Occupational hypersensitivity pneumonitis in Japan: data on a nationwide epidemiological study

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Abstract

Objectives—Diagnostic criteria were prepared for hypersensitivity pneumonitis (HP) and a nationwide survey was conducted to investigate epidemiological and clinical characteristics of HP in Japan. The results are presented with special focus on occupational HP and on the key to the diagnosis of HP.

Methods—A questionnaire was completed by 185 doctors from 185 hospitals (response rate 89.5%). All cases were verified according to diagnostic criteria; 835 cases were classified as HP (653 definite and 182 probable). These 835 cases (total HP) and 99 possible cases of HP diagnosed during the 1980s were analysed and presented as a case series study.

Results—Occupational HP was noted in 115 cases (13.8%). 21 occupations, and 20 aetiological antigens were listed. Farmer's lung: 68 cases (59% of occupational HP) was the most prevalent diagnosis followed by 19 industrial workers who handled chemicals (for example, isocyanate) and 10 office workers. Unique cases of mushroom, greenhouse, and silkworm farmers, and a new type of bagassosis are also described. Adverse environmental conditions, immunological findings on examination, antigen challenge, and pathological findings were all significantly lower for possible than for total HP. This was not true for clinical findings. The differences in antibody analysis (6% positive of possible HP *v* 59% of total HP) and environmental challenge (3% *v* 74%) were notable.

Conclusion—These data suggest that a careful interview about the environment and an antigen panel matched to variations in exposure are the key to the diagnosis.

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Keywords: hypersensitivity pneumonitis; allergic alveolitis; diagnostic criteria; occupational pulmonary disease

Hypersensitivity pneumonitis (HP) or allergic alveolitis is a complex syndrome characterised by a varying intensity of response to different antigens and variable clinical presentations.¹⁻⁹ The prevalence of HP (farmer's lung, bird fancier's lung, ventilation pneumonitis, summer HP, etc) varies from country to country

and even within a country it varies with the local climate, season, and geographical conditions as well as the local customs or the industries located there. The prevalence of disease and rates of attack are likely to vary depending on one or more of the exposure variables, host risk factors, and case definition.^{6,7}

The diagnosis of HP is based on a history of exposure to antigens, signs and symptoms, and laboratory findings. Attempts have been made to present uniform criteria for diagnosis of HP,⁸⁻¹⁵ but acceptance of these criteria has been limited.

In Japan, summer HP is the most prevalent distinctive type,¹⁶⁻¹⁸ and is not related to occupational exposure, but to inhalation of seasonal moulds present in home environments. We clarified the pathogenesis, clinical characteristics, epidemiology, and treatment of summer HP.¹⁶⁻²² There have been no recent nationwide reports on the epidemiology of occupational HP or HP in general. We designed diagnostic criteria and did a survey to investigate epidemiological and clinical characteristics of HP in Japan in the 1980s.^{18,19} We describe the results, with special focus on occupational HP and on the key to the diagnosis of HP.

Materials and methods

The research committee on diffuse pulmonary disease organised by the Ministry of Health and Welfare of Japan conducted a survey on HP. Cases of HP identified from 1 January 1980 to 31 December 1989 were collected throughout the country. A questionnaire on HP was sent to 209 hospitals to members of the research committee or leaders authorised by the Japan Society of Chest Diseases. The diagnostic criteria of HP were prepared by the research committee (table 1).

The questionnaire consisted of two parts. The first part related to the personal history of the patient taken by doctors and the second part related to clinical data and diagnosis (the details of the questionnaire are available from the authors on request).

Data on each patient were described by members of the committee or by members of the Japan Society of Chest Diseases working at the hospitals. One hundred and eighty five hospitals participated (response rate 89.5%). A total of 963 cases was collected from 168 participating hospitals (55 university hospitals and 113 other hospitals). All cases were verified according to the diagnostic criteria and 835 were classified as HP:

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Table 1 Criteria proposed by the Japan Research Committee on Diffuse Pulmonary Disease for Hypersensitivity Pneumonitis

1 Clinical features:
(positive if two or more signs and symptoms and two or more laboratory data findings (including chest x ray films) are present)
Signs and symptoms:
Cough
Dyspnoea
Fever
Fine or coarse crackle
Laboratory data:
Diffuse interstitial shadows on chest x ray film*
Restrictive impairment of pulmonary function
Decreased PO_2
Increased RSR
Positive CRP
Lymphocytosis in BAL cells
Negative tuberculin test
2 Environmental condition:
(positive if one of the following environmental conditions is present)
HP from hot and humid conditions or as in summer months (summer HP)
HP from handling mouldy hay (farmer's lung)
HP from handling birds (bird fancier's lung)
HP from the use of an air conditioner or a humidifier (ventilation pneumonitis)
HP from environments with an organic or inorganic inhaled antigen (other types of HP) (symptoms and signs may occur 4-8 hours after exposure to the antigen and disappear spontaneously after removal from the environment)
3 Immunological examination (positive if one of two is present)
Presence of specific antibodies to offending antigen
Positive lymphocyte proliferative response to offending antigen
4 Inhalation challenge (positive if one of two is present)
Positive natural challenge to environment
Positive bronchial challenge to offending antigen
5 Pathological findings (positive if two of three are present)
Granuloma formation
Alveolitis
Masson's body

* Chest x ray film might be normal if symptoms are mild.

PO_2 = oxygen tension; RSR = red cell sedimentation rate; CRP = C-reactive protein; BAL = bronchoalveolar lavage.

Definite HP = if either 1 + 2 + 4 or 1 + 2 + 3 + 5 is positive; probable HP = if three criteria including 1 are positive; possible HP = if two criteria including 1 are positive.

Table 2 Occupational hypersensitivity pneumonitis in Japan (115 cases in the 1980s)

Industry or occupation	Cases (n)	Identified aetiology	Cases (n)
Agriculture:	79		
Farmer	68	<i>Micropolyspora faeni</i> and <i>Thermoactinomyces vulgaris</i>	26
		<i>Micropolyspora faeni</i>	12
		<i>Thermoactinomyces vulgaris</i>	11
		<i>Candida albicans</i>	1
		Others*	3
Mushroom worker	3	Mushroom spores	2
Greenhouse worker	4	<i>Aspergillus glaucus</i> †	1
		<i>Sphaerotheca fuliginea</i>	1
		<i>Aspergillus fumigatus</i>	1
Others	4	Agricultural chemicals	1
		Silkworms	1
Industry handling chemicals:	19	Toluene diisocyanate‡	5
		Organic solvent	1
		Antioxidant	1
Polyurethane painter	7		
Welder	4		
Car repairer	3		
Petrochemical plant worker	3		
Furniture maker	1		
Electrical product maker	1		
Other manufacturing industry:	7		
Baker	1	Wheat flour	1
Noodle maker	1	Buckwheat flour	1
Soy sauce brewer	1	<i>Aspergillus oryzae</i>	1
Shell-buttons maker	1	Shell dust	1
Straw mat maker	1	Moulds §	1
Carpenter	1		
Craftsman using bagass	1	<i>Thermoactinomyces vulgaris</i>	1
Office worker and others:	10		
Ventilation pneumonitis in work place	5		
Bird shop worker (bird fancier's lung)	1	Budgerigar droppings	1
Water purification plant worker	1		
Bed clothes laundry worker	1	Moulds ¶	1
Others	2		
Total	115		75

Unmarked aetiological agents were identified by precipitating antibodies.

* Others include *Mucor* species, *Aspergillus* species, *Cryptosporidia corticatae*. Detected antigens were not mentioned in another seven cases with positive precipitins.

† Inhalation test was applied.

‡ Two cases were identified by inhalation test, another two were by lymphocyte proliferation test, and another was by precipitating test.

§ The case reacted to *Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *Alternaria kikuchiana*, *Aspergillus oryzae*, *Cryptococcus neoformans*.

¶ The case reacted to *Aspergillus fumigatus*, *Cladosporium* species, *Penicillium* species.

653 were definite and 182 were probable. Of the other 128 cases, 99 were diagnosed as possible HP and 29 as cases of other lung diseases. In the present study, 835 cases of definite and probable HP (total HP) and 99 possible cases of HP were subjected to analysis and presented as a case series of HP, not as a population based study. All the data obtained were on patients at the symptomatic stage of the disease.

Precipitin analysis was conducted with the double diffusion method as previously described.²¹ Antigens used were commercially available and consisted of 10 antigens related to HP and six antigens to *Aspergillus* species (Hollister-Steir, Spokane, Washington), or antigens were prepared in each hospital, as required. Serum antibodies to *Trichosporon cutaneum* were assayed in 262 cases of summer HP in the First Department of Internal Medicine, Kumamoto University School of Medicine, with the indirect fluorescent antibody method described elsewhere.¹⁹ The procedure of antigen challenge was not standardised.

Analysis by χ^2 was conducted as required.

Results

HP IN JAPAN

During the 1980s 835 patients with HP were identified in Japan. Of these 621 cases (74.4%) had summer HP; 68 cases (8.1%) had farmer's lung; 36 cases (4.3%) had ventilation pneumonitis (28 humidifier lung and eight air conditioner lung); 34 cases (4.1%) had bird fancier's lung; 19 cases (2.3%) had other types of HP; and 57 cases (6.8%) had HP of unknown aetiology. Summer HP was the most frequent type of HP and the number of these patients doubled in the second half of the 10 year period from 205 cases in 1980-4 to 416 cases in 1985-9.

OCCUPATIONAL HP

One hundred and fifteen cases (13.8%) were related to work. Table 2 shows a list of occupations, industries involved, and causative agents. Farmer's lung (68 cases; 59%) was the most frequent among them. Ninety one per cent were identified in the northern part of Japan, at a latitude of 38° or over and 9% were identified in Kagoshima Prefecture in southern Japan. Most cases in the north of Japan were related to *Saccharopolyspora rectivirgula* (formerly known as *Micropolyspora faeni*) or *Thermoactinomyces vulgaris* whereas those in the south were related to *Candida* species or *Mucor* species. The number of cases identified each year was almost constant (6.8 (2.6)) but the ratio to total number of cases of HP decreased from 9.5% (6/63) in 1980 to 3.7% (5/134) in 1989. Cases in women accounted for 44% of classic farmer's lung and 71% of other types of farmer's HP. The agricultural working population was reduced by more than one million people during the 1980s (6.3% of total working population) and the ratio of women to men labourers was six:four.²³

Table 3 Diagnostic aspects of hypersensitivity pneumonitis (HP) in Japan

Types	Cases (n)	Definite (%)	Clinical features	Observed frequency (%)			
		definite+probable		Environmental condition	Immunological examination	Inhalation challenge	Pathological findings
Summer HP	621	83*	100†	96†	61*	76†	52†
Farmer's lung	68	78	100	99	88‡	50‡	51
Ventilation HP	36	70	100	80	17‡	72	51
Bird breeder's HP	34	76	100	100	76	65	50
Other HP	19	74	100	84	63	78	61
Unknown aetiology	57	40‡	100	63‡	16‡	72	49
Total HP	835	78	100	93	59	74	52
Possible HP	99	—	100	58§	6§	3§	33§

*The variation among types was significant with χ^2 test ($P < 0.005$).

†The variation among types was not significant.

‡Significantly different from the other types of HP with χ^2 test ($P < 0.005$).

§Significantly different from those of total HP with χ^2 test ($P < 0.005$).

As mushrooms are usually cultivated indoors in Japan, workers are exposed to concentrated spores such as *Lentinus edodes* (Shiitake) or *Pholiota nameko* (Nameko) and specific contaminants such as *Aspergillus glaucus*, from which HP may result.²⁴⁻²⁷ Total floor space of greenhouses increased by 150% in the 1980s and cases of greenhouse worker's HP were identified.²⁸ These workers are exposed to concentrated pollen as well as microorganisms in the closed environment.

The number of agents causing HP, including inorganic chemicals, increased during the 1980s.²⁹ The first case of HP related to isocyanates in Japan was reported in 1981 and the number of cases newly identified each year has grown.³⁰⁻³¹ Bagassosis was the first HP recognised in Japan,³² and occurrences in sugar refineries have now disappeared.³³ A new case (a lacquer craftsman identified in this study) was not unexpected.³³

We also reviewed 99 possible cases of HP, and adverse environments were identified in 57 of them. These 57 cases included 40 cases of non-occupational HP (36 summer HP, two bird fancier's lung, one ventilation pneumonitis, and one drug induced HP) and 17 of occupational HP (nine farmer's lung, three related to toluene diisocyanate, three agricultural HP of two silkworm growers and one mushroom worker, one straw mat maker, and one textile worker).

DIAGNOSTIC ASPECTS

To evaluate our diagnostic criteria and to estimate the need for a more precise diagnosis, we noted the frequency of each type of HP diagnosed by each of the criteria (table 3). The frequency of HP of unknown aetiology (40%) was significantly lower than other types of HP (70%–83%) in the definite cases ($P < 0.005$). The reason why only 40% of the cases of unknown aetiology were definite (although 72% (41/57) were positive on natural inhalation challenge) was that 18 of these 41 positive cases were not related to adverse environmental conditions (table 3), but to homes or offices in winter without air conditioners. When a patient had recurrent HP on natural challenge tests and worked in adverse environmental conditions (table 3) the case was regarded as definite even if the antigen

was not identified by clinical features, immunological examination, or pathological findings. These have been categorised as confirmed types of HP—for example, summer HP—and not as HP of unknown aetiology. The observed frequency is the ratio of cases with positive results to total cases (including those examined and not examined)—that is, the positive rate (positive cases/examined cases) multiplied by examined frequency. The observed frequency of clinical features was 100% (see previous reports for details of the characteristics¹⁸⁻¹⁹). Only the variation in immunological examination was significant for different types of HP (table 3, $P < 0.005$). For possible HP only clinical features were not significantly lower than for total HP, and the difference was most obvious for immunological examination and inhalation challenge.

Environmental conditions

Among 57 cases of unknown aetiology, 15 were cases where workers were exposed to organic dust, 13 to chemicals or solvents, and the other 29 were related to office or home environments if they were not typical summer HP, ventilation pneumonitis, or bird fancier's lung.

Immunological examination

Table 4 shows the analysis of the frequency and positive rate of specific antibodies shown in table 3. The variation of positive rate for farmer's lung (94%), ventilation pneumonitis (18% (21% of these were humidifier lung and 0% air conditioner lung)), and HP due to unknown aetiology (28%) were significant ($P < 0.005$). Both frequency and positive rate were significantly lower for possible than total cases of HP. Table 2 lists the identified antigens. A lymphocyte proliferative response test was carried out in a few people. Out of 20 cases in which the subject's humidifier water was searched for antigens, only two cases of humidifier lung reacted to the isolates (*Cephalosporium acremonium* and *Candida* species). Nine cases that were antibody positive but of unknown aetiology were those who reacted to commercially available common antigens without useful environmental information.

Table 4 Observation of specific antibodies

Types	Cases examined (n)	Examined frequency (%)	Positive rate (%)	Observed frequency (%)
Summer HP	490	79*	77†‡	61†
Farmer's lung	64	94§	94§	88
Ventilation pneumonitis	34	94	18§	17§
Bird breeder's lung	29	85	90	76
Other	14	72	87	63
Unknown aetiology	32	56§	28§	16§
Total HP	660	79	75	59
Possible HP	51	52¶	12¶	6¶

*The variation among types of HP with χ^2 test was NS.

†The variation among types of HP was significant with χ^2 test ($P < 0.005$).

‡Average of positive findings of 99.2% in 262 cases examined by indirect fluorescent antibody test to *Trichosporon cutaneum* in Kumamoto University School of Medicine¹⁸ and of 52.2% in 228 cases by precipitating antibody test to *Trichosporon cutaneum* or to other unrelated antigens.

§Significantly different from the other types of HP with χ^2 test ($P < 0.005$).

¶Significantly different from the other types of HP with χ^2 test ($P < 0.005$).

Inhalation challenge

The procedure of environmental challenge varied in every case but was carried out for 91% of the total cases of HP without significant variation between the types of HP (82%–95%) and on 62% of the possible cases of HP ($P < 0.005$). False negatives were attributed to out of season summer HP, prior medication with a steroid, prior removal of an aetiology (humidifier or birds), or too short a provocation time. The observed frequency of positive inhalation challenge was significantly lower in cases of farmer's lung (50%, $P < 0.005$), although we could find fault with the challenge itself. Bronchial challenge to an offending antigen was conducted in 33 cases (4%). These subjects were also examined for environmental challenge.

Pathological findings

Pathological examination was made on 83% of the total cases of HP and 78% of possible HP. The results were positive for 52% and 33% ($P < 0.005$) of the observed frequencies, respectively. The pathologies of possible HP were less specific than those of total HP. We screened cases for organic dust toxic syndrome (ODTS) among 200 people with alveolitis alone and 29 with normal findings. One carpenter was suspected to have ODTS and one textile worker byssinosis.

Discussion

In Japan, the first epidemiological study of HP was conducted in 1980.³⁴ There were 59 cases of HP, of which 42 were suspected to be summer HP. The occupations or environments of the cases with other types of HP were not identified. The objective of the present nationwide survey was to design diagnostic criteria that cover all types of Japanese HP and draw up a comprehensive list of occupations and their aetiological antigens.

OCCUPATIONAL HP

More than 50 different occupational and environmental sources of antigens associated with HP were described. In agriculture in Japan, new methods led to an increase in the number of female patients with HP and induced new types of HP such as mushroom worker's lung (due to mushroom spores^{24, 25} or specific cont-

aminants²⁶ instead of thermophilic actinomycetes²⁷) and greenhouse worker's lung.²⁸ These are related to indoor farming, where the closed environment is a risk factor for respiratory diseases, as noted in other countries.³⁵ Farmer's lung was an important problem in northern Japan where the main antigens were thermophilic actinomycetes.^{19, 36} Findings in the southern part of Japan differed as the climate is warmer.^{19, 37} Although silk-worm farming is not as common in Japan as in the past,³⁸ among Chinese workers over 200 000 have been exposed to high (13–328 mg/m³) concentrations of silk dusts, and there is a high prevalence of respiratory signs and symptoms. A survey of HP among these workers has apparently not been documented (personal communications).

Despite increasing numbers of cases of HP in industries in Japan where isocyanates are extensively used in the manufacture of cars, upholstery, and polyurethane foam, workers and health administrators have only a superficial understanding of HP induced by isocyanates.^{29–31} Although an in vitro diagnostic technique is not available yet, up to date knowledge and precise observations about temporal relations between exposures and typical illness should help to identify potential cases in high risk occupations and to prevent the disease.

DIAGNOSTIC ASPECTS

The clinical features of HP were well documented. Related symptoms are often mistaken for those of bacterial or viral pneumonia and an accurate diagnosis of chronic cases can be difficult. An attempt by the EEC Working Party showed wide differences in the diagnosis of chronic farmer's lung.³⁹ Our diagnostic criteria should assist physicians to make a correct diagnosis, and are based on the guidelines reported by the subcommittee on HP in 1989.⁸ The proposed criteria may be less useful for the diagnosis of mild or chronic forms of HP. We also recognise the following weaknesses in our diagnostic criteria; any diffuse lung disease will satisfy the clinical features and common diffuse lung disease (sarcoidosis), will satisfy the pathological findings, and it may be argued that the presence of precipitating antibodies should not be an inclusion criterion. We think that clinical features are important to avoid false negatives. To make differential diagnosis correctly, we sent the questionnaire to members of the research committee or leaders authorised and verified by the Japanese Society of Chest Diseases. There were 29 (3%) false positive cases (other lung diseases). We think that the presence of antibodies to *Trichosporon cutaneum* is significant in summer HP as opposed to other lung diseases that occur in humid homes in summer because these antibodies were identified in 99.2% of cases with summer HP but in none of 100 cases with other lung diseases or of 100 normal subjects.^{18, 21} Most authors from other countries^{8–15} refer to difficulties in establishing diagnostic criteria for epidemiological studies on the prevalence of HP. Our

proposed criteria were designed for a case series study, and would require modification for use in a population based epidemiological study. With evaluation of each of the criteria, we confirmed the key to diagnosis as follows.

A precise environmental history—that is, an observable pattern of recurrent HP illness (clinical features) in relation to exposures—is essential for an accurate diagnosis of HP. The presence of precipitating antibodies to inhaled antigens was useful evidence in confirming the diagnosis of HP when environmental history and characteristic clinical features were present. Specific antibodies were found in more than 85% of cases examined when an adequate antigen panel was used but only 30% were recognised when an inadequate antigen panel was used. Based on these results, we stress that precipitin tests should not be relied on to replace the history and are not useful as a screening method when conducting epidemiological studies. We suggest that an antigen panel that matches variations in exposure in each country be prepared. Pepys indicated that commercially supplied antigen extracts from the United States for use in tests in HP had been inadequate for practical use in the United Kingdom and that appropriate standardised reference materials were needed to make comparisons between findings in different situations and in different countries.¹ We are designing an antigen panel to cover most types of HP in Japan that will be useful for epidemiological studies and comparison with data from other countries.

We conclude that although the criteria we proposed are not complete for a population based epidemiological study, the new data will be useful for clinicians to make an accurate diagnosis of occupational HP and will pave the way for further epidemiological studies of HP.

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- Pepys J. Antigens and hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1978;61:201-3.
- Pepys J. Hypersensitivity diseases of the lung. *Monogr Allergy* 1969;4:1-147.
- Fink JN. Hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1984;74:1-10.
- Rose C, King TE Jr. Controversies in hypersensitivity pneumonitis. *Am Rev Respir Dis* 1992;145:1-2.
- Pitcher WD. Southwestern internal medicine conference; hypersensitivity pneumonitis. *Am J Med Sci* 1990;300:251-66.
- Fink JN. Epidemiologic aspects of hypersensitivity pneumonitis. *Monogr Allergy* 1987;21:59-69.
- Lopez M, Salvaggio JE. Epidemiology of hypersensitivity pneumonitis/allergic alveolitis. *Monogr Allergy* 1987;21:70-86.
- Richerson HB, Bernstein IL, Fink JN, Hunninghake GW, Novoy HS, Reed CE, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis: report of the subcommittee on hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1989;84:839-44.
- Fink JN. Hypersensitivity pneumonitis. In: Merchant JA, Bohelecke BA, Taylor G, eds. *Occupational respiratory diseases*. Washington DC: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 1986:481-500.
- Marx JJ Jr, Emanuel DA, Dovenbarger WV, Reinecke ME, Roberts RC, Treuhaft MW. Farmer's lung disease among farmers with precipitating antibodies to the thermophilic actinomycetes: a clinical and immunologic study. *J Allergy Clin Immunol* 1978;62:185-9.
- Solal-Celigny PH, Laviolette M, Hebert J, Cormier Y. Immune reactions in the lungs of asymptomatic dairy farmers. *Am Rev Respir Dis* 1982;126:964-7.
- Terho EO. Diagnostic criteria for farmer's lung disease. *Am J Ind Med* 1986;10:329.
- Depierre A, Dalphin JC, Pernet D, Dubiez A, Faucompre C, Breton JL. Epidemiological study of farmer's lung in five districts of the French Doubs province. *Thorax* 1988;43:429-35.
- Malmberg P, Rask-Andersen A, Hoglund S, Kolmodin-Hedman B, Guernsey JR. Incidence of organic dust toxic syndrome and allergic alveolitis in Swedish farmers. *Int Arch Allergy Appl Immunol* 1988;87:47-57.
- Muller VS. Diagnostische Aspekte der allergischen Alveolitis. *Z Gesamte Inn Med* 1990;45:581-4. (In German)
- Ando M. Summer-type hypersensitivity pneumonitis. In: Sharma OP ed. *Lung disease in the tropics. Lung biology in health and disease*. New York: Marcel Dekker, 1991:449-78.
- Kawai T, Tamura M, Murao M. Summer-type hypersensitivity pneumonitis: a unique disease in Japan. *Chest* 1984;85:311-7.
- Ando M, Arima K, Yoneda R, Tamura M. Japanese summer-type hypersensitivity pneumonitis: geographic distribution, home environment, and clinical characteristics of 621 cases. *Am Rev Respir Dis* 1991;144:765-9.
- Ando M, Konishi K, Yoneda R, Tamura M. Difference in the phenotypes of bronchoalveolar lavage lymphocytes in patients with summer-type hypersensitivity pneumonitis, farmer's lung, ventilation pneumonitis, and bird fancier's lung: report of a nationwide epidemiologic study in Japan. *J Allergy Clin Immunol* 1991;87:1002-9.
- Yoshida K, Ando M, Sakata T, Araki S. Environmental mycological studies on the causative agent of summer-type hypersensitivity pneumonitis. *J Allergy Clin Immunol* 1988;81:475-83.
- Shimazu K, Ando M, Sakata T, Yoshida K, Araki S. Hypersensitivity pneumonitis induced by *Trichosporon cutaneum*. *Am Rev Respir Dis* 1984;130:407-11.
- Yoshida K, Ando M, Sakata T, Araki S. Prevention of summer-type hypersensitivity pneumonitis: effect of elimination of *Trichosporon cutaneum* from patient's homes. *Arch Environ Health* 1989;44:317-22.
- The Tsuneta Yano Memorial Society. Labor. In Arima H, ed. *Nippon: a charted survey of Japan 1993/1994*. Tokyo: The Kokusei-sha Corp; 1993:50-63.
- Nakazawa T, Kanatani K, Umegae Y, Fueki R, Kobayashi S. Mushroom worker's lung due to inhalation of spores of the *Cortinus schiitake*. *Japanese Journal of Chest Diseases* 1981;11:934-8. (In Japanese.)
- Nakazawa T, Tochigi T. Hypersensitivity pneumonitis due to Mushroom (*Pholiota nameko*) spores. *Chest* 1989;95:1149-51.
- Yoshida K, Ando M, Ito K, Sakata T, Arima K, Araki S, Uchida K. Hypersensitivity pneumonitis of a mushroom worker due to *Aspergillus glaucus*. *Arch Environ Health* 1990;45:245-7.
- Sakula A. Mushroom-worker's lung. *BMJ* 1967;3:708-10.
- Yoshida K, Ueda A, Yamasaki H, Sato K, Uchida K, Ando M. Hypersensitivity pneumonitis resulting from *Aspergillus fumigatus* in a greenhouse. *Arch Environ Health* 1993;48:260-2.
- Bernstein IL. Isocyanate-induced pulmonary diseases: a current perspective. *J Allergy Clin Immunol* 1982;70:24-31.
- Yoshizawa Y, Ohtsuka M, Noguchi K, Uchida Y, Suko M, Hasegawa S. Hypersensitivity pneumonitis induced by toluene diisocyanate: sequelae of continuous exposure. *Ann Intern Med* 1989;110:31-4.
- Hujimura N. Hypersensitivity pneumonitis induced by chemical substances. *Igaku No Ayumi* 1992;162:775-80. (In Japanese.)
- Tsugu M. Studies on bagassosis. *Iryo (Japanese Journal of the National Medical Service)* 1969;23:26-38. (In Japanese.)
- Ueda A, Aoyama K, Ueda T, Obama K, Ueno T, Hokama S, Nomura S. Recent trends in bagassosis in Japan. *Br J Ind Med* 1992;49:499-506.
- Murao M, Tamura M, Kawai T, Honma Y, Takishima T, Konno J, et al. A clinical study of hypersensitivity pneumonitis in Japan. *Japanese Journal of the Thoracic Soc* 1980;18:373-80. (In Japanese.)
- Zhou C, Hurst TS, Cockcroft DW, Dosman JA. Increased airways responsiveness in swine farms. *Chest* 1991;99:941-4.
- Tamura M, Konishi K, Komuro A. Prevalence of farmer's lung disease and antibodies to thermophilic actinomycetes in an Iwate farming population. In: Oda T, ed. *Internal medicine. Excerpta medica*. Amsterdam: Elsevier, 1986:99-105.
- Ueda A. Farmer's lung in Kagoshima Prefecture. *Chikusan No Kenkyu* 1990;44:512-30. (In Japanese.)
- Nakazawa T, Umegae Y. Sericulturist's lung disease: hypersensitivity pneumonitis related to silk production. *Thorax* 1990;45:233-4.
- Farebrother MJB, Kelson MC, Heller RF. Death certification of farmer's lung and chronic airway diseases in different countries of the EEC. *Br J Dis Chest* 1985;79:352-60.