Idiopathic Pulmonary Fibrosis
Epidemiologic Approaches to Occupational Exposure

KAZURO IWAI, TOHRU MORI, NORIO YAMADA, MOMOKO YAMAGUCHI, and YUTAKA HOSODA

Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, National Institute of Health and Nutrition, Tokyo and Radiation Effect Research Institute, Hiroshima, Japan

Idiopathic pulmonary fibrosis (IPF) risk-related factors were epidemiologically investigated on the basis of 1,311 Japanese IPF autopsy cases selected from the annual compilations of autopsy data records in Japan during a 12-yr period. Age and sex distribution of the subjects revealed a high peak in their seventh decade with males predominating. The IPF rate was more than two times higher ($p < 0.01$) among subjects engaged in occupations that exposed them to dust or organic solvents compared with those in other jobs. To ascertain job characteristics, an autopsy-case control study was conducted using other annual volumes of the autopsy data records and a similar tendency was observed. Then, a live-case control study was undertaken of 86 subjects with IPF. A significantly higher odds ratio was noted among metal production workers and miners compared with healthy and hospital control subjects (1.37 and 1.34, respectively, $p < 0.01$), and also a significantly lower odds ratio among subjects who frequently eat fish. Taken together with results of recent *in vitro* studies, the intrapulmonary deposition of hazardous dusts, especially metallic dusts, appears to play at least a partial role in initiating IPF. **Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med 1994;150:670-5.**

Idiopathic pulmonary fibrosis (IPF), initially described by Hamman and Rich (1) in 1944 as acute interstitial fibrosis of the lung, is now accepted as a chronic disease entity (2). Its pathologic findings are nearly identical to UIP (usual interstitial pneumonia) according to Liebow's classification (3). The term "cryptogenic fibrosing alveolitis" is also synonymous (4).

An autoimmune mechanism has been implicated in chronic IPF pathology because fibrotic changes in IPF are sometimes similar to those in collagen vascular disorders. Deposition of immune complex and neutrophil accumulation in the alveolar walls have been suspected to be followed by complement or platelet activation, causing endothelial damage through oxygen radicals of neutrophil origin, resulting in alveolar damage in the acute phase of the disease (5–8). In relation to the fibrotic process, studies have also demonstrated the activation of alveolar macrophages that regulate collagen fiber synthesis (9–11) and on the cytokine network involving agents such as transforming growth factor (TGF) and fibroblast growth factor (FGF) released from alveolar or interstitial macrophages and others (12–14).

Pathologic changes of IPF mimic lung fibrosis associated with collagen diseases in which the autoimmune mechanism is considered an important pathogenic factor. However, characteristics of IPF pathology are exclusively the development of pulmonary interstitial fibrosis with no extrapulmonary or systemic lesions. These findings suggest that some environmental noxious agents inhaled into the lung initiate and regulate IPF pathologic processes. In our previous epidemiologic study using an X-ray population survey, a higher incidence of IPF was found in older males than in females and in rural populations than in urban (15). To investigate the involvement of environmental factors in the initiation of IPF, epidemiologic studies were conducted including three substudies: two autopsy record studies and one live-case control study.

METHODS

Substudy 1. Epidemiologic Studies by Pathologic Data Books

The *Annuals of the Pathological Autopsy Cases in Japan* (APACJ), published annually since 1957 by the Japanese Society of Pathology, collect annual autopsy records from medical institutions that have more than 100 beds and with which members of the Society are affiliated. The items reported are: sex, age, job, clinical diagnosis, main and associated pathologic diagnosis, and whether treated with antibiotics, anticancer drugs, radiation, and steroid hormone, along with the code of the institution. Such information is kept in the Society's host computer (ACOS; NEC, Inc., Tokyo, Japan), using custom software written for this purpose. APACJ covers about 90% of autopsy cases in Japan, where overall autopsy rate ranges from 5 to 6%. A complete autopsy is performed on almost all of the subjects reported. Histologic examinations are usually made of one or more sections of each organ, and one or more sections of each lobe of affected lungs. The information on the computer is available only to members of the Society and to scientists introduced by a member with APACJ Committee approval.

Of 393,258 cases included in APACJ during the 12-yr period from 1974 through 1985, 2,714 cases with the main pathologic diagnosis of chronic interstitial pneumonia or pulmonary fibrosis were reported. After their records were reviewed, 1,403 cases of nonidiopathic pulmonary fibrosis were excluded according to the following criteria: (*1*) persons under 15 yr of age, to exclude viral pneumonia; (*2*) persons having pulmonary fibrosis associated with collagen disease; (*3*) persons treated with radiation therapy; (*4*) persons treated with anticancer drugs and those with suspected

(Received in original form November 8, 1993 and in revised form March 9, 1994)

Supported by grants from the Research Committee of Interstitial Lung Disease and of Intractable Disease Epidemiology, Ministry of Health and Welfare, Japan.

Correspondence and requests for reprints should be addressed to Kazuro Iwai, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, 3-1-24 Matsuyama, Kiyose, Tokyo, 204, Japan.

TABLE 1

NUMBER OF IPF AND TOTAL AUTOPSIES BY AGE AND SEX (1974–1985)

Age (yr)	Male			Female			Both Sexes		
	IPF Autopsy	Total Autopsy	%	IPF Autopsy	Total Autopsy	%	IPF Autopsy	Total Autopsy	%
15–19	1	2,147	0.05	0	1,223	0.00	1	3,370	0.03
20–29	8	4,996	0.16	11	3,720	0.30	19	8,716	0.22
30–39	18	10,046	0.18	25	7,751	0.32	43	17,797	0.24
40–49	43	23,535	0.18	47	14,893	0.32	90	38,428	0.23
50–59	129	43,318	0.30	71	24,673	0.29	200	67,991	0.29
60–69	236	55,902	0.42	123	33,336	0.37	359	89,238	0.40
70–79	294	53,897	0.55	157	33,162	0.47	451	87,059	0.52
80–	107	16,486	0.65	41	12,890	0.32	148	29,376	0.50
Total	836	210,327	0.40	475	131,648	0.36	1,311	341,975	0.38

drug-induced pneumonitis; (*5*) lung fibrosis associated with pneumoconiosis; (*6*) lung fibrosis associated with viral or bacterial infection; (*7*) lung fibrosis of localized or unilateral involvement; and (*8*) cases of bronchiolitis obliterans and diffuse alveolar damage (BIP), desquamative interstitial pneumonia (DIP), giant cell interstitial pneumonia (GIP), and lymphoid interstitial pneumonia (LIP) according to Liebow's classification.

The remaining 1,311 autopsy cases were assessed as IPF, and analyzed by age, sex, residence, job (according to the Japanese Standard Job Category), clinical diagnosis, and other factors. To make a random control sampling from the same APACJ used for the case selection, every 100th case was selected from all 393,258 cases in the annuals to identify their jobs. The number of jobs thus obtained from 1/100 sampling was multiplied by 100 to compare job categories between the cases and control subjects.

Substudy 2. An Autopsy Case Control Study on the APACJ Annuals

Although the APACJ reporting instructions request the longest or last job category, the following three groups were excluded because of the limited information on their actual job types: (*1*) unemployed older persons, because previous jobs were not available; (*2*) company or governmental employees, because they were a mixture of white and blue collar workers; (*3*) housewives, because some of them worked part-time in dusty environments. To compare job distribution in terms of occupational exposure between case and control subjects, a case control method was employed. The number of workers in each job category was so small that the following dust-related and organic solvent vapor-related jobs were combined into an occupational exposure group in reference to results of Substudy 1: metal production workers, iron production workers, miners, shipbuilding workers, lathe workers, plasterers, glassworkers, wood production workers, texture workers, boilermen, painters, leather workers, gild workers, and laundry workers. On the other hand, a nonoccupational exposure group was defined consisting of teachers, lawyers, students, doctors, and workers in 33 other job categories. These IPF cases and control subjects were obtained from more recent annuals of APACJ for the years 1986 through 1989.

In Substudy 2, the cases evaluated as interstitial pneumonia were also subjected to study with interstitial lung fibrosis (IPF). All cases were reviewed to exclude nonidiopathic cases as was done in the preceding substudy. The 615 revised cases were divided into the following three groups: Group 1, 63 cases evaluated as acute interstitial pneumonia; Group 2, 266 cases evaluated as chronic interstitial pneumonia or interstitial lung fibrosis (IPF); and Group 3, 286 cases evaluated as interstitial pneumonia without acute or chronic qualification.

Two control subjects to each case, chosen from the same APACJ annuals, were matched by sex, age (± 5 yr), and residential area. These controls consisted of persons who died from a nonrespiratory disease and those who died from non-IPF respiratory disease, mostly lung cancer. A job comparison was made between the case group and both types of controls.

Substudy 3. A Live-Case Control Study

This study was performed as a joint undertaking of two research committees. The Research Committee on Interstitial Lung Disease and the committee on Intractable Disease Epidemiology; it was sponsored by the Ministry of Health and Welfare. Eighty-six IPF cases evaluated by the committee members were collected from 12 prefectures according to the following criteria: bilateral reticulonodular shadows with honeycombing predominantly situated in the outer zone of the lower lung field on routine chest X-ray or computed tomographs, in association with three or more clinical findings of cough, dyspnea, fine crackles, accelerated blood sedimentation rate, decreased lung volume, decreased diffusion capacity or hypoxemia. Diffuse lung fibrosis of known etiology, e.g., pneumoconiosis, tuberculosis, chronic bronchitis, diffuse panbronchiolitis, hypersensitivity or drug-induced pneumonitis, and sarcoidosis or collagen disease-associated lung fibrosis were excluded.

Two healthy control subjects from the voter's list and a hospital control of non-IPF respiratory diseases from the same hospitals as the cases were chosen. These controls were matched with each case regarding sex, age (± 5 yr of age), and residential area.

A total of 344 case and control subjects (86 cases in each group) who consented to join the study were requested to be interviewed by experienced interviewers at clinic or bedside for the cases and at home or elsewhere for healthy control subjects. Questionnaire items covered 217 variables relating to food, beverage, smoking habits, hobbies, previous illness, domestic chemicals, occupational history, residential area, and so forth. These variables were analyzed by an unconditional logistic model to estimate relative risks for IPF cases. Statistical significance of the differences was evaluated by chi-square tests.

RESULTS

Statistical Analysis of IPF Cases Reported in APACJ

Initial studies were made on the 1,311 IPF cases (0.38%) over 15 yr of age selected from 341,945 autopsy cases reported in the APACJ from 1974 through 1985. IPF cases demonstrated a marked increase with age in males, peaking in the seventh decade (Table 1). Because the autopsy rate in each sex and age group of the general population differs, the number of IPF autopsy cases was adjusted by autopsy rate in each gender and age group to estimate IPF mortality in the general population. Estimated mortality increases markedly with age in both sexes, peaking in the eighth decade. Males older than 40 yr of age consistently showed higher rates than females of corresponding ages (Figure 1). IPF mortality per 100,000 population was estimated to be 3.3 in males, 2.5 in females, and 3.0 in both sexes.

The frequency of IPF cases in each job group was calculated to compare with that of control cases (equal to all cases minus specific job cases). Occupations showing significantly higher IPF frequency ($p < 0.01$) were laundry workers, barbers, beauticians, painters, production metalworkers, and production woodworkers (Table 2).

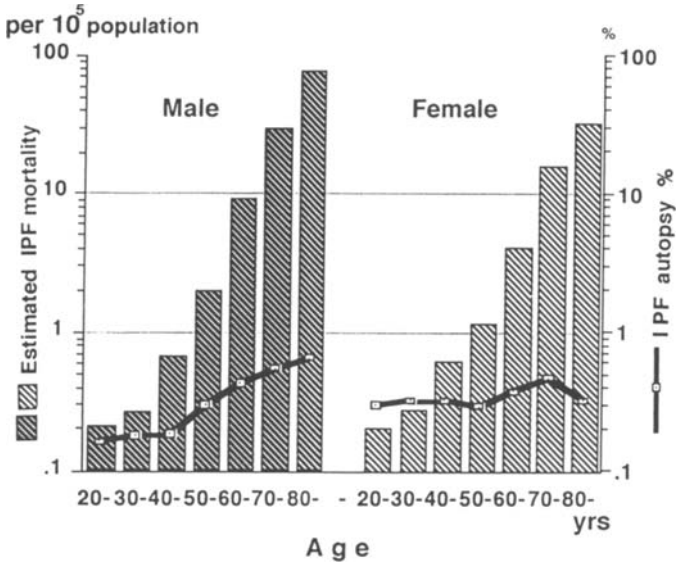

Figure 1. Estimated IPF mortality in the general population and IPF autopsy rate by age and sex. IPF mortality was estimated by adjusting the IPF autopsy number using autopsy rates of each age group and sex. After this adjustment, IPF mortality showed a markedly high rate in old people with males predominating.

Autopsy Case Control Study

The second substudy included three groups of IPF cases: acute interstitial pneumonia (Group 1), chronic IPF (Group 2), and cases of unknown course (Group 3) recorded in APACJ during the 4-yr period from 1986 through 1989.

In Group 1, composed of 63 acute cases, no difference in occupational exposure was noted between case and control groups for nonrespiratory disease. Group 2, composed of 266 subjects with chronic IPF, showed an odds ratio of 2.80 (95% confidence interval [CI]: 1.09–7.22, $p < 0.05$) to the nonrespiratory disease controls, and Group 3, composed of 286 cases of unknown course, showed a ratio of 1.86 (CI: 0.98–3.55, not significant [NS]) to the nonrespiratory disease controls. The odds ratio over the total 615 cases to the nonrespiratory disease controls was 2.0 (CI: 1.16–3.08, $p < 0.01$). The odds ratios to the respiratory disease controls showed no significant differences in any of the three groups (Table 3).

Live-Case Control Study

Sex and age distribution of the cases revealed that males predominated, especially in subjects 60 to 79 yr of age (Table 4) in both the case and control groups, as seen in the preceding autopsy cases. The results of analysis of these 53 male and 33 female sets are shown in Table 5. A statistically significant relative risk was observed in the job group of cadmium, chromium, and lead metal production and mine workers. This group produced a relative risk of 1.34 (CI: 1.14–1.59, $p < 0.01$) to the healthy control group and 1.37 (CI: 1.08–1.73, $p < 0.01$) to the hospital control group. One factor showing a significantly low relative risk to both control groups was "often eat fish." The relative risk was 0.48 (CI: 0.30–0.88, $p < 0.05$) to healthy control subjects and 0.35 (CI: 0.15–0.83, $p < 0.05$) to hospital control subjects.

Variables that showed a positive odds ratio above unity to healthy control subjects only were smoking (RR = 2.9, $p < 0.01$), previous pneumonia (RR = 3.12, $p < 0.01$), previous antibiotics intake (RR = 3.34, $p < 0.01$), residence in agricultural area (RR = 3.10, $p < 0.05$), and inhalation exposure to agricultural chemicals (RR = 3.32, $p < 0.05$). A significantly lower odds ratio below unity

TABLE 2

FREQUENCY OF IPF IN AUTOPSY CASES OF VARIOUS JOBS

Job Category	No. Jobs in Total Autopsy* (A)	No. IPF Autopsies (B)	IPF in Jobs (B/A, %)	p Value†
Company worker, teacher, lawyer, author, clergy, student, live-in renter	77,300	243	0.31	NS
Artist, sculptor, photographer	1,200	6	0.50	NS
Doctor, pharmacist, nurse, midwife, physical therapist	8,600	26	0.30	NS
Housewife, housekeeper, hotelkeeper, cook	87,900	245	0.28	NS
Shopkeeper, house-to-house salesperson	15,900	72	0.45	NS
Driver, busguide, railwayworker, ship's crew, boilerman	8,000	24	0.30	NS
Laundry worker, barber, beautician	1,300	12	0.92	< 0.001
Painter	800	10	1.25	< 0.001
Production metalworker	2,300	29	1.26	< 0.001
Production woodworker	800	8	1.00	< 0.001
Other factory production worker	15,400	56	0.36	NS
Carpenter, door-and-window fitter, plasterer	8,400	27	0.32	NS
Farmer, forestry, livestock worker	27,100	93	0.34	NS
Fishery worker	1,600	3	0.19	NS
Miner	1,500	5	0.33	NS
Physical laborer	4,300	11	0.26	NS
Occupation unknown, unemployed	130,600	441	0.26	
Total	393,000	1,311	0.33	

* Number of cases extracted from the total autopsy cases at a 1/100 extraction rate was multiplied by 100.

† p Value in chi-square test was obtained by comparison between the IPF rate in a job and that in the total job from which the objective job was excluded.

TABLE 3

ODDS RATIO ABOVE UNITY FOR OCCUPATIONAL EXPOSURES TO NONRESPIRATORY AND RESPIRATORY DISEASE CONTROL SUBJECTS IN THE THREE DISEASE GROUPS

	Nonrespiratory Disease Controls		Respiratory Disease Controls	
Cases*	Odds Ratio	95% CI	Odds Ratio	95% CI
Group 1	1.55	0.37–6.70	1.05	0.31–3.64
Group 2	2.80	1.09–7.22†	1.22	0.68–2.20
Group 3	1.86	0.98–3.55‡	1.10	0.64–1.90
Total	2.00	1.27–3.16§	1.04	0.60–1.80

* Group 1: Acute interstitial pneumonia. Group 2: Chronic IPF cases. Group 3: Acute or chronic, indeterminable.
† $p < 0.05$.
‡ $p < 0.10$.
§ $p < 0.01$.

TABLE 4

AGE DISTRIBUTION OF IPF CASES AND CONTROL SUBJECTS

Age (*yr*)	IPF Cases	Hospital Controls	Healthy Controls
Total	86	86	172
20–29	1	1	2
30–39	1	1	4
40–49	7	5	14
50–59	20	20	37
60–69	26	33	55
70–79	26	20	51
80–	5	6	9
Male:female	53:33	53:33	106:66

to healthy control subjects only was found for frequent intake of black tea (RR = 0.13, $p < 0.01$), alcohol (RR = 0.43, $p < 0.01$), and antihypertension drugs (RR = 0.44, $p < 0.05$). A significantly higher odds ratio above unity only to hospital controls was noted in subjects with a history of previous rubella infection (RR = 11.0, $p < 0.05$). A significantly lower odds ratio to hospital controls only was noted in previous tuberculosis (RR = 0.22, $p < 0.01$) and bronchiectasis (RR = 0.16, $p < 0.01$).

No significant difference to both control groups was noted for the following variables:

Foods: meat products, soybean products, vegetables, fruit, and green tea.

Previous illness: measles, pertussis, varicella, mumps, herpes, hepatitis, pleurisy, asthma, chronic bronchitis, and hypertension.

Medicines: antituberculous drugs, analgesics, cardiac stimulants, antidiabetic drugs, tranquilizers, and hormones.

Domestic chemicals: detergents, softeners, bleaching agents, other cleaning agents, aromatics, antimold agents, insecticides, and herbicides.

Womens' cosmetics: hair sprays, astringents, perfumes, hair dyes, lipsticks, and depilatories.

Men's cosmetics: hair tonics, aftershave lotions, colognes, and hair dyes.

DISCUSSION

IPF mortality estimated from autopsy data after adjustment by autopsy rate in each age group and sex, revealed male predominance and an increase with advancing age, as seen in our previous report on IPF morbidity detected by an X-ray population survey (15). This pattern resembles that of chronic obstructive airway disease or lung carcinoma.

Occupational histories available from the autopsy records are of limited value for evaluation purposes. Some subjects might have changed jobs during their lifetime, and detailed features and doses of exposed substances are difficult to obtain. Some autopsied subjects who died at an advanced age were often reported as "no job" or "unknown." Company or government employees and even housewives who worked part-time may have worked in dusty workplaces. However, most Japanese employees rarely change jobs because of the lifetime employment system, and many craftsmen continue the same type of work because they hold an occupational license, hence the job before retirement is usually the one held the longest. Finally, taking an occupational history may result in a bias between autopsy cases and live cases.

TABLE 5

RELATIVE RISKS IN LIVE-CASE CONTROL STUDY

	Hospital Controls		Healthy Controls	
Variables	Relative Risk	95% CI	Relative Risk	95% CI
Food, beverage and smoking				
Meat	0.72	0.39–1.32	0.57	0.32–1.00
Fish	0.35	0.15–0.83*	0.48	0.26–0.88*
Shell	1.28	0.69–2.36	1.20	0.70–2.05
Milk	1.06	0.55–2.05	1.67	0.94–2.94
Vegetable	0.78	0.29–2.08	0.66	0.31–1.41
Green tea	0.67	0.19–2.36	0.70	0.26–1.91
Tobacco	1.49	0.70–3.58	2.94	1.37–6.30†
Occupational exposure				
HCN, H_2SO_4	1.00		0.43	0.05–3.87
SO_2, CS_2, Cl, dye	1.00		0.86	
Cd, Cr, Pb, Zn, metal, mine	1.37	1.08–1.73†	1.34	1.14–1.59†
Spining, paint, oil, medicine	1.28	0.97–1.67	1.61	1.06–2.42*
Residential area				
Agriculture area	2.50	0.86–6.40	3.01	1.29–7.43*
Agricultural chemicals	2.02	0.77–5.34	3.32	1.22–9.05*
Factory area	1.50	0.25–8.92	1.99	0.40–9.90
Urban and polluted area	2.18	0.74–6.48	3.33	1.26–8.79*

* $p < 0.05$.
† $p < 0.01$.

In Substudy 1, the IPF autopsy case rate was significantly high in jobs that have a probability of dust or vapor inhalation. No single job or specific substance could be identified, and exposure to mixed dust was possible in many jobs. In the group of laundry workers, barbers, and beauticians, laundry workers may be exposed to irritating vapor of organic solvents; additionally painters may be exposed to solvent vapor from painting materials. Production metal workers and woodworkers may sometimes inhale metal or wood dusts in the workplace. Although the precise exposure dose of metal or wood dusts is unknown, it is certainly higher in this group than in other job groups.

The autopsy case control study in Substudy 2, which contained more precise exposure histories, also indicated a significantly high rate of workers exposed to dusts or vapors in chronic IPF cases in comparison with control subjects with nonrespiratory disease. No difference was found in comparison with control subjects with respiratory disease, who mainly had lung cancer. It is well known from clinical observations that approximately 10% of IPF cases are associated with lung cancer (16), and our autopsy series shows an association rate of approximately 30% (unpublished data). Therefore, negative results for respiratory disease controls may be caused partly by this high proportion of lung cancer autopsy cases inevitably included with respiratory disease controls, and may be partly attributable to dust or vapor exposure related both to IPF and to non-IPF lung diseases.

Occupational exposure showed no correlation to acute cases in Substudy 2. Acute cases in this study were thought to correspond partly to Hamman-Rich syndrome, partly to acute interstitial pneumonia recently described by Katzenstein and coworkers (17), and partly to an antemortem acute exacerbation of IPF, all of which show hyaline membrane and/or cellular alveolitis as a main histologic feature with a clinical course shorter than 3 mo before death. Chronic cases are usually identified as having predominant fibrosis and honeycombing pathologically with a clinical course longer than 6 to 12 mo. The difference in occupational exposure between acute and chronic IPF cases may indicate a different pathogenicity affecting the two groups. Group 3 showed an intermediate odds ratio between Group 1 (acute) and Group 2 (chronic), probably reflecting a mixture of acute and chronic cases.

IPF cases in the live-case control study were diagnosed by using consensus clinical criteria adopted by the Japanese Committee for IPF. Sex and age distribution in this substudy resembled that reported elsewhere (4) and in the present autopsy data (Table 1). Results obtained in the present study demonstrate a significantly higher rate of metallic dust workers in IPF cases in comparison to both healthy and hospital control subjects. This result resembles that in the case-control study reported by Scott and coworkers in which a significantly higher rate of cryptogenic fibrosing alveolitis was observed in the workers exposed to metal dust, wood dust, and other workers (18). In this study, a significantly higher difference was noted between the cases and healthy control subjects than between the cases and hospital control subjects, probably because of the inclusion of many subjects with non-IPF respiratory diseases in the hospital control group. Because there is a possibility that a common pathogen or pathogens are implicated in IPF and other respiratory diseases, this may be a reason to have lowered odds ratios to hospital control subjects.

The factor of "often taking fish" showed a significantly low odds ratio regardless of the characteristics of the control groups. This unexpected result may draw some attention because there is growing consensus that the intake of polyunsaturated fatty acid, which is abundantly present in fish oil, may reduce the risk of cardiovascular diseases (19), as well as promote metabolism and excretion of chemicals such as chlorobenzene compounds given experimentally (20). Parenteral administration of fish oil has been reported to suppress bleomycin-induced lung fibrosis in rats (21). The suppressive effect of lung fibrosis by eicosanoic acid, which is found in fish oil, is an attractive subject for further studies.

In regard to dust deposition in IPF-affected lungs, Inoue (22) and Honma and colleagues (23) found a high content of silicon in IPF-affected lung tissue by using the elementary analysis, particle-induced X-ray emission (PIXE). Monso and coworkers (24) found a high Si/S ratio in IPF-affected lung, and Ogawa and coworkers (25) demonstrated a high content of silicon, magnesium, and titanium in IPF-affected lung tissue. Hashimoto and colleagues (26) examined metal elements in the hilar and mediastinal lymph nodes using fluorescent X-ray analysis and demonstrated a significantly high content of nickel with a slightly higher content of silicon. From a histologic standpoint, typical occupational asbestosis is sometimes difficult to distinguish from IPF histology. Recent pathologic observation of silicosis autopsies also demonstrated the presence of diffuse interstitial fibrosis similar to IPF in approximately 4% of the cases in addition to typical silicotic nodules (27).

It has been reported that industrial exposure to metal elements such as nickel, chromium, and cadmium might also induce lung fibrosis and/or lung cancer. The frequent association and possible shared pathogenesis of lung fibrosis and lung cancer are a recent topic of interest. Long-term inhalation studies of carbon black, diesel exhaust particles, TiO_2, SiO_2, talc, and asbestos fibers revealed that all kinds of particles or fibers deposited would induce fibrosis and cancer in the same lung to various extents (28). *In vitro* studies in which a mammalian cell line was cultured with a low concentration of silica particles provoked transformation of the cells which developed to sarcoma when subcutaneously injected into mice (29). Fibroblast cell lines cultured with asbestos fibers have demonstrated chromosomal aberration, depending on fiber length (30). Furthermore, cytokines such as FGF, platelet-derived growth factor (PDGF), and TGF are known to promote fibroblast growth as well as oncogenic expression and growth of the cells.

Taken together with the results in the previously cited study series and in the present study, it is possible to propose a hypothesis that in some IPF cases, hazardous dusts, especially metallic dusts deposited in the lung, or irritable vapor of organic solvents repeatedly inhaled may continuously stimulate lung cells and induce an inflammatory reaction in the lung tissue, with subsequent progressive fibrosis. The mechanisms that regulate promotion and continuous progression of the pathologic changes remain to be studied, and other factors relating to IPF pathogenesis should also be studied.

References

1. Hamman L, Rich A. Acute diffuse interstitial fibrosis of the lungs. Bull Johns Hopkins Hosp 1944;74:177–212.
2. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Raynolds HY. Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic and biochemical aspects (NIH conference). Ann Intern Med 1976;85:769–88.
3. Liebow AA. New concepts and entities in pulmonary diseases. In: Liebow AA, Smith DE, eds. The lung. Baltimore: Williams & Wilkins, 1968;332–65.
4. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980;35: 171–80.
5. Kaplan RL, Schockert AL, King TE. A model of immune complex-mediated pleuropulmonary injury. Evidence of deposition of circulating immune

complexes in the lung. Am J Pathol 1980;100:115–30.
6. Robbins RA, Russ WD, Rasmussen JK, Clayton MM. Activation of the complement system in the adult respiratory distress syndrome. Am Rev Respir Dis 1987;135:651–8.
7. Heffner JE, Sahn SA, Repine JE. The role of platelets in adult respiratory distress syndrome. Culprits or bystanders? Am Rev Respir Dis 1987; 135:482–92.
8. McCormick JR, Harkin MM, Johnson KL, Ward PW. Supression by superoxide dimutase of immune-complex-induced pulmonary alveolitis and dermal inflammation. Am J Pathol 1981;102:55–61.
9. Thrall RS, McCormick JR, Jack RM, McReynolds RA, Ward PA. Bleomycin-induced pulmonary fibrosis in the rat. Inhibition by indomethacin. Am J Pathol 1979;95:117–30.
10. Fantone JC, Feltner DE, Brieland JK, Ward PA. Phagocytic cell-derived inflammatory mediators and lung disease. Chest 1987;91:428–35.
11. Suwada A, Takahashi K, Yasui S. Bleomycin-stimulated hamster alveolar macrophages release interleukin-1. Am J Pathol 1988;132:512–32.
12. Adamson IYR, Letourneau HL, Bowden DH. Enhanced macrophage-fibroblast interactions in the pulmonary interstitium increases fibrosis after silica infection to monocyte-depleted mice. Am J Pathol 1989; 134:411–8.
13. Broekelman TJ, Limper AH, Colby TV, McDonald JA. Transforming growth factor β_1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. Proc Natl Acad Sci USA 1991;88:6642–6.
14. Pierce GF, Tarpley JE, Yanagihara D, Mustoe TA, Fox GM, Thomason A. Platelet-derived growth factor (BB homodimer), transforming growth factor-β_1, and basic fibroblast growth factor in dermal wound healing. Am J Pathol 1992;140:1375–88.
15. Iwai K, Nakajima T, Miyagi Y, Oota S, Rokusha M, Okada S, Moritani Y, Yamamoto Y, Nobechi T. Epidemiological studies on idiopathic diffuse interstitial fibrosis of the lung (in Japanese with English abstract). Jap J Thorac Dis 1980;18:800–8.
16. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980;35:496–9.
17. Katzenstein ALA, Myers TL, Mazur MT. Acute interstitial pneumonia. A clinco-pathologic, ultrastructural and cell kinetic study. Am J Surg Pathol 1986;10:256–67.
18. Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. Br Med J 1990;301:1015–7.
19. Herold PM, Kinsella JE. Fish oil consumption and decreased risk of cardiovascular disease: a comparison of findings from animal and human feeding trials. Am J Clin Nutr 1986;43:566–98.
20. Ikegami Y, Dobashi F, Inagaki K, Ichikawa T. Effect of dietary lipids on accumulation of pentachlorobenzene (in Japanese with English abstract). J Food Hyg Soc 1991;32:420–5.
21. Kennedy JI Jr, Chandler DB, Fulmer JD, Wert MB, Grizzle WE. Dietary fish oil inhibits bleomycin-induced pulmonary fibrosis in the rat. Exp. Lung Res 1989;15:315–29.
22. Inoue M. Quantitative and qualitative analysis of inorganic dusts in idiopathic interstitial pneumonia (IIP) (in Japanese). Hokkaido Med J 1986;61:745–54.
23. Honma Y, Tanimura K, Kusaka H. Minakata M. Inhaled dust and collagen vascular diseases as the possible causes of idiopathic interstitial pneumonia (IIP). In: Harasawa M, Fukuchi Y, eds. Intestinal pneumonia of unknown etiology. Tokyo: University of Tokyo Press, 1989;23–32.
24. Monso E, Tura JM, Marsal M. Mineralogical microanalysis of idiopathic pulmonary fibrosis. Arch Environ Health 1990;45:185–8.
25. Ogawa J, Kubota K, Yaegashi J, Maiya N, Tamura M, Sera K. Quantitative analysis by particle induced X-ray emission (PIXE) of trace elements in lung tissue of idiopathic interstitial pneumonia patients. Intl J PIXE 1992;2:547–50.
26. Hashimoto N, Iwai K, Tajima H, Mizoguchi I. Elementary analysis of hilar and mediastinal lymph nodes in idiopathic pulmonary fibrosis (in Japanese with English abstract). Jap J Thorac Dis 1992;30:11–18.
27. Honma J, Chiyotani K. Diffuse interstitial fibrosis in non-asbestos pneumoconiosis—a pathological study. Respiration 1993;60:120–6.
28. Dungworth DL, Mohr U, Heinrich U, Emst H, Kittel B. Pathologic effects of inhaled particles in rat lungs: association between inflammatory and neoplastic processes. Reported at the 4th International Inhalation Symposium: Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. Hannover, March 1993.
29. Saffiotti U, Ahmed N, Williams AO. Effects of different silica samples in BALB/3T3/A31-1-1 cells: uptake, cytotoxicity and neoplastic transformation. Reported at the 4th International Inhalation Symposium: Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. Hannover, March 1993.
30. Koshi K, Kohyama N, Myojo T, Fukuda K. Cell toxicity, hemolytic actions and clastogenic activity of asbestos and its substitutes. Ind Health 1991;29:37–56.