, alveolar macrophages, and alveolar type II epithelial cells.

METHODS

Isolation of Cells

Neutrophils were isolated from human blood by dextran settling and centrifugal elutriation.[14] Isolated neutrophils (93% pure) were resuspended in HEPES-buffered medium (145 mM NaCl, 5 mM KCl, 10 mM HEPES, 5 mM glucose, and 1 mM $CaCl_2$; pH = 7.4). Cell number and volume were determined with an electronic cell counter equipped with a sizing attachment.

Rat alveolar macrophages were obtained by pulmonary lavage with Ca^{2+}, Mg^{2+}-free Hanks balanced salts solution.[15] Alveolar macrophages (94% pure) were resuspended in HEPES-buffered medium, counted, and sized electronically.

Rat alveolar type II cells were isolated by enzymatic digestion for 35 minutes at 37°C with 40 μ/ml type I elastase and 0.1% collagenase and purified by centrifugal elutriation.[16,17] Type II cells (92% pure) were resuspended in HEPES-buffered medium for measurement of membrane potential, oxygen consumption, and trypan blue exclusion. Type II pneumocytes were resuspended in 0.1 M NaCl plus 0.05 M HEPES (pH = 7.8) to measure cytochrome P450-dependent activities and aggregation. Cell size and number were determined electronically.

Measurement of Transmembrane Potential

Membrane potential of isolated cells in suspension was measured using a fluorescent probe, Di-S-C_3,[5] as described previously for neutrophils,[14] alveolar macrophages,[18] and type II cells.[19] Fluorescence was monitored at excitation and emission wavelengths of 622 and 665 nm, respectively. An increase in the fluorescence emission from the cell suspension indicated membrane depolarization.

Measurement of Respiratory Burst Activity

Release of reactive forms of oxygen by phagocytic cells was determined at 37°C by measuring the generation of chemiluminescence, secretion of hydrogen peroxide, or release of superoxide anion. Chemiluminescence from neutrophils (1×10^6 cells/5 ml of HEPES-buffered medium) was measured in the presence of 1×10^{-8} M luminol using a liquid scintillation counter operated in the out-of-coincidence mode.[20] Chemiluminescence from alveolar macrophages (3×10^6 cells/0.5 ml of HEPES-buffered medium) was measured in the presence of 1×10^{-5} M luminol using a Berthold 9505 Luminometer.

Hydrogen peroxide release from neutrophils or alveolar macrophages (1×10^7 cells/2.5 ml or 4×10^6 cells/3 ml, respectively) in HEPES-buffered medium containing 2.5 μM scopoletin, and 40 μg/ml horseradish peroxidase (type IX) was monitored fluorometrically at an excitation wavelength of 350 nm and an emission wavelength of 460 nm.[21,22]

Superoxide anion secretion from neutrophils or alveolar macrophages (1×10^7 cells/2.5 ml or 4.5×10^6 cells/6 ml, respectively) in HEPES-buffered medium was monitored spectrophotometrically at 550 nm as the reduction of 0.12 mM cytochrome C.[21,15]

Measurement of Cellular Viability

Oxygen consumption was measured at 37°C with an ox-

ygraph equipped with a Clark electrode. Type II cells (10^7 cells), neutrophils (6.5×10^6 cells), or alveolar macrophages (5×10^6 cells) were suspended in 1.7 ml of HEPES-buffered medium for these measurements.[16, 21,23]

Membrane integrity was determined by measuring the exclusion of trypan blue dye under light microscopy.[24]

Functional Measurements with Type II Cells

Cytochrome P450-dependent ethoxyphenoxazone dealkylase (EtOPhase) (EC 1.14.14.1) activity of type II cells was monitored at 36°C in a direct kinetic assay based upon the formation of a fluorescent product, resorufin, measured at an excitation wavelength of 530 nm and an emission wavelength of 585 nm.[17] NADPH was maintained at 0.5 mM by a glucose-6-phosphate dehydrogenase generating system.

Aggregation of type II cells was monitored at 37°C using a Lumi Aggregometer. Increased aggregation was measured as increased light transmission.

Type II cells used for measurement of cytochrome P450 and aggregation were isolated from rats metabolically induced by pretreatment with β-naphthoflavone. For these assays, cells were suspended in 0.1 M NaCl and 0.05 M HEPES (pH = 7.8).

Statistical Analysis

Data are expressed as means ± standard errors of n experiments conducted with cells obtained from different preparations. Data were analyzed by a Student's t test with significance set at $p < 0.05$.

RESULTS

Platelet activating factor can initiate a wide variety of pulmonary responses.[1,4-9] However, details concerning the cellular mechanisms responsible for the activities of PAF are not fully defined. Therefore, this investigation characterized the actions of PAF on three types of lung cells, i.e., two types of pulmonary phagocytes (neutrophils and alveolar macrophages) and alveolar type II epithelial cells.

The effects of PAF on pulmonary phagocytes are summarized in Table I. PAF was a direct stimulant of neutrophils *in vitro*. PAF induced substantial depolarization of the plasma membrane which was rapid (peaking within 15 sec after addition of PAF) and transient (returning to the resting level within 2 min). The effect of PAF on the membrane potential (E_m) of neutrophils was dose-dependent, exhibiting a $K_{1/2}$ value of 2.5 μM. This PAF-induced depolarization was sodium-dependent, i.e., removal of extracellular sodium eliminated the effect. PAF (10 μM) was also a potent activator of neutrophils, i.e., it induced significant generation of chemiluminescence and release of hydrogen peroxide. As was the case for membrane depolarization, stimulation of the secretary activity of neutrophils by PAF was dependent on extracellular sodium. In contrast to the above responses, *in vitro* treatment of neutrophils with PAF (10 μM) resulted in only a small increase in superoxide anion release and no significant elevation of oxygen consumption.

As with neutrophils, *in vitro* treatment of alveolar macrophages with PAF (12 μM) resulted in membrane depolarization. This response was rapid (peaking within 40 sec) and prolonged (not returning to resting Em). In contrast to neutrophils, *in vitro* treatment of alveolar macrophages with PAN (12 μM) did not activate the respiratory burst in these cells, i.e., there was little or no PAF-induced increase in chemiluminescence, hydrogen peroxide release, superoxide secretion, or oxygen consumption (Table I). However, PAF(12 μM) did potentiate activation of alveolar macrophages by zymosan (2 mg/ml), i.e., PAF increases zymosan-stimulated superoxide release by 36% (Figure 1) and zymosan-induced chemiluminescence by 55% (Figure 2).

The *in vitro* effects of PAF on isolated type II cells were also characterized. At levels of 12 μM or below, PAF did not affect membrane integrity or oxygen consumption, i.e.,

Table I

Effects of Platelet Activating Factor on Phagocytes

Cell Types	Em	Oxygen Consumption	Superoxide Release	Chemiluminescence	Hydrogen Peroxide Release
Neutrophils	transient depolarization	0	+	+++	+++
Alveolar Macrophages	prolonged depolarization	0	0	0	0

Maximal responses of neutrophils and alveolar macrophages after in vitro exposure to 10 μM or 12 μM PAF, respectively. The relative magnitude of enhancement is signified by +. No response is signified by 0. Data for each assay are taken from four separate experiments.

trypan blue exclusion was 81 ± 2% before and 82 ± 1% after PAF treatment while oxygen consumption levels were 0.23 ± 0.04 and 0.19 ± 0.03 nmoles O_2/min/10^6 cells, respectively. However, PAF (12 μM) did cause depolarization of type II cells which was rapid (peaking within 1 min) and prolonged. This depolarization exhibited dependence on extracellular sodium. PAF also enhanced the activity of cytochrome P450-dependent ethoxyphenoxazone dealkylase (EtOPhase). A maximum stimulation of 2.5 fold was noted at 10 μM PAF (Figure 3). Such activation was demonstrated in intact cells but not in sonicated preparations (Table II) or microsomes. The decline in P450 activity at higher levels of PAF may be due in part to PAF-induced aggregation of type II cells which was significant at PAF levels above 18 μM (Figure 4).

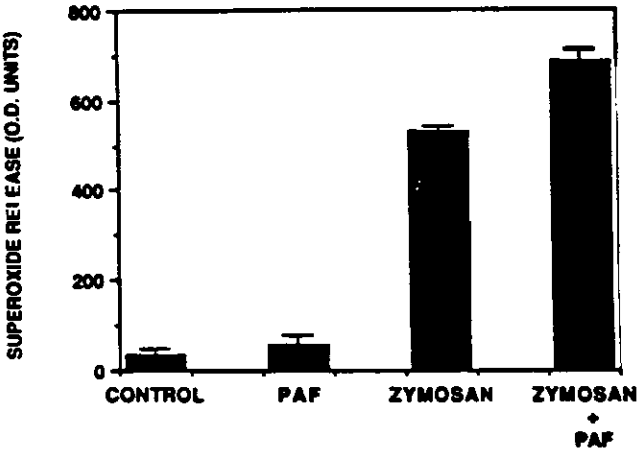

Figure 1. Effects of PAF on superoxide anion release from rat alveolar macrophages. Superoxide secretion at 37°C was monitored spectrophotometrically by measuring the reduction of cytochrome c over 30 minutes at a wavelength of 550 nm. Cells (4.5×10^6 cells/6 ml) were treated *in vitro* with 12 μM PAF and/or 2 mg/ml zymosan. Values are means ± standard errors of four different preparations.

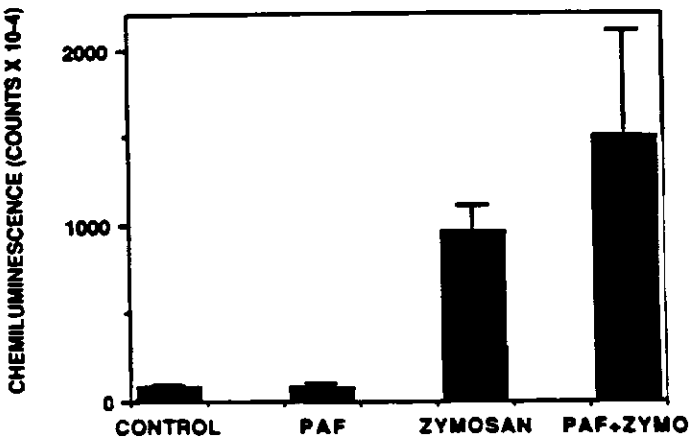

Figure 2. Effects of PAF on chemiluminescence generated from rat alveolar macrophages. Chemiluminescence was measured for 10 minutes at 37°C in the presence of 10^{-5}M luminol. Cells (3×10^6 cells/0.5 ml) were preincubated at 37°C in the presence or absence of 12 μM PAF for 15 minutes prior to addition of 2 mg/ml zymosan and measurement of chemiluminescence. Values are means ± standard errors of three different preparations.

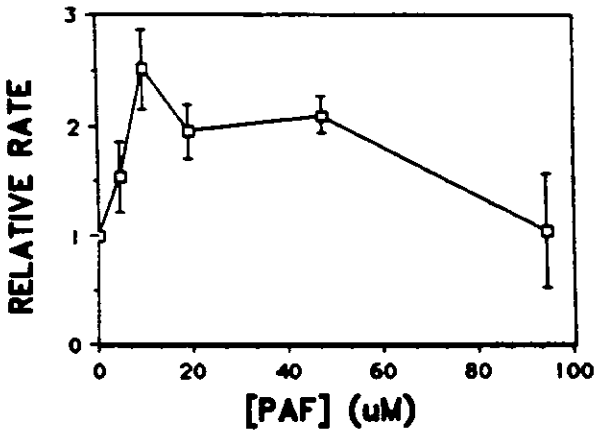

Figure 3. Effect of PAF on cytochrome P450-dependent EtOPhase activity in rat alveolar type II cells. Type II cells were obtained from β-naphthoflavone-treated rats. Cells ($1.6–2.5\times10^6$/ml) were suspended in 0.1M NaCl, 0.5 nM NADPH, and 0.05 M HEPES (pH = 7.8) at 36°C, a fluorescence baseline established, and the reaction initiated with 2.5 μM EtOPh. In the absence of PAF, EtOPhase activity of 3 separate preparations of type II cell was 1.06, 1.38, and 0.50 pmoles resorufin formed/min/10^6 cells, respectively. Data after addition of PAF are rates relative to these controls (means ± standard errors).

DISCUSSION

Neutrophils are blood phagocytes which are recruited into the pulmonary air spaces following inhalation of foreign substances, such as, bacteria, virus, or dusts.[25] Alveolar macrophages are free lung phagocytes located on the surface of the small airways and the alveoli.[26] Upon exposure to microorganisms or occupational dust these phagocytes exhibit a respiratory burst releasing reactive oxygen species, such as, superoxide anion, hydrogen peroxide, and hydroxyl radicals.[27-29] Evidence indicates that dust exposure may cause hyperactivation of these phagocytes. The resultant secretion of reactive products may result in inflammation, cellular damage, and in extreme cases fibrosis or emphysema.[30,31]

In this investigation we evaluated the ability of platelet activating factor (a potentially important mediator of pneumo-

Table II

Effect of Sonication on the Responsiveness of Alveolar Type II Cell Cytochrome P450-Dependent Activity to Platelet Activating Factor

Additive[b]	P450-Dependent Activity[a] Cells	Sonicate[c]
None	16.6 ± 3.4	38.7 ± 5.6
BSA-HEPES	16.2 ± 2.4	38.6 ± 11.0
PAF (19 μM)	34.0 ± 6.4	34.2 ± 4.9

a) Specific activity expressed as pmoles resorufin formed/min/mg protein. Protein determined by the procedure of Lowry et al. (25). Data are means ± standard errors of two experiments.

b) Additive: None - 0.1M NaCl, 0.5 mM NADPH, and 0.05M HEPES (pH = 7.8); BSA-HEPES - 10 μl of 0.5% BSA in 0.01M HEPES (pH = 7.8) added to the above solution; PAF - 10 μl of PAF in 0.5% BSA and 0.01M HEPES (pH = 7.8) added.

c) Disrupted type II cells were obtained by pulse sonication (0.33 sec on, 0.67 sec off) of the cell suspension for 30 seconds at 3 Watts at 2°C.

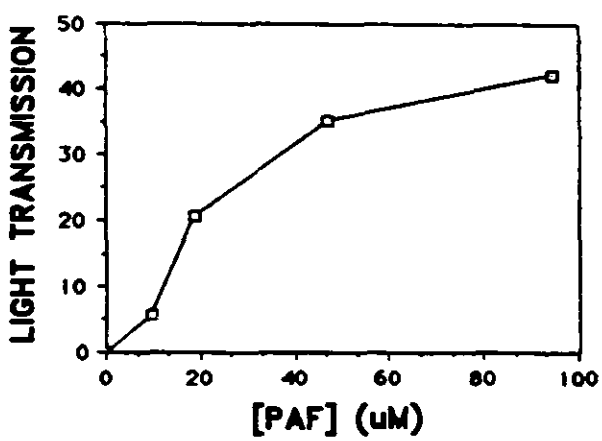

Figure 4. Effect of PAF on aggregation of rat alveolar type II cells. Type II cells were obtained from β-naphthoflavone-treated rats. Cells (2.5–2.7×10^6 cells/ml) were suspended in 0.1M NaCl and 0.05M HEPES (pH = 7.8) at 37°C and aggregation monitored as light transmission. Data are means of two experiments.

conioses) to activate phagocytes. The data indicate that PAF depolarizes neutrophils by increasing membrane permeability to sodium. Such depolarization may trigger secretary activity in neutrophils.[20] Indeed, PAF does activate neutrophils to secrete hydrogen peroxide and generate chemiluminescence (Table I). However, activation of the respiratory burst is incomplete in neutrophils since PAF does not stimulate oxygen consumption and elevates superoxide release only slightly.

Although PAF depolarizes alveolar macrophages, it does not directly activate a respiratory burst (Table I). However, PAF treatment does prime the cells to be more responsive to subsequent exposure to particles (Figures 1 and 2). Since PAF may be released following dust exposure, the potentiating action of PAF could have important consequences in escalating the cycle of inflammation and tissue damage seen in certain occupational lung diseases.

Cytochrome P450-dependent monooxygenases are responsible for the metabolism of organic chemicals in pulmonary tissue.[32] We have shown that within the lung high levels of P450-dependent activities are found in alveolar type II cells.[17] Recent studies have suggested that endogenous factors released from phagocytes may depress P450-dependent activity in hepatocytes.[33-35] Since PAF is released from

phagocytes,[10-13] we tested its effect on P450-dependent activity of type II cells. In contrast to the hepatic system, PAF (a phagocyte-derived mediator) enhances P450-dependent activity of alveolar type II cells (Figure 3). This effect seems to be mediated through the cell membrane, since PAF fails to activate P450 in sonicated cells or microsomes (Table II). It is possible that PAF may alter membrane structures which translate into increased P450 activity. Action of PAF at the plasma membrane is supported by our evidence of PAF-induced changes in membrane permeability to ions and membrane potential. In addition, higher concentrations of PAF alter the membrane surface of type II cell sufficiently to cause aggregation (Figure 4).

In conclusion, PAF may be released from phagocytes following occupational exposures. This PAF would be inflammatory by directly activating neutrophils and potentiating the response of macrophages to particulates. In addition, xenobiotic metabolism by alveolar type II cells would be enhanced affecting the detoxication and/or activation of foreign compounds. The role which these cellular changes play in pneumoconioses remains to be defined.

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This research has been supported by the Department of the Interior's Mineral Institute Program administered by the United States Bureau of Mines through the Generic Mineral Technology Center for Respirable Dust under grant number G1175142.

EVALUATION OF THE FIBROGENIC POTENTIAL OF SANDBLASTING SUBSTITUTES

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ABSTRACT

Sandblasting may lead to severe and progressive silicosis. Sand substitutes, derived from slag and coal ash, are now increasingly being used. They are comprised of amorphous silicates of Fe, Al, Ca, and Mg in various proportions. The fibrogenic potential of STANBLAST, a sand substitute derived from coal ash, was evaluated in a rat model. Male rats were exposed by inhalation to the substitute (10.8 ± 3.5 mg/m^3) for 6 hrs/day, 5 days/week for one year. Rats were sacrificed 6, 12, 18 and 24 months from onset of exposure and were evaluated for: lung weights, mineral burden, hydroxyproline (HP) content and histology using H & E, Gomoris' silver impregnation and Masson's trichrome stains. Lung weights and HP of exposed rats were not statistically significant from controls. Histologic examination of lung tissue of exposed rats revealed a nonfibrogenic tissue reaction to the dust. Small distinct foci of alveolar macrophages containing dust particles were diffusely scattered throughout the lung parynchyma. These cellular collections were frequently found in peribronchial, perivascular and subpleural locations. Although extracellular particles were also evident, cell lysis, acute inflammation and collagen deposition were absent. Absence of biochemical changes corroborate these findings.

No Paper provided.

STUDIES OF SILICOSIS AMONG MIGRANT WORKERS (REPORT 2) MORTALITY AMONG MIGRANT WORKERS FOR TUNNELLING WORKS

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ABSTRACT

We investigated the morbidity and mortality among migrant workers exposed to dust, such as that encountered during tunnel construction. Questionnaires on occupational pattern were sent to all male inhabitants aged 30 or over in a selected area between 1977 and 1978. Two thousand two hundred and fifty-six respondents were followed-up until the end of July, 1985. Among those who died, the causes and dates of death were confirmed by death certificates.

The mortality rate per 1,000 person-years of migrant workers who had worked in jobs with exposure to dust was 23.0, significantly higher than that of migrant workers not exposed to dust (15.5) and that of non-migrant workers whose jobs did not expose them to dust (9.5). The mortality rate was particularly high in migrant workers exposed to dust who were in age group 50 to 79.

Among migrant workers exposed to dust, the highest mortality rate per 1,000 person-years was associated with malignant neoplasms (5.4) followed by pulmonary tuberculosis (4.9), pneumoconiosis (4.0), heart diseases (3.6) and cerebrovascular diseases (2.2). The mortality rates for pulmonary tuberculosis and pneumoconiosis among migrant workers exposed to dust were significantly higher than those among non-migrant workers.

INTRODUCTION

In farming households in parts of Japan, it is impossible to subsist on the income from farming alone due to the natural and social environment, and seasonal migration of the working population for employment has long been a customary phenomenon. In Japan, such a practice is called "dekasegi" or working-away-from-home. These workers are generally employed under inferior working conditions, and long working hours as well as insecurity of their positions as subcontracting adds to their liability to work-related accidents and occupational diseases.

As shown in Report 1,[1] the eastern part of Toyama prefecture in Japan is well known as being one of the areas that supply many migrant workers who engage in tunnel construction for the development of electric power plant. We[1,2] conducted a questionnaire survey on the workers of this area for the screening of silicosis patients combined with a subsequent physical examination for suspicious cases, and demonstrated a prevalence of silicosis in 18% of the male population over 30 years of age, and 84% of the migrant workers engaged in dust-exposure operations.

Silicosis generally shows an unfavorable prognosis, and the symptoms are known to progress gradually even after cessation of exposure to dust.[3] This high prevalence of silicosis is considered to exert profound effects on health conditions, mortality rate, and causes of death in this area. Health management of migrant workers engaged in dust-exposure operations, therefore, must be regarded as an important problem of local health administration.

METHODS

A questionnaire survey was conducted on the male population over 30 years of age residing in the eastern Toyama prefecture for an epidemiological study of silicosis during the summer of 1977 and 1978. The questionnaire forms were distributed, and each examinee was requested to give written answers to questions mainly concerning his occupational history. Replies were obtained from 2260 people (87% of all those questioned) including those who later supplemented their initial inadequate entries.[1,2]

Analysis of data was carried out, in which survival, death, or loss of them from the area of the survey by the end of June, 1985 were examined. Causes of death were studied by death certification, and classified according to the 9th Revision of the Basic Classification of Causes of Death.

The mortality rate was calculated by the person-year method. The examinees were divided into three groups according to whether they had done migrant work and of the exposure

to dust for comparison of the mortality rate. Statistical significance was corrected for age and tested by the Mantel-Haenzel's X^2 method.

After eliminating those who could not be followed up for reasons such as leaving the area at an unknown date, 2116 people (94% of those returning the questionnaire) were included in this study. Table I shows the number of examinees and the duration of their follow-up in each occupational history group. The study encompassed a total of 15253.75 person-years, and the mean duration of follow-up per examinee was 7.2 person years.

RESULTS

Mortality and Age

During the observation period from the summer of 1977 (from the summer of 1978 in part of the area) to the end of June, 1985, 218 subjects (9.8% of all the subjects) died. Death occurred in 16% of migrant workers who engaged in dust-exposure occupations such as tunnel construction as opposed to 7.0% of those who had no history of migrant works or occupational dust exposure. The death rate in those who had a history of migrant work but no dust exposure was 11.2%.

The incidence of mortality per 1,000 person-years was highest (23.0) in those with a history of dust exposure during migrant work, followed by those with a history of migrant work but not of dust exposure (15.5), and lowest in those with no history of migrant work or dust exposure (9.5). The mortality rate in each age group classified according to the age is shown in Table II: It was higher by 200–250 in those with a history of dust exposure during migrant work than in those without a history of migrant work or dust exposure in all age groups from 50 to 79. The differences between the two groups were significant ($p<0.01$) in the 3 age groups between 50 and 79 years. The mortality was also slightly higher in those with a history of migrant work but not of dust exposure except in those in their 50's.

Mortality and Relevant Factors

For the migrant workers with dust exposure the ratio of actual number of death to expected number of death (A/E ratio(%)) distributed separately by relevant factors, such as cigarette consumption, total duration of migrant works with dust exposure and the number of respiratory symptoms (those as recorded at the initial survey), were calculated using the number of deaths and age distribution of overall migrant workers with dust exposure as the standard. For the migrant workers with exposure to dust, there was no significant difference of the A/E ratio among the groups divided by smoking consumption.

The A/E ratio distributed by duration increased in a graded fashion. The A/E ratio was significantly higher in the group who had worked for 30 or more years than in those who had worked less than 19 years (Table III).

The seven symptoms were investigated in present survey. These symptoms are: the production of phlegm in the morning or during the day on most days for at least three months of the year, the occurrence of cough in the morning or during the day on most days for at least three months of the year, the presence of shortbreathness graded by the criterion of Hugh-Jones, the occurrence of wheezing, the occurrence of nasal obstruction or nasal discharge, the frequent occurrence of colds and the occurrence during the past three years of chest illness which kept from usual activities for as much as a week. Table IV shows the A/E ratio for migrant workers with exposure to dust reporting the number of symptoms. The A/E ratio distributed by the number of symptom increased progressively as the prevalence of symptoms increased. The A/E ratio was significantly higher in the group with five or more symptoms than in those without symptoms.

Mortality and Cause of Death

Table V shows the incidence of mortality from different causes in each occupational history group. The mortality from malignant neoplasms was highest in those without a history of migrant work or dust exposure (3.2 per 1,000 of population over 30 years), followed by heart diseases (2.4), cerebrovascular diseases (1.8), suicide (0.3) and pneumonia and bronchitis (0.2). In those with a history of migrant work but not of dust exposure, the mortality due to cerebrovascular diseases was highest (4.9), followed by malignant neoplasms (4.4), pneumonia and bronchitis (1.9), and heart diseases and suicide (1.5 for both).

Table I

Subjects Investigated

	Non-migrant worker	Migrant worker without a history of dust exposure	Migrant worker with a history of dust exposure
No. of subjects	1,185	286	645
Total person-years of observation	8719.5	2,060	4474.25
Mean person-years of observation per person	7.36	7.20	6.94

In the above two groups, so called adult diseases (diseases closely associated with aging) accounted for large percentages of death but pulmonary tuberculosis was not observed. However, malignant neoplasms along with pulmonary tuberculosis was the most common cause of death (5.4 and 4.9 respectively) in those with a history of dust exposure during migrant work. Moreover, pulmonary tuberculosis in this group was invariably complicated by silicosis. In this group, the mortality from pneumoconiosis was 4.0, heart diseases 3.6, and cerebrovascular diseases 2.2, besides adult diseases, disorders, presumably related to dust-exposure activities such as pulmonary tuberculosis, pneumoconiosis, accounted for large percentages of death in this group.

Mortality with Age and Cause of Death

Since the 3 occupational history groups varied in the age distribution and duration of follow-up, the A/E ratio was calculated for the two groups with a history of migrant work (Table VI), using the number of death in the group without a

Table II

The Number of Deaths and Mortality Rate per 1,000 Person-Years According to the Age

	Non-migrant worker	Migrant worker without a history of dust exposure	Migrant worker with a history of dust exposure
Total	83 (9.52)	32 (15.53)	103 (23.02) ***
Age 30 – 39	2 (1.09)	0 (–)	0 (–)
40 – 49	6 (2.42)	3 (6.46)	6 (6.10)
50 – 59	13 (6.36)	2 (3.25)	21 (12.73) *
60 – 69	15 (10.61)	6 (13.14)	29 (26.16) **
70 – 79	26 (33.22)	11 (42.51)	34 (67.23) **
80 –	21 (124.81)	10 (142.35)	13 (133.68)

* $P<0.05$, ** $P<0.01$, *** $P<0.001$

(Comparison with the group without a history of migrant work)

Table III

Effect of Duration of Migrant Works with Dust Exposure on Mortality in Migrant Workers

	Duration of migrant works with dust exposure (years)			
	– 9	10 – 19	20 – 29	30 –
Actual No. of deaths	23	14	24	28
Expected No. of deaths[a]	35.9	21.3	22.9	18.5
A/E ratio (%)	64.0	65.8	104.8	151.0 *

a. The number of deaths and age distribution of overall migrant workers with exposure to dust are standard.

* There is a significant difference ($P<0.05$) between a group with more than 30 year duration and 2 groups with less than 19 year duration of migrant works.

Table IV

Effect of Respiratory Symptom and Total Duration on Mortality in Migrant Workers with Dust Exposure

	Number of symptoms [b]			
	0	1～2	3～4	5～
Actual No. of deaths	17	34	21	19
Expected No. of deaths [a]	31.8	35.8	21.4	12.1
A／E ratio (%)	53.5	95.0	98.2	157.6 *

a. The respiratory symptoms investigated are the occurrence of cough, phlegm shortness of breath, wheezing, nasal obstruction or nasal discharge, chest illness which has kept from usual activities for a week and the frequent occurrence of common colds.

b. The number of deaths and age distribution of overall migrant workers with dust exposure are standard.

* There is a significant diffrence ($P<0.05$) between a group without symptom and a group with 5 or more symptoms.

history of migrant work as the expected number. In the group with a history of migrant work but not of dust exposure, the overall A/E ratio was relatively high (117); among individual causes, high causes for cerebrovascular diseases (178%), pneumonia and bronchitis (774%), and accidents or suicides (326%) were noted. The group with a history of dust exposure during migrant work showed a still higher overall A/E ratio (192%); the value was moderately increased for lung cancer (176%) as well as accidents and suicides (351%), but smaller for ischemic heart disease (76%). In this group, the A/E ratios for pneumoconiosis and pulmonary tuberculosis were markedly increased, as might be expected.

DISCUSSION

Silicosis, a well established occupational disease, develops due to inhalation of dust containing free SiO2. Measures to protect workers from this disease have been attempted by legislation (Special Act for Protection of Workers from Silicosis and other Diseases, Pneumoconiosis Law) since 1955. However, the number of clinical cases of pneumoconiosis has been increasing every year, and among these patients, a rapid increase in the proportion of migrant workers engaged in tunnel construction has been noted.[4] Eastern Toyama and southern Oita in Japan have a long history of attracting migrant workers for tunnel construction and have shown abnormally high incidences of silicosis.

Une et al.[5] and Hisashige et al.[6] studied the causes of death and their interrelationships in southern Oita by dynamic statistical analysis of mortality. According to these studies, the overall mortality among the male population of southern Oita was significantly higher than the national average. The mortalities due to silicotic tuberculosis, pulmonary tuberculosis (Classification of causes of death was made according to the 8th Revision), all types of cancer, gastric cancer, pneumoconiosis, and work-related accidents in the industrial sector were also high.[5] These tendencies except for the mortality due to accidents, were more notable in the areas densely populated by migrant workers than in other areas of southern Oita.[6] Furthermore, death due to silicotic tuberculosis and pneumoconiosis occurred more frequently among those engaged in tunnel construction.[5] These findings suggested that the accumulation of silicosis patients associated with the migration of workers engaged in tunnel construction exerted grave effects on the health status of the region.

A study of morbidity or mortality with its impact on the local health status generally requires accurate recording of clinical courses from the onset of the disease to the complete recovery or death of patients during a long-term follow-up of the follow-up of the same group of subjects. For this reason, we conducted a follow-up study with a mean duration of 7.2 years (maximum, 8.0 years) in those who were previously examined in a questionnaire survey for all male residents over 30 years of age of eastern Toyama Prefecture.

A high mortality among workers engaging in dust-exposure occupations was demonstrated in follow-up studies in coal miners.[7-9] The mortality was particularly high among retired workers, pneumoconiotic patients exhibition severe radiographic manifestations, those with subjective symptoms, smokers, and those with decreased pulmonary function.[7-9] Migrant workers have been observed often to suffer from deterioration of chronic diseases due to stressful working conditions and to develop such fatal conditions as apoplexy and heart failure. The results of follow-up of our subjects with an experience of migrant work were consistent with the above observations. In those engaged in dust-exposure occupations, however, work-related diseases such as pneumoconiosis and pulmonary tuberculosis appeared to be more responsible for the poor health status than the adverse conditions commonly

Table V
The Number of Deaths from Different Causes

Causes of deaths	ICD code[a]	Non-migrant worker	Migrant worker without a history of dust exposure	Migrant worker with a history of dust exposure
All causes	000 – 999	83 (9.52)[b]	32 (15.53)	103 (23.02)
Cerebrovascular diseases	430 – 458	16 (1.84)	10 (4.85)	10 (2.23)
Ischemic heart diseases	410 – 414	8 (0.92)	0 (–)	4 (0.89)
Non-ischemic heart diseases	393-398, 402, 415, 416, 420-429	13 (1.49)	3 (1.46)	12 (2.68)
Malignant neoplasms	140 – 208	28 (3.21)	9 (4.37)	24 (5.36)
Stomach	151	9 (1.03)	2 (0.91)	6 (1.34)
Trachea, Bronchus and Lung	162	7 (0.80)	2 (0.97)	8 (1.79)
Pneumonia and Bronchitis	480 – 486 490, 491	2 (0.23)	4 (1.94)	2 (0.45)
Pulmonary tuberculosis	011	0 (–)	0 (–)	22 (4.92)
Pneumoconiosis	500 – 508	0 (–)	0 (–)	18 (4.02)
Accidents	E800 – E848 E880 – E899 E910 – E929	1 (0.11)	1 (0.49)	7 (1.56)
Suicides	E950 – E959	3 (0.34)	3 (1.46)	2 (0.45)
Others		12 (1.38)	2 (0.97)	2 (0.45)

a Classified according to the 9th Revision of the Basic Classification of Causes of Death.

b Figures in brackets are the crude mortality rates per 1,000 person-years over 30 years.

affecting all migrant workers. Although there was no relationship between smoking and mortality, the mortality increased progressively as the duration of migrant works with dust exposure increased in length and as the prevalence of respiratory symptoms increased.

Effect of dust exposure in migrant workers must be assessed by a long-term observation of their physical conditions besides the analysis of mortality. Progression of the disease was suggested to be more rapid in those engaged in tunnel construction.[10] We also noted a rapid development of subjective complaints and a decrease in pulmonary function over a short period of time in migrant workers engaged in dust exposure operation.[11] Radical approaches are considered to be necessary for health management of migrant tunnel construction workers and silicosis patients, who are offered inadequate administrative health-related service, as shown in Report 1,[1] and turn to medical aid only after considerable progression of the disease.

Table VI

The Ratio of Actual Number of Death to Expected Number of Death

	Migrant worker without a history of dust exposure			Migrant worker with a history of dust exposure		
	Actual No. of deaths	Expected No. of deaths[a]	A/E radio (%)	Actual No. of deaths	Expected No. of deaths[a]	A/E radio (%)
All causes	32	27.6	116.5	103	53.7	191.8 ***
Cerebrovascular diseases	10	5.6	177.9	10	9.9	101.4
Ischemic heart diseases	0	2.9	0.0	4	5.3	76.0
Non-ischemic heart diseases	3	4.9	61.3	12	8.2	146.3
Malignant neoplasms	9	8.4	107.2	24	18.7	128.3
stomach	2	2.3	86.1	6	5.6	108.0
Trachea, Bronchus and Lung	2	2.2	92.7	8	4.6	175.7
Pneumonia and bronchitis	4	0.5	773.7	2	1.0	192.2
Pulmonary tuberculosis	0	0	—	22	0	— ***
Pneumoconiosis	0	0	—	18	0	— ***
Accidents and Suicides	4	1.2	325.5	9	2.6	350.7

[a] The number of deaths and age distribution in the group of non-migrant worker are standard

*** $P < 0.001$

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STUDIES OF SILICOSIS AMONG MIGRANT WORKERS (REPORT 1) THE FREQUENT OCCURRENCE AND RELEVANT FACTORS OF SILICOSIS

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ABSTRACT

During the 1970's many cases of serious silicosis occurred among migrant workers doing tunnel construction. Migrant workers are known in Japanese as "dekasegi". This term refers to workers who migrate seasonally from their home towns to areas where work is more available. The eastern part of Toyama, Japan is well known as being one of the areas which supply many migrant workers doing tunnel construction.

Questionnaires were sent to all male inhabitants aged 30 or over in the five selected areas between 1977 and 1978. Nine hundred and thirty-one of respondents (41%) had worked as migrant workers. Of these, 645 men (69%) had worked on the jobs with exposure to dust such as tunnel construction. Of this number, 566 men were examined by chest roentgenography. Silicosis was found in 84% (477 cases). These patients included 248 cases of category 1, 122 cases of category 2, 54 cases of category 3 and 53 cases of category 4 silicosis.

Most of the patients retired and returned to their home towns without having been given any diagnosis and medical care at their places of employment. The silicosis in 332 cases (70% of the total number of disease patients) was first detected in the course of our research.

It was considered that the important social factors which may have caused the frequent occurrence of silicosis were poor working and living conditions of migrant workers in the tunnel and poor measures for prevention of silicosis such as health examinations, educations about silicosis and wearing of a dust respirator.

INTRODUCTION

Migrant work is defined in Japan to be employment for 1 month or more to less than a year away from the place of permanent residence followed by return to the place of residence, and such a practice is called "dekasegi". Migrant workers have often been victims of deterioration of health, work-related accidents, and occupational diseases as they have generally been forced to work for long hours under inferior working environments in addition to instability of the position and poor health management under the subcontract and the sub-subcontract employment systems.[1]

Eastern Toyama Prefecture, which is under the jurisdiction of Kurobe Health Center, is one of the areas with a high incidence of silicosis among migrant workers.[2,3] In this study, the statistical facts and the state of silicosis patients in this jurisdiction were surveyed, and factors in the high incidence and severity of their condition were examined.

METHODS

Five areas under the jurisdiction of Kurobe Health Center, Toyama Prefecture (Figure 1) were selected arbitrarily, and questionnaire surveys primarily concerning the occupational history were conducted in summer, 1977 and 1978 in all males in these areas aged 30 years or above. The questionnaires were distributed to each subject and filled in by the subject himself. Including those whose answers were initially incomplete and who have been incorporated in the survey later through follow-up works, a total of 2,260 individuals (87% of the 2,604 to whom the questionnaires were sent) were available for the study. On the basis of the questionnaires, screening for pneumoconiosis was carried out for those who had engaged in migrant work in occupations involving dust exposure. The screening consisted of interview, somatometry, direct chest roentgenographic examination, lung function test, and arterial blood gas analysis. The radiograms were evaluated by 5 doctors including the authors according to the classification of the Pneumoconiosis Law of Japan,[4] which is based on ILO/UICC Classification, 1971. When opinion differed among the doctors, the diagnosis was made by the majority rule.

RESULTS

Results of Questionnaires and Screening for Pneumoconiosis

Table I shows the results of the questionnaires about migrant

work carried out in the summer of 1977 and 1978. Nine hundred and thirty-one individuals, or 41% of the valid respondents, had experienced migrant work. Of these 931 subjects, 645 (29% of valid respondents) had been exposed to dust in work. Tunnel construction was predominant among the works involving dust exposure, accounting for nearly 90%, followed by mining of minerals other than coal and coal-mining.

Of the 645 subjects, 566 have undergone screening for pneumoconiosis, the results of which are shown in Table II. Signs of silicosis were observed in 477 subjects (84% of those

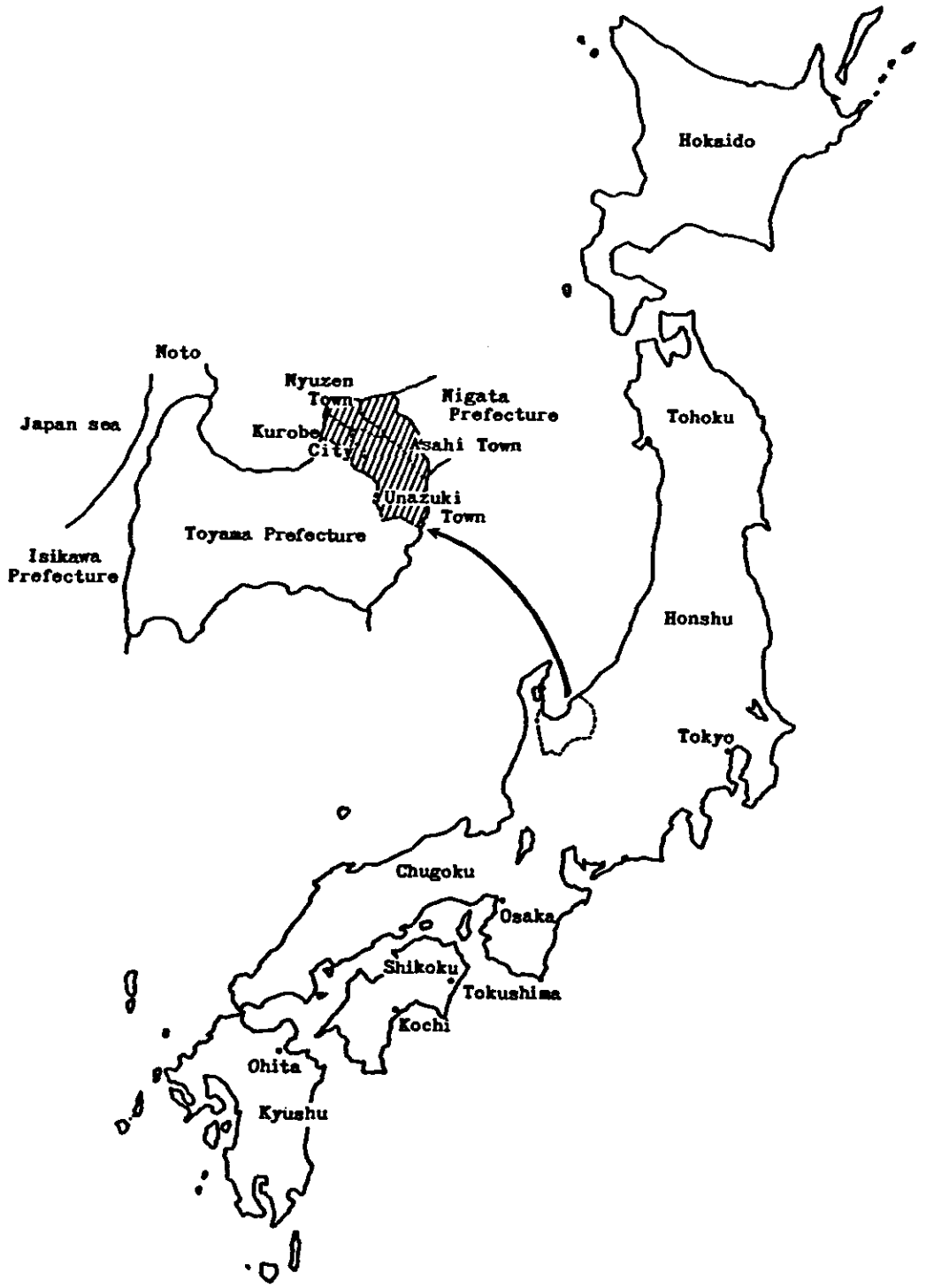

Figure 1. Study area and its location in Japan.

Table I

The Number of Migrant Workers Based on Questionnaires

	Total	Age group (years)						
		30 ~ 39	40 ~ 49	50 ~ 59	60 ~ 69	70 ~ 79	80 ~	Unknown
No. of respondents	2260 * (100)	496 (100)	643 (100)	531 (100)	376 (100)	177 100)	33 (100)	4
Migrant Workers	931 (41.2)	83 (16.7)	287 (44.6)	265 (49.9)	194 (51.6)	87 (49.2)	15 (45.5)	
Migrant Workers with expoure to dust	645 (28.5)	42 (8.5)	203 (31.6)	196 (36.9)	141 (37.5)	52 (29.4)	11 (33.3)	

* Figures in brackets are percentage

Table II

Chest Roentgenographic Findings of Silicosis in Migrant Workers with Exposure to Dust by the Age at Their First Examination in the Course of This Research

	Total	Age group (years)					
		30 – 39	40 – 49	50 – 59	60 – 69	70 – 79	80 –
No. of subjects	586 ** (100)	25 (100)	160 (100)	200 (100)	134 (100)	43 (100)	4 (100)
Silicosis patiemts	477 (84.3)	14 (56.0)	124 (77.5)	180 (90.0)	112 (83.6)	41 (95.3)	4 (100)
Classification of silicosis *							
1	248	10	69	85	58	23	3
2	122	4	27	50	31	10	0
3	54	0	16	19	17	2	0
4	53	0	14	26	6	6	1

* Classification of silicosis according to the Pneumoconiosis Law of Japan

** Figures in brackets are percentages

undergoing screening). According to the roentgenographic categories, 248 (52%) belonged to type I, 122 (26%) to type II, 5 (11%) to type III, and 53 (11%) to type IV silicosis.

Table III shows the relationship between the X-ray grading of the disease and the duration of dust exposure. Silicosis was noted in 94%, 80%, and 70% of those exposed to dust for 20 years or more, 10–19 years, and less than 10 years, respectively, indicating an increase in the incidence with the duration of dust exposure.

The subjective symptoms were examined with regard to cough (continuing for 3 months or more per year), phlegm (continuing for 3 months or more per year), shortness of breath (Hugh-Jones grade III or more severe dyspnea), wheezing, and palpitation (Table IV). Cough was reported by 24%, phlegm by 25%, shortness of breath by 29% , wheezing by 19%, and palpitation by 17% of patients with silicosis. The frequencies of these symptoms were all higher than in those showing no signs of silicosis.

According to the Pneumoconiosis Law of Japan, patients showing values of %VC <60%, FEV_1% <standard value (SV, 91.79-0.373 * age)–3 * residual standard deviation (RSD, 7.19)(%), or $AaDO_2$ >SV (2.5 + 0.21 * age) + 3 * RSD (7.1) are considered to have marked impairment of pulmonary function.[4] Table V shows the percentage of patients with abnormal values in each roentgenographic category. By evaluating the 3 items together, 83 (15%) of all migrant workers exposed to dust were considered to have

Table III

Total Duration of Migrant Works with Exposure to dust According to the Roentgenographic Category

	Total	Roentgenographic category of silicosis *				
		0	1	2	3	4
No. of Subjects	561 **	89	245	120	54	53
Tatal duration (years)						
– 9	208	62	108	24	6	9
10 – 19	136	18	68	26	16	8
20 – 29	129	5	40	44	18	22
30 – 39	64	3	22	19	8	12
40 –	24	1	8	7	6	2
Mean duration (Mean+S.D.)	16.0±11.8	7.7±8.1	14.0±11.2	20.6±11.5	22.5±11.4	21.8± 9.9

* Classified according to the Pneumoconiosis Law of Japan

** Durations of 5 migrant workers (type 1 : 3, type 2 : 2) are unknown

Table IV

The Prevalence Rates of Symptoms of Respiratory Disease According to the Roentgenographic Category

	Total	Roentgenographic category of silicosis				
		PR 0	PR 1	PR 2	PR 3	PR 4
No of subjects	566 (100)*	89 (100)	248 (100)	122 (100)	54 (100)	53 (100)
Cough in the morning	212 (37.5)	23 (25.8)	80 (32.3)	57 (46.7)	26 (48.1)	26 (49.1)
Cough for 3 or more months/year	126 (22.3)	12 (13.5)	51 (20.6)	33 (27.0)	11 (20.4)	19 (35.8)
phlegm in the morning	215 (38.0)	33 (37.1)	87 (35.1)	47 (38.5)	24 (44.4)	24 (45.3)
Phlegm for 3 or more months/year	136 (24.0)	17 (19.1)	57 (23.0)	32 (26.2)	14 (25.9)	16 (30.2)
Persistent cough and phlgem for 3 or more months/year		27 (15.4)	10 (11.2)	31 (12.5)	23 (18.9)	13 (24.5)
Shortness of breath	228 (40.3)	24 (27.0)	91 (36.7)	50 (41.0)	26 (48.1)	37 (69.8)
Shortness of breath for Hugh-Janes grade 3 or over	148 (26.1)	9 (10.1)	61 (24.6)	32 (26.2)	18 (33.3)	28 (52.8)
Wheezing[a]	100 (17.7)	9 (10.1)	35 (14.2)	20 (16.5)	17 (31.5)	19 (35.8)
Attack of shortness of breath with wheezing[a]	46 (8.1)	3 (1.2)	15 (6.0)	12 (9.8)	7 (13.0)	9 (17.0)
Palpitation[b]	72 (15.1)	5 (5.7)	33 (13.6)	20 (20.6)	4 (10.0)	10 (37.0)

* Figures in brackets are percentage

a. Symptoms of 2 migrant workers are unknown (Type 1 : 1 ; type 2 : 1)

b. Symptoms of 88 migrant workers are unknown (Type 0 : 2, type 1 : 8, type 2 : 25, type 3 : 29, type 4 : 26)

Table V

The Number of Migrant Workers with Exposure to Dust, Classified by the Values of the Pulmonary Function Tests According to the Pneumoconiosis Law of Japan

	Total	Roentgenographic category of silicosis				
		0	1	2	3	4
No. of subjects	561 ** (100)*	88 (100)	246 (100)	121 (100)	64 (100)	52 (100)
%VC < 80%	28 (5.0)	1 (1.1)	9 (3.7)	5 (4.1)	3 (5.6)	10 (19.2)
FEV1% < SV−3RSD[a]	10 (1.8)	1 (1.1)	2 (0.8)	2 (1.6)	1 (1.9)	4 (7.5)
No. of subjects	521 *** (100)*	68 (100)	232 (100)	115 (100)	54 (100)	52 (100)
A-DO2 > SV+3RSD[b]	45 (8.6)	1 (1.5)	20 (8.6)	10 (8.7)	7 (13.0)	7 (13.5)

* Figures in brackets are percentages
SV: Standard values RSD: Residual standard deviation
a: SV = 91.79 − 0.373 × Age (RSD = 7.19) (%)
b: SV = 2.5 + 0.21 × Age (RSD = 7.1) (TORR)
** Spirometry was not performed on 5 migrant workers (type 0: 1, type 1: 2, type 2: 1, type 4: 1)
*** Arterial blood gas analyses were not performed on 45 migrant workers (type 0: 21, type 1: 16, type 2: 7, type 4: 1)

marked impairment of pulmonary function. These consisted of 80 patients with established silicosis (20%) and 3 showing no signs of the disease (3%). According to roentgenographic categories, type I silicosis was observed in 33 patients (13%), type II in 17 (14%), type III in 10 (19%), and type IV in 20 (38%), with more patients in advanced roentgenographic categories showing more severely impaired pulmonary functions.

Of the 477 patients with silicosis, 332 had not known that they had contracted the disease and were given the diagnosis for the first time by our examination. Those patients naturally more often belonged to milder roentgenographic categories, accounting for 95% of type I and 64% of type II patients, but also for 22% and 11% of patients with more advanced type III and type IV lesions, respectively (Figure 2). Twenty to thirty percent of patients who were first diagnosed to have silicosis complained of cough, phlegm and Hugh Jones grade III or more severe dyspnea, and 12% were considered to have marked impairment of pulmonary function on the basis of the criteria of the Pneumoconiosis Law. Thus, this study showed that the disease was left undetected in many of migrant workers exposed to dust, even when they had relatively advanced roentgenographic profiles, notable subjective symptoms, or severe pulmonary dysfunction.

Status of Employment of Migrant Workers of Eastern Toyama Prefecture, Japan in Occupations Involving Dust Exposure

The status of migrant work in 566 individuals who underwent screening for silicosis is summarized in Table VI. Thirty-four percent of them began migrant work in 1940–1944, 25% in 1950–1959, and 23% in 1930–1939. Those who began migrant work after 1960 were very few. A predominant portion of the subjects had stopped migrant work by the time of the present screening, 30% quitting in 1960–1969, another 30% after 1970, and 16% in 1950–1959. The greatest proportion of the subjects (63%) started migrant work in their teens, and 30% in their 20's. The age of stopping migrant work (those still engaged were excluded) was most frequently the 30's (26%), followed by the 40's (23%), 20's (22%), and 50's (18%). The annual duration of migrant work was most frequently 7–8 months (31%), followed by 9–10 months and 5–6 months (24% for both), and 10–11 months (21%). In eastern Toyama Prefecture, many of the migrant workers started migration during the 10 years after World War II during Japan's economic rebuilding, contributed to the high economic growth since 1960, and stopped migration rapidly just prior to the oil crisis in 1973. More than half the migrant workers engaged in tunnel construction started migrant work before they were 20 years old, many of them having become migrant workers immediately after compulsory education. Most of these workers were seasonal migrant workers, who migrated during the agricultural off-season, and only one-fifth were round-the-year migrant workers migrating for 11 months or more per year.

DISCUSSION

The percentage of migrant workers in the total working population is considered to be higher in areas where the productivity of the farming industry is lower.[1] In eastern

Toyama, 61% of migrant workers from this area had to be engaged in migrant work for pure subsistence, and only 19% did so for more than subsistence. In addition to these inherent economic circumstances, several tunnels were constructed in this region between 1920 and 1960 for the development of rivers for hydroelectric power sources. The Kurobe River flowing in the eastern part of Toyama Prefecture was developed for hydroelectric power development programs since 1920's because of its rich water supply and steepness of the river bed. These programs, which peaked with the completion of the Fourth Kurobe River Power Plant in 1962, yielded 4 dams and 14 power plants (a total output of 800,000 kw) by 1970. The above survey of migrant workers employed in occupations involving dust exposure showed that the

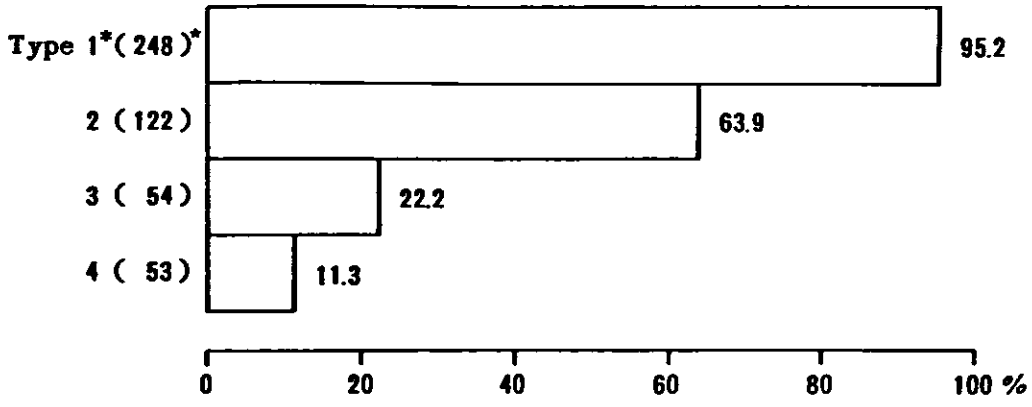

Figure 2. The rates of the silicosis patients who were first detected in the course of this research according to the roentgenographic category.
*Type 1, 2, 3, 4: Roentgenographic categories of silicosis.
*Figures in brackets are numbers of subjects.

Table VI
The Years in which Migrant Workers Began and Finished Their Jobs

	The year of finish as migrant worker						Working at this survey as migrant worker	Total
	1920 / 1929	1930 / 1939	1940 / 1949	1950 / 1959	1960 / 1969	1970 /		
The year of begining								
1910 ~ 1919	2	1	2	4	1	1	0	11 (2.0)
1920 ~ 1929	4	6	8	7	14	20	3	62 (11.1)
1930 ~ 1939		10	20	20	20	49	9	119 (22.9)
1940 ~ 1949			10	34	69	47	29	189 (33.8)
1950 ~ 1959				25	55	30	28	138 (24.6)
1960 ~ 1969					6	14	3	23 (4.1)
1970 ~						5	4	9 (1.6)
Total	6 (1.1)	17 (3.0)	40 (7.1)	90 (16.1)	165 (29.5)	166 (29.6)	76 (13.6)	560 * (100)**

* Data are unknown for 6 migrant workers

** Figures in brackets are percentage

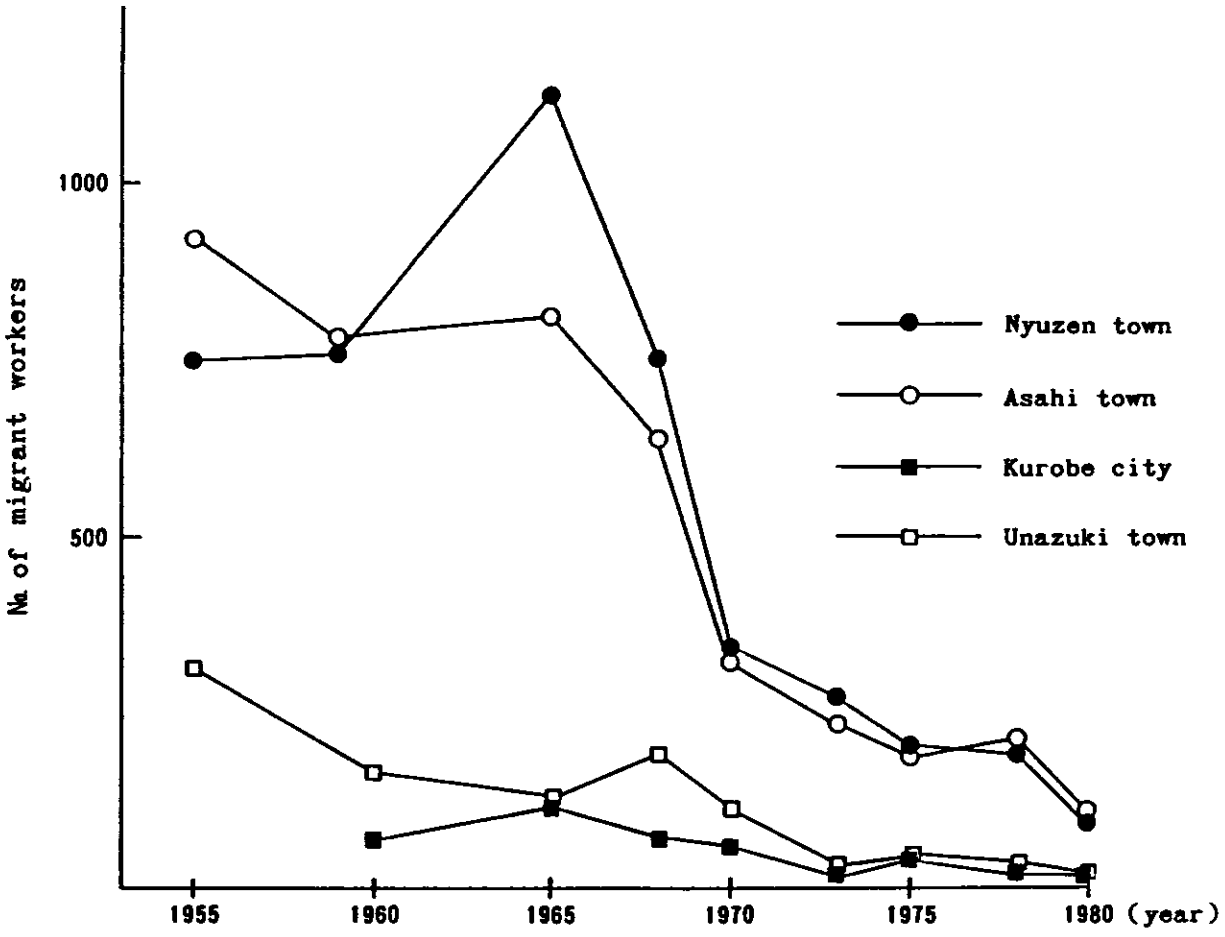

Figure 3. The number of migrant workers who had worked away from home.
(Source: Agriculture Census, Japan and Report of Fundamental Agricultural Survey of Toyama Prefecture, Japan)

number of migrant workers increased during the period of development of power sources and declined with its termination.

In eastern Toyama Prefecture, 70% of the silicosis patients had not known that they had the disease and were first diagnosed by our survey. Those who knew they had the disease at the survey had been diagnosed relatively recently (69% after 1970), and the disease was detected in many of these patients by the mass screening for tuberculosis carried out by the health center. Of the 166 patients with silicosis registered at Kurobe Health Center in 1977, when this study was started, the disease was detected in 95 (57%) by local health check-up programs rather than by examinations at work places.

In many patients, silicosis was not noted during migrant work but was first detected more than 10 years after discontinuation of the employment, first because most of them were seasonal workers not covered even by the minimum health management at the work place. The Pneumoconiosis Law of Japan requires health check-up at the beginning, during (periodic), and end of employment.[4] However, of the migrant workers employed in occupations involving dust exposure in eastern Toyma, only 60% had undergone health examinations at the work place; the percentages were lower in those in their 50's (25%) and those over 60 (10%). Migrant workers employed on monthly basis not only could seldom take periodic health check-ups (once every 3 years for those constantly exposed to dust and once every year for pneumoconiosis patients) or the examination at dismissal, which was intended for those who worked for 1 year or more, but were often excluded from the examination list. Moreover, since these workers were employed at irregular times, not many of them received the check-up at the time of employment. In addition, even after they contracted silicosis, they were not regarded as employees in operations involving dust exposure during intervals or after discontinuation of migrant work and were not covered by the follow-up programs provided by the Pneumoconiosis Law. For these reasons, migrant workers with silicosis visited medical institutions only after considerable progression of their disease and were first diagnosed. This situation lasted until 1972, when the Law of Labor Safety and Hygiene was enforced to provide free annual health check-up for those radiologically diagnosed after retirement to have type II or more advanced pneumoconiosis. However, this health check-up requires the certificate of employment at the last work place, which is

often difficult to obtain for many migrant workers employed as subcontractors and sub-sub-contractors. Furthermore, those who discontinued migrant work before the enforcement of the Pneumoconiosis Law are not covered by this law and are left unattended. As shown in Table VI, 27% of migrant workers in eastern Toyama had retired before 1960.

Secondly, the insufficient education about pneumoconiosis at the work place is considered to be a factor in the poor management of workers with the disease.[5,6] According to our survey, 84% of the patients were aware of the risk of pneumoconiosis associated with works involving dust exposure, but only 21% received education at the work place about the possible hazard of dust exposure, and 49% obtained the knowledge from friends or by observing colleagues developing silicosis. Six percent of the patients became aware of the danger of dust exposure for the first time after they began to be treated for silicosis. Dust masks were worn by only 51% and worn consistently by one-third of them.

As mentioned earlier, migrant workers were not regarded as workers after discontinuation of migrant work and were, therefore, excluded from the coverage of labor administration. In addition, general hygienic measures were mot extended to them in time, because silicosis has been considered an occupational disease. These factors contributed to the lack of recognition and neglect of a number of patients.

As observed above, the present legislation provides inadequate protection and management for migrant workers who engaged in occupations involving dust exposure. The 1977 amendment of the Pneumoconiosis Law, which provides for physical examinations during and after (silicosis patients) the period of employment, is still insufficient. At Kurobe Health Center, silicosis patients within its jurisdiction are registered as a major target of local health administration, and disease-control programs including annual physical assessment are executed also for those patients who had previously been excluded from public health care service, because they retired before 1960, could not obtain certificate of employment from the place of their last employment, or type I radiographic evaluation at the time of retirement.

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A CASE STUDY ON FIBERGLASS PNEUMOCONIOSIS WITH UNDIFFERENTIATED CANCER —FIBERGLASS, CANCEROGENOUS MATERIAL

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Fiberglass has been used as a substitute for asbestos and its consumption has increased year after year. We know that foreign bodies, which are inhalted into tissues and remain there, can develop various types of harmful pneumoconiosis.

Since the industrial use of fiberglass started in Japan, we have warned that fiberglass should have been used under dust control; X-ray finding of this material has caused concerned.

Tables I and II show sorts of substitutes, and experimental results of various substitutes.

Glassfiber, experimentation has provoked mesothelioma, Stanton et al.[1]. Now, an autopsy case has been found.

A CASE STUDY ON FIBERGLASS PNEUMOCONIOSIS WITH INDIFFERENTIATED CANCER

Whether glassfiber is harmful or inert has not been determined. From the results of an autopsy case, it is shown to be "harmful."

Autopsy Record

A.S ♂ 65 years old
Death: 1957. 3. 21 01.00
Autopsy: 1957. 2. 11 12.00—14.00

Tatsuo SANO
Hirosi OSANAI

Skin:
dried post mortem purpura in back.
post mortem stiffen submaxilla joint.
Abdominal cavity subcutaneous, muscle tissue poor
Omentum:
hang down from stomach, partially adhere to spleen, ascites become muddy, a little; position normal
The thoracic cavity:
thymus fatty, in pericardial cavity 30 cc
yellow serosa has been found in epicardium sinistra 5–20 cm white squad.
Pleura sinistra, dextra fibrinofibröse

Organen

Lung:
cut surface a little swollen, 2–3 mm large black nodule has been vorhanden, 2–3 mm large emphysema vorhanden (Inner side about 12 cm – 2 cm – 5 cm) in lung area undifferentiated Cancer, intra cancer degeneration noted
Heart:
405 gr Segumentation remarkable
Liver:
1150 gr nutmeg liver
Kidney:
r 155 gr l 155 gr Rinden glommelus hyperplasia remarkable in mark fatty
Spleen:
55 gr

Diagnosis

(1) Fiberglass Pn with undifferentiated Cancer
(2) Cor pulmonale
(3) Localized peritonitis
(4) Congestion (kidney)

Causal Event

1939–1949 (11 years) Glassfiber exposure

Conclusion

Is the cancer, except Lung "I saw it naturally" (Asbestosis like pn. by Ca compounds, *Jap. J. Ind. Health*, Vol 27 (7) 1985)

Stanton (Member of National Cancer Institute) has done an experiment on 37 sorts of substitutes of various sizes Over 0.25 μm—8 μm Mesothelioma or Sarcoma have been revealed. This Hypothesis is useful. Metaphoshat polymer has been analysed by phosphatase *in vivo* minimal reaction.

From the viewpoint of pathomorphology and pathogenesis it is not rewarding to discriminate between organic and inorganic dust. Long term inhalation of dust, organic or inorganic and its sustained deposit in alveoli can cause pneumoconiosis of various types, if the dust is unsoluble, scarcely soluble or soluble.

The foreign body reaction or inflammation is the process in which the action of phagocytes and the cell proliferation containing the fibroblaste and the fibrocyte occur, resulting in cell degeneration and fibrosis of various grades. In this sense, it is reasonably concluded that the fundamental and common cause of pneumoconiosis is the inflammatory changes of the lung to excessive dusts as foreign matters.

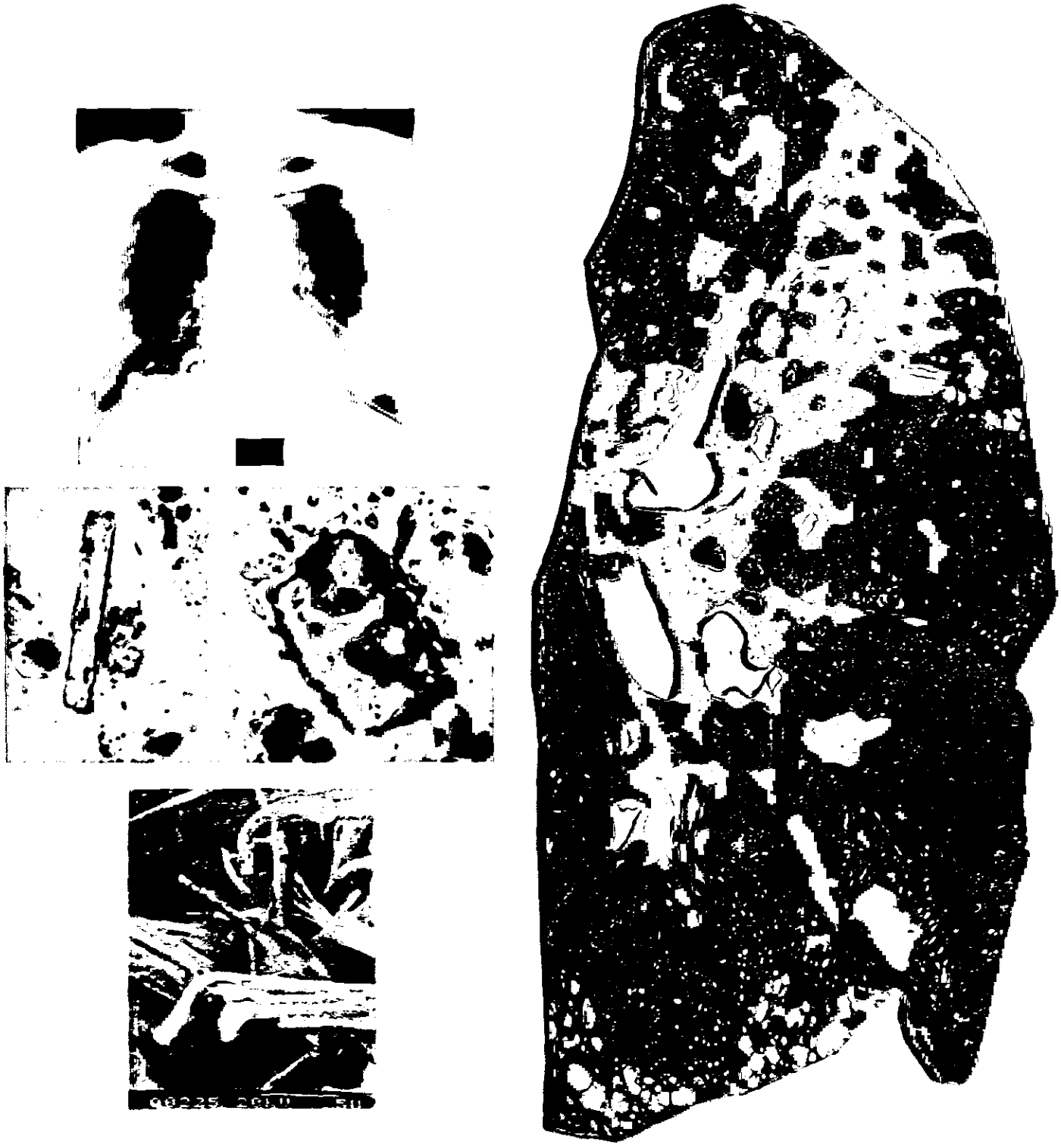

Table I
Sorts of Artificialfiber (Mineral)

- Artificial Fiber (Mineral)
  - Ammorphous Silicate Wisker
    - Rockwool
    - Glassfiber etc
    - Ceramicfiber etc
  - Mononuclear Wisker
    - K titacium
    - Ca sulphate etc
  - Others
    - Metaphosphate polymer etc
    - Carbon fiber etc

Table II
Substitutes and Chief Experimental Result

Material	Methods	Animal	results	Reporter
Glass fiber	Intra thoracheal Infusion	rats	Mesothelioma	**Stanton**
,,	,,	,,	,,	**Pott** (1974)
,,	,,	,,	,,	**Stanton** (1977)
Ceramic fiber	,,	,,	,,	**Wagner** (1973)
K titanium	,,	,,	Pleural sarcoma	**Stanton** (1978)
,,	Inhalaton	Hamster	mesothelioma	**Lee** (1981)

Consequently, it should be concluded that every kind of dust is active and every pneumoconiosis is harmful. As Arlidge advocated, there is no inert dust and no benign pneumoconiosis.

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ECOLOGIC ANALYSIS OF COAL WORKERS PNEUMOCONIOSIS MORTALITY IN ILLINOIS

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INTRODUCTION

In a pneumoconioses surveillance system, states collect data on numbers of cases and calculate rates by geographical areas such as countries. Exposure data are often collected at the county level, especially when person-specific data are not available. Associations between disease and exposure at the county level can be explored through ecologic analysis. The distinguishing feature of ecologic studies is that the group (i.e., county) rather than the individual is the unit of analysis. Statistical methods employed in the analysis of such data include correlations and regression.

Ecologic designs have often been used to study diseases of unknown etiology. For example, intercounty differences in mortality from non-Hodgkin's lymphoma have been correlated with environmental and industrial exposures at the county level.[1] While the etiologies of pneumoconioses are known, ecologic studies may identify new sources of dust exposure. This study explores the ability of ecologic analysis to statistically detect an association between coal production and CWP mortality in the state of Illinois. If the technique is able to detect a known association, it may prove useful in generating new hypotheses regarding industries associated with pneumoconioses.

METHODS

All cases of CWP from 1980–1984 were identified through a review of computer tapes of Illinois death certificates. Cases were coded with International Classification of Disease (Ninth Revision) code 500 as the underlying or contributing cause of death. Five-year crude rates for white males were calculated by county. Denominators were derived from the 1980 Census and county population estimates from the non-census years, for white males age 35 and over.[2]

Two indices of coal mining in Illinois counties in 1965 were used as surrogate measures of exposure to coal dust.[3] The first index, tons of coal mined, was a direct measure of production. The second index, the average tons of coal mined per worker per 8-hour day, was a measure of mine productivity. These two indices were further subdivided into underground, surface and total coal mining. Exposure data from 1965 were selected to allow for a 15 to 20 year lag period between first exposure and death.

The association between CWP mortality and coal mining was analyzed using weighted least-squares regression. Six different univariate regression models were fitted to the data. Counties with both zero death and zero production were excluded from each of these analyses. Rates were log-transformed and weighted by the inverse of the square roots of the denominators, in order to meet the assumptions of regression analysis. The SAS Regression Procedure program was used to perform the analysis.[4]

RESULTS

There were 367 white male CWP deaths from 1980 to 1984, 7 deaths among black males and 1 among white females. Mortality rates ranged from zero in 61 counties to 322.4/100,000/5 years in Franklin County, with a state average of 3.7/100,000/5 years. Forty-six out of a total 102 Illinois counties met the study criteria of having either CWP mortality in 1980–1984 or coal production in 1965. Forty-one of these counties reported CWP deaths and 5 produced coal but reported no CWP deaths.

Seven counties had underground but no surface mining, 9 had surface but no underground mining, 6 had both types and 24 had neither. Non-zero values for 1965 underground coal production ranged from 16,731 tons in Henry County to 6,182,282 tons in Franklin County, with a state mean of 1,766,958 tons for coal producing counties. Non-zero surface production ranged from 1,938 tons in Johnson County to 8,220,858 tons in Fulton County, with a state mean of 1,047,647 tons. Underground mine productivity in tons/worker/day was highest in Franklin County (23.0) and lowest in Henry County (9.1) with a mean of 18.1 for coal-producing counties. Surface mine productivity was highest in Knox County (56.1) and lowest in Gallatin County (14.2) with a state mean of 34.3 tons/worker/day.

Table I presents the results of linear regressions of the exposure indices on the log of CWP mortality rates. CWP mortality was significantly ($p \geq .005$) associated with tons of underground, surface and total production. In the underground models, production explained 51% of the variability in CWP mortality rates, while in surface models, production explained 18%. Corresponding values were lower with productivity as the surrogate exposure variable: 22% for underground tons/worker/day and 9% for surface tons/worker/day. The associations between underground, surface and total tons/worker/day and CWP mortality were also statistically significant ($p \geq .05$).

In Figure 1, the CWP mortality rates are plotted on a log scale against the 1965 underground tons produced. Franklin County stands out as having the highest CWP mortality and

Table I

Linear Regression of Log CWP Mortality Rates on Selected Measures of Coal Mine Production in Illinois

Variable	B_0	B_1	p	r^2
Underground				
Tons	1.036	7.223×10^{-7}	.0001	.51
Tons/worker/day	1.084	6.790×10^{-5}	.0016	.22
Surface				
Tons	1.122	3.497×10^{-7}	.0032	.18
Tons/worker/day	1.124	2.100×10^{-5}	.0498	.09
Total				
Tons	0.879	4.492×10^{-7}	.0001	.55
Tons/worker/day	0.992	2.340×10^{-5}	.0041	.17

Figure 1. CWP mortality by 1965 underground tons.

1965 underground mine production. Other notable characteristics of Franklin County are that it had the highest cumulative coal production of all Illinois counties from 1882 to 1965, and all its mines are underground.[3]

DISCUSSION

This study demonstrates that ecologic analysis is able to detect the known association between CWP mortality and exposure to coal dust in underground mines. As expected, CWP mortality was more strongly associated with underground mining than surface mining. The significant association of surface mining and CWP mortality may be due to the concurrence of surface and underground mining in counties of high production and high CWP mortality. For example, Williamson County, which had the second highest mortality rate in the state (100.3/100,000/5 years), produced more than 3 million tons in surface mines and more than 3 million tons in underground mines in 1965.

While surface mining was statistically associated with CWP mortality, we cannot determine whether any individual death was a result of exposure in surface mines without obtaining individual work histories. Inferences about individuals drawn from data on groups are susceptible to the "ecologic fallacy."[5]

A commonly used measure of dust exposure is the product of the dust concentration and duration of exposure. Surrogate exposure measures used in ecologic studies should be close approximations of the workers cumulative dust exposure. The type of data available at the county level often determines what surrogate variables will be used in an analysis, and conceivably, a disease-exposure association may be missed when a poor surrogate variable is selected. In this study, county coal production and mine productivity were both significantly associated with CWP mortality. Productivity, however, was a poorer predictor of mortality than actual production in underground, surface and total mining models. One possible explanation for this result is that high productivity by definition reflects high production relative to person-work time. Decreased person-work time may mean less exposure to coal dust and thus lower CWP mortality rates.

Several biases may be present in this study. Measurement bias may result from the use of cross-sectional exposure data from just one year, since that year could be atypical for coal production in any given county. Age confounding may occur because rates are not age-adjusted. We did not have access to national multiple-cause CWP mortality rates, and rates based solely on underlying cause would have missed 72% of all CWP deaths in Illinois. Another potential confounder, intercounty migration from mining to non-mining areas, would weaken the association between coal mining and CWP mortality. Migration may also occur from one type of mining to another, both within and between counties, although the effects of this are more difficult to predict. Other unmeasured variables which may confound or modify the disease-exposure relationship include mining techniques (i.e., longwall vs. panel) and dust control.

A major advantage of ecologic studies is that they do not require primary data collection but may rely instead on preexisting sources of data. For ecologic studies to be feasible, there must be a sufficient number of disease events at the group level, as well as suitable exposure data. For example, Illinois was the fifth highest coal-producing state in the U.S. as of 1984, and has the largest bituminous coal resources in the country. Thus, Illinois has incurred substantial CWP morbidity and mortality, and data on coal production is easily obtained.

As an adjunct to simple geographic mapping, ecologic analysis is useful for identifying predictor variables of CWP mortality in Illinois. In addition to examining the data cross-sectionally, CWP mortality trends can be studied through time-series analysis in future research. Ecologic analysis may prove useful in identifying predictor variables of disease outcomes for other pneumoconioses.

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DEATH CERTIFICATE-BASED SURVEILLANCE OF SILICOSIS AND ASBESTOSIS IN ILLINOIS

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INTRODUCTION

Surveillance is fundamental to the prevention and control of pneumoconioses. In the U.S., pneumoconiosis reporting systems have been proposed and also piloted by several state health departments.[1,2] The pneumoconioses are considered good target diseases for nascent occupational disease surveillance systems because they are of known etiologies, are almost always related to workplace exposures, are relatively easy to diagnose, and are preventable.

Sources of data in occupational disease surveillance include workplace surveys, laboratory logs, hospital discharge records, employee health records, disability files, physician reports and death certificates.[3,4] Death certificates are limited by inaccuracies in diagnosis and certification of the cause of death, and by misclassification of the decedent's occupation. They are not early indicators of outbreaks for diseases of long latency or duration and are not suitable for studying nonfatal conditions.[5]

Nevertheless, death certificates are a vast and easily accessed data source. Other states have used them to quantify pneumoconiosis mortality and to describe the demographic and geographic distribution of cases.[6] Follow-back investigations of cases may lead to the detection of exposure sites. This study explores the usefulness of death certificates as a surveillance tool for silicosis and asbestosis in the state of Illinois.

METHODS

Computerized death records from the Illinois Department of Public Health were obtained for the years 1969 to 1984. Cases were identified by International Classification of Disease (ICD) codes 5150 and 5152 of the eighth Revision, and codes 501 and 502 of the Ninth. The study diseases were coded as the underlying or contributing cause of death, although prior to 1979, four-digit codes precluded the differentiation of the pneumoconioses as contributing causes on Illinois death tapes. Additional variables abstracted from the tapes were sex, race, age and year of death, and the geographical subunit county of residence.

Crude state and county-specific mortality rates were calculated by year and also for the five-year period 1980–1984. The calculation of rates was limited to white males because of sparse data for other sex-race groups. Population estimates were used in the denominators for all years except 1980, when census data were available.[7,8] Denominators included individuals age 35 and over, since persons below this age were not believed to be at risk of pneumoconiosis mortality.

Correlations between observed geographical patterns of mortality and associated industries were explored. An annual statewide manufacturer's directory was used to identify asbestos products plants in the counties where asbestosis cases resided.[9] Silicosis death rates were superimposed on maps showing the location of industries and mineral deposits associated with silica dust exposure.[10] The industrial data spanned a period of thirty years to account for past exposures and to ascertain the current status of specific worksites and industries.

RESULTS

There were 76 silicosis cases reported by underlying and contributing cause of death from 1979–1984 (ICD-9). White males constituted 78% of the total, black males 20% and white females 2%. The mean age of death was 68 years with a range of 28 to 89 years. An additional 55 silicosis cases were identified by underlying cause of death from 1969 to 1978 (ICD-8). Of these, 87% were white males, 11% black males and 2% white females. Their mean age of death was 69 years and the range was 34 to 88 years.

The five-year state silicosis mortality rate for white males, which included underlying and contributing causes of death in the numerator, was 0.5/100,000. A rate of 40.2/100,000/5 years—based on 4 deaths in the numerator—was found in Alexander County, at the southwestern tip of Illinois. In Figure 1, the five-year rates overlay a section of a map showing siliceous mineral deposits in this area. In addition to a crude rate over 40 times the state rate, Alexander County cases died at an average age which was 13 years younger than the mean for Illinois white male silicotics (57.2 vs. 70.5 years).

For white males throughout Illinois, silicosis was more likely to be listed as an underlying rather than contributing cause of death in younger cases. Of the 22 who died younger than 70.5 years of age, 14 (64%) had silicosis certified as the underlying cause, compared to 18 out of 37 (49%) in the 70.5 or above age group.

There were 53 asbestosis cases reported during the ICD-9 period from 1979 to 1984, of which 83% were white males,

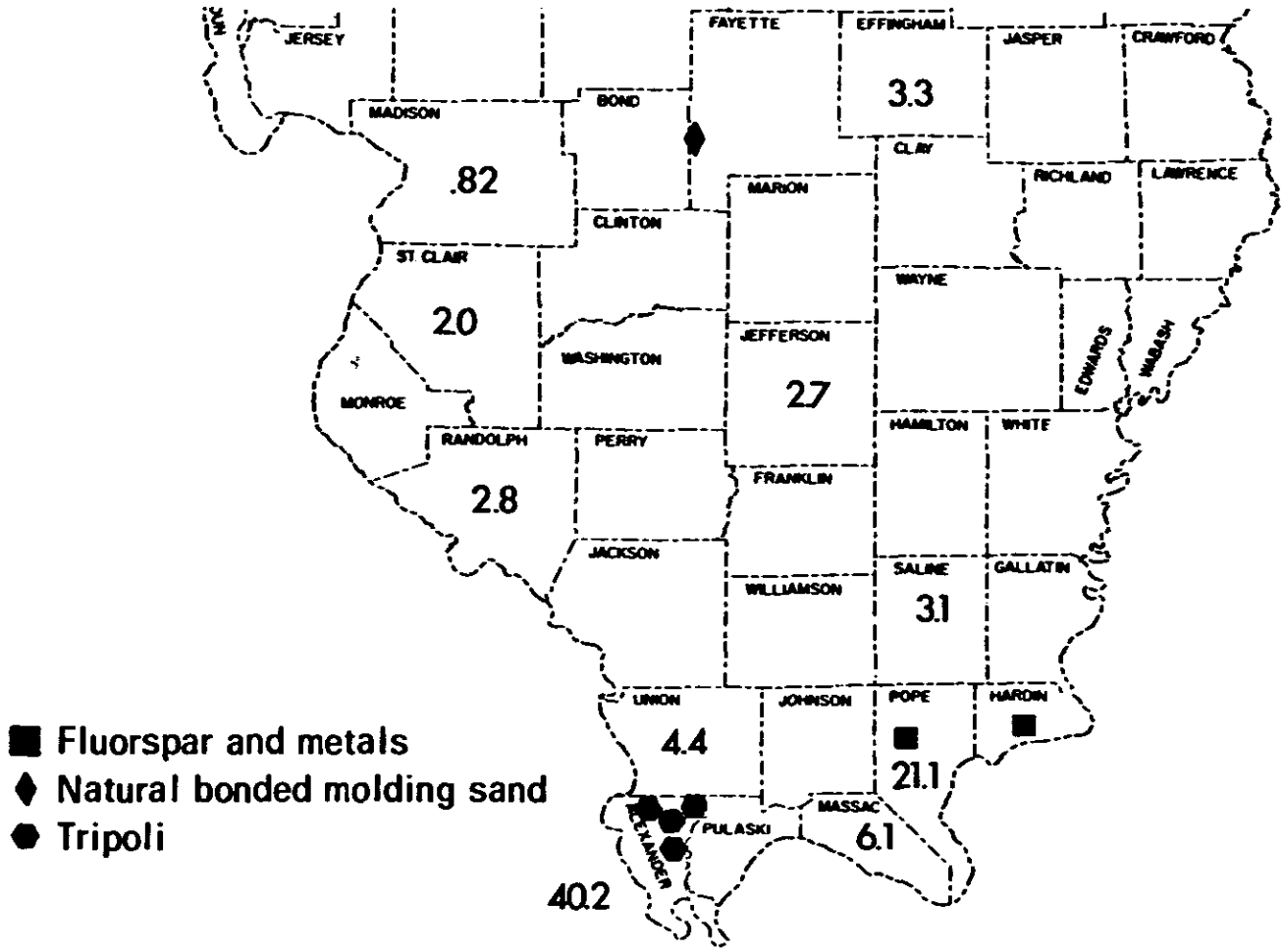

Figure 1. Siliceous mineral deposits and five-year silicosis mortality in southern Illinois.

6% black males and 11% white females. The mean age of death was 66 years and cases ranged from 44 to 84 years. There were 22 cases during the ICD-8 period from 1969–1978 with asbestosis coded as the underlying cause of death. White males were 77% of the total, black males 5% and white females 18%. The mean age was 63 years, with a range of 42 to 81 years.

The Illinois asbestosis mortality rate for white males was 0.41/100,000 per 5 years. Asbestosis deaths were reported in 11 out of 102 Illinois counties, 4 of which consistently had annual rates above zero: Cook, Lake, McLean and Madison. The five-year rates per 100,000 in these counties were 0.28, 3.0, 6.1 and 1.2, respectively.

DISCUSSION

The results of this study demonstrate that death certificate-based surveillance in Illinois is useful for identifying point sources of exposure in areas where pneumoconiosis deaths occur. The extraordinarily high silicosis mortality rates in Alexander County are a striking example of this.

As the map in Figure 1 indicates, Alexander County is a center of tripoli production, a mineral from which microcristalline silica is obtained for use as a filler and abrasive. Two tripoli mines and mills were surveyed by the National Institute for Occupational Safety and Health in 1979, following six years of high dust levels in air sampled by the Mine Safety and Health Administration. The survey documents simple silicosis in 26% of the 61 participants and progressive massive fibrosis in 11%.[11] The mean duration of exposure for the former group was 7.7 years with a 1–9 year range, and 7.1 years for the latter, with a range of 2.5–14 years.

Our study reviewed Illinois death certificate data back to 1969. The first death we identified in Alexander County occurred in 1969, 10 years prior to the morbidity survey. Five more deaths with silicosis as the underlying cause occurred in Alexander and adjacent counties before the survey. Thus, an annual review of Illinois death records would have alerted authorities to this serious outbreak years earlier. Prompt intervention to correct exposures could have reduced the number of Illinois workers dying from pneumoconiosis.

Probable point sources of asbestos exposure were identified in the four counties with high concentrations of asbestosis deaths. In the 1955 edition of the manufacturer's directory, Cook County listed nine asbestos products plants employing about 2500 workers. Lake County had one major plant with 2200 workers and McLean had a single plant with 200. Madison County listed a small asbestos products plant in the 1965 edition. Possible asbestos containing products plants were located in these counties as well. As of 1987, only one of the identified plants was still listed and not as an asbestos products operation.

Cases who died at an early age may be indicative of recent high exposures. We were surprised that silica dust exposures severe enough to result in early death were still occurring, as evidenced by 3 cases of black males who died at ages 28, 33 and 34 between 1974 and 1980. This indicates that in the calculation of silicosis mortality rates, the 35-year cutoff in the denominators may not always be applicable. Another aspect of our rates is that they are not age-adjusted to the U.S. population, since national age specific pneumoconiosis mortality rates based on multiple causes of death are not readily available. It is unlikely that large differences in crude rates, such as those seen in this study, can be attributed to the confounding effects of age.

Death certificates have proven to be an important component of pneumoconiosis surveillance in Illinois. We have identified Illinois counties of high risk for silicosis and asbestosis mortality together with potential point sources of exposure. Follow-back studies are now underway to verify exposures on a case-by-case basis. While mortality is not generally a timely surveillance measure for the pneumoconioses, the experience in Alexander County demonstrates that death certificates can be used to detect outbreaks that result in high mortality or early death. The clustering of cases over time in a given geographical area, and an age of death markedly below the mean would clearly be cause for further investigation.

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