Pulmonary Mycotoxicosis*

Dean A. Emanuel, M.D., F. J. Wenzel, B.S., and B. R. Lawton, M.D.

Mycotoxicosis is a term used to define a toxic reaction due to the ingestion of toxins produced by fungi. Oral ingestion, however, may not be the sole means of exposure. We have recently observed ten patients who had inhaled massive amounts of fungi, which resulted in an apparent toxic pulmonary reaction. Immunologic studies showed no sensitivity to various fungal antigen preparations and histologic study of the lung showed a multifocal acute process, with primary involvement of the terminal bronchioles containing large numbers of various spores. Cultures from lung biopsy material revealed at least five fungal organisms. A one to ten year followup indicates that avoidance of massive reexposure to fungal dust is the key to the prevention of recurrent pulmonary mycotoxicosis.

Mycotoxicosis, a term familiar to veterinarians and agricultural workers, refers to a toxic reaction or poisoning due to the ingestion of toxins produced by fungi.[1,2] Mycotoxins may also be injurious to plants.[3,4] Reports of human mycotoxicosis have been mostly associated with oral ingestion.[5-8] In the Ukrainian Soviet Socialist Republic, however, inhalation was recognized by Samsonov[9] as another important route of entry. Our own experience supports that of Samsonov.

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Ten patients (nine male and one female) ages 16 to 56 years were exposed to massive fungal inhalation in their silos, and have been observed for one to ten years (Table 1). Their duration of illness ranged from a few days to four weeks, and the history was strikingly similar. They had all cleaned the mold from the top of silos prior to feeding the forage to livestock. Once the silo has been filled, it is a common practice to cover the silage with a large plastic sheet and then blow additional silage over the sheet to secure it. This seals the inner silage, protecting it from spoilage. The top layer becomes extremely moldy from exposure, and must be removed before the good silage can be fed to livestock. All ten patients had inhaled large quantities of airborne material while removing the moldy outer silage, and their clothing was covered with white dust consisting mostly of fungal hyphae and spores.

*From the Marshfield Medical Foundation and the Marshfield Clinic, Marshfield, Wis.

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Reprint requests: Dr. Emanuel, 510 St. Joseph's Avenue, Marshfield, Wisconsin 54449

Case Reports

Case 1

A 40-year-old healthy, nonsmoking, white farmer developed burning in his eyes, throat, and chest after exposure to extremely moldy silage. There was no wheezing or dyspnea. The exposure lasted for about an hour. He worked in fresh air for the remainder of the day. In the evening, he developed chills, fever, and a dry, irritating cough. He felt worse the next morning and complained of extreme malaise, weakness, and his cough became very distressing. Two of his children, ages five and nine years, were playing in the barn at the base of the silo chute and were also exposed. They became ill with fever and cough. Their exposure was minimal and the symptoms resolved in a short time. They developed transient leukocytosis, but findings on their chest roentgenograms remained normal.

The farmer was seen 24 hours after exposure. He was acutely ill, and coughed excessively. His blood pressure was 130/60 mm Hg, pulse rate 100 beats per minute, and temperature 38.5° C. His conjunctivae were diffusely inflamed, and the mucous membranes of his nose and throat were intensely injected. The tonsils were slightly enlarged, but no exudate was noted. There were numerous crepitant râles heard throughout both lungfields, but no wheezing, cyanosis, or other evidence of bronchospasm. The remainder of his physical examination revealed no other abnormalities. The chest roentgenogram on admission to the hospital revealed reticular and fine nodular densities scattered throughout the lower two-thirds of both lungfields, compatible with interstitial pneumonitis (Fig 1). Findings on previous chest roentgenograms were normal. The white blood cell count was 15,750/cu mm, with 78 percent segmented neutrophils, 17 percent lymphocytes, 4 percent monocytes and 1 percent eosinophils.

The following day, bronchoscopy and a limited pulmonary biopsy were performed. The tracheobronchial tree was markedly hyperemic throughout. The exposed lung was somewhat firm on palpation. Biopsy specimens were submitted for histopathologic and microbiologic study.

On histologic examination there was a multifocal acute process which appeared related, for the most part, to the terminal bronchioles, the alveoli, and interstitial areas (Fig

Table 1—*Data of Patients with Pulmonary Mycotoxicosis*

Case, No	Age, Yrs	Sex	Exposure, Date	Temp, °C	Illness, Duration	WBC/mm³	X-ray Film Findings	Biopsy
1	40	M	Aug '63	38.3	2 wk	4,300	diffuse interstitial disease, lower 2/3 both lungs	acute interstitial pneumonitis & bronchitis, many fungi
2	45	M	Aug '72	37.8	30 da	12,300	diffuse interstitial disease, some fine nodular disease	0
3	16	F	Aug '72	39.6	10 da	5,700	normal	0
4	50	M	July '71	37.0	1 mo	7,700	diffuse interstitial disease, calcified granulomata	0
5	32	M	Aug '71	37.8	9 da	8,800	diffuse interstitial disease	0
6	41	M	Aug '72	37.0	7 da	4,300	normal	0
7	55	M	Oct '72	37.0	14 da	7,000	normal	0
8	30	M	May '72	38.9	10 da	7,700	normal	0
9	56	M		37.0	30 da	5,000	normal	0
10	17	M	Aug '71	39.1	10 da	11,000	diffuse interstitial disease, lower lobes	0

2). Most of the bronchioles were filled with an exudate composed of neutrophils and numerous histiocytes. The exudate extended into the surrounding interstitial tissues as well as into a number of the alveoli, with extensive consolidation in some areas. There were a few scattered plasma cells, chiefly in the interstitial tissue and about the small blood vessels and bronchi. Aggregates of lymphocytes were also seen in these areas. Many corpora amylacea were present in the alveoli. They seemed to be more numerous in the areas involved by the exudate, but they were also seen in areas where there was no inflammatory reaction.

Methenamine silver stains (Fig 3) demonstrated a large

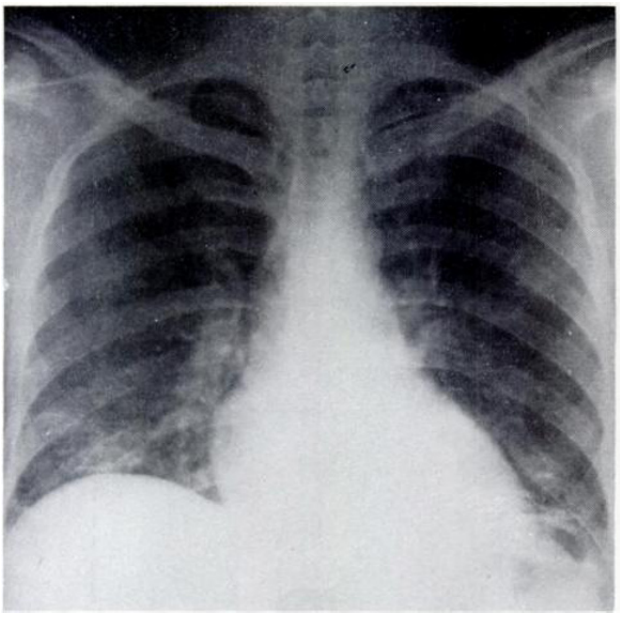

FIGURE 1. Chest x-ray film 24 hours after massive exposure to mold. *Note* reticular and fine nodular densities scattered throughout lower two-thirds of both lungfields compatible with interstitial pneumonitis.

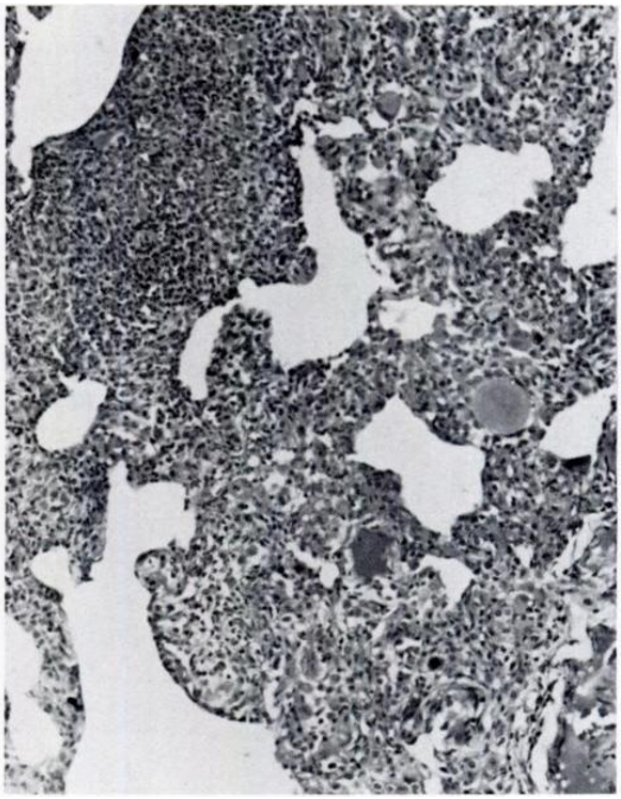

FIGURE 2. Diffuse interstitial pneumonitis (H & E stain × 40).

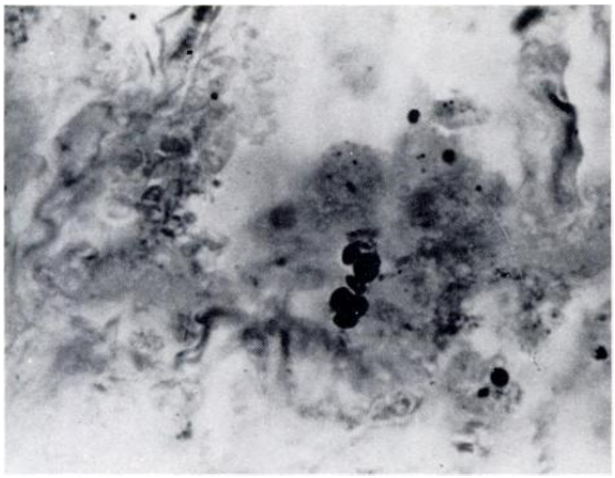

FIGURE 3. Fungal elements found scattered throughout lung parenchyma varying in size from 1 to 10 μ in diameter (silver methenamine $\times$ 1,200).

number of stained organisms, generally ovoid in shape, measuring from 1 to 9 μ in their greatest diameter. They were located in the areas of acute inflammatory reaction, as well as in the bronchioles.

Culture of the lung biopsy on blood agar was performed at 22° C and 37.5° C and revealed an amazing array of organisms (Fig 4). At least five different fungi were noted, one of which was of the genus Fusarium and another of the genus Penicillium.

The patient was carefully observed in the hospital for a week following his biopsy. Because of the unusual nature of his illness it was elected not to treat him with antibiotics or steroids. There was a gradual improvement in his fever and cough, and his followup chest x-ray films showed continued clearing over the next few weeks. The patient has been examined at frequent intervals for the last ten years and has not developed serologic evidence of hypersensitivity to the thermophilic actinomycetes, moldy hay, or moldy forage. He has continued farming but has carefully avoided the silo or exposure to the molds present in the silage. He has had no further illness.

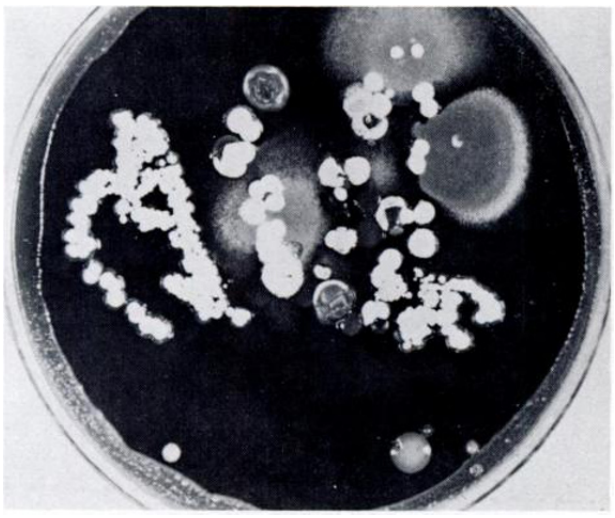

FIGURE 4. Culture of fresh lung biopsy material on blood agar at 22° C. At least five different types of microorganism can be seen.

CASE 2

A 45-year-old white farmer became ill on Aug. 2, 1972. On the day of his illness he cleaned the top of his silo, assisted by his 16-year-old daughter. The silo was filled with haylage in June and covered with a plastic sheet. During the removal of the moldy material the patient and his daughter were exposed to a large amount of white mold that completely filled the air, the silo chute and the adjacent areas. He noted some irritation of his eyes, nose, and throat, but no particular dyspnea or wheezing. That same evening he developed a temperature of 39.8° C and a harassing, dry cough. His fever and cough persisted for three days. He was seen as an outpatient three days following his exposure.

Physical examination at that time revealed a temperature of 37.4° C. His nose and pharynx were diffusely injected. No evidence of expiratory wheeze was noted, although there were numerous crepitant râles present throughout both lungs.

His chest roentgenogram revealed minimal interstitial change, confined to the lower two-thirds of both lungs. Laboratory studies revealed a white blood cell count of 12,300/cu mm, with 62 percent segmented neutrophils, 3 percent eosinophils, and 35 percent lymphocytes. Serologic studies for farmer's lung were negative. A followup chest roentgenogram on Aug. 13, 1972 revealed slight clearing of the interstitial disease. His temperature had returned to normal and his cough was subsiding.

The patient has been examined at three-month intervals since his initial exposure. His findings on chest roentgenogram have returned to normal. Results of serology tests remain negative to a battery of the thermophilic actinomycetes, a crude extract of moldy hay, and five Aspergillus organisms. He has continued farming and has had no further illness but has avoided exposure to mold, especially in his silo.

CASE 3

A 16-year-old white girl was exposed to a large amount of white mold while helping her father (the patient in case 2) clean the silo. She developed some irritation of her nose and throat and burning sensation in her chest. That evening she developed a fever of 39.6° C and a dry cough. She was seen as an outpatient three days later. Her temperature remained at 39.6° C. She complained of headache, generalized malaise, and a dry cough.

Physical examination revealed blood pressure of 134/70 mm Hg, pulse rate 120 beats/min, and temperature 39.6° C. There were occasional râles heard on deep inspiration in the lower one-third of the lungs, but no expiratory wheeze. The patient was, however, moderately tachypneic at rest, with a respiratory rate of 40/min.

Her chest roentgenogram revealed no interstitial infiltrate. Her white blood cell count was 15,700/cu mm, with 86 percent neutrophils, 12 percent lymphocytes, and 2 percent monocytes. No eosinophils were found. Serologic studies with the farmer's lung panel were negative. Because of the acuteness of her illness therapy was started with 25 mg of methylprednisolone, which was decreased 4 mg per day over a six-day period.

On Aug. 13, 1972 her temperature had returned to normal and she was feeling much better. Her cough, although improved, was still present. Findings on a repeated chest roentgenogram remained normal.

The patient has been examined at frequent intervals since that time and results of serology have remained negative to the farmer's lung antigen panel. She has developed no

further respiratory disease, although she does avoid exposure to moldy silage.

Discussion

More fungi that produce toxic metabolites are discovered every day.[10] Brook and White[11] estimated that 19 species of fungi are known to produce natural poisoning of animals, and 68 other species contain substances that are toxic when fed experimentally. It has also been estimated that there are at least 97 toxic metabolites from the genus Penicillium alone and 64 toxic metabolites from the genus Aspergillus. Thus, there is a tremendous potential for these toxic substances to affect man. Both the Penicillium and Aspergillus genus have been isolated frequently from moldy hay and silage by our group.

While these toxins are usually ingested[6,7,12-15] or affect the skin, it is not inconceivable that they can affect a person through other routes of entry into the body. We propose that the patients we present were exposed to the fungal toxins via the respiratory route. Samsonov,[9] in 1960, provided observations on several cases of toxic lung disease dating back to 1927. Inhalation exposure in these subjects came from a variety of industries, including a binder twine factory, cotton seed oil processing plants, grain elevators, plants for reprocessing moldy grain, breweries, and textile mills. Samsonov proposed that this toxic lung disease was due to the inhalation of fungi from these environments. However, neither he nor our own group has conclusively ruled out the possibility of inhalation of bacterial toxins. We do suggest that the toxins were of fungal origin, since these organisms were found in the lung biopsy and no bacteria were observed or cultured. The tremendous overabundance of fungal elements as opposed to bacteria also favors toxins of fungal origin.

Both men and animals are exposed to massive concentrations of spores and molds in farm buildings. It has been estimated, for example, that moldy hay may contain over a billion spores per gram.[16] Most people are familiar with the hypersensitivity reactions produced by the inhalation of fungal spores and hyphae but the possible toxic effect of fungi has been given very little attention in the medical literature.

The similarity of the illness in all of these patients suggests a common etiology. The clinical picture of sudden acute illness without recurrence is strikingly different from that of farmer's lung disease.[17] Since all of the patients have remained well while continuing to farm, it is difficult to relate the disease to the usual type of hypersensitivity-immune reaction expected in patients with farmer's lung disease. Without question they have had continued though minimal exposure, yet none has developed further illness. On the contrary, patients with farmer's lung disease will usually suffer relapse with minimal exposure.

We have ruled out nitrogen dioxide exposure, since all of the patients became ill well beyond the usual time that nitrogen dioxide is present in the silo.

The question of a hypersensitivity-type reaction must be raised. None of the patients listed in Table 1 developed positive serologic reactions to the thermophilic actinomycetes or to extracts of fungi obtained from hay or silage. These included tests with extracts prepared from moldy silage, moldy hay, milo, Penicillium, Mucor, *Aspergillus fumigatus*, *Aspergillus clavatus*, *Aspergillus niger*, *Aspergillus sydowi*, and *Aspergillus glaucus*, as well as the thermophilic group of organisms, *Micropolyspora faeni*, *Thermoactinomyces vulgaris* (three strains), *Thermomonospora viridis*, *Thermoactinomyces sacchari*, air conditioner thermophile, pigeon serum, and *Cryptostroma corticale*. Admittedly, we may not have the correct antigen and it would have been desirable to check the serology of the patient on whom the biopsy was performed against organisms recovered from his lung. Unfortunately, such extensive serologic testing was not available to us at that time. He was tested, however, with the same species of organism as those isolated from his lung at a later date, with no precipitin found.

Further evidence of a toxic reaction is the marked inflammatory reaction and obliterative bronchiolitis observed in the lung biopsy of the patient in case 1. There was no evidence of granulomatous hypersensitivity reaction. A careful review of some 60 pulmonary biopsies performed on patients with farmer's lung in our own institution has not shown a similar pathologic picture or the presence of fungal elements.

Further studies are indicated to determine the exact nature of the fungal toxin or toxins, their short, and longterm effects on the host, in order that methods for the control of this environmental disease can be developed.

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Self-Assessment in Chest Diseases

The American College of Chest Physicians Self-Assessment Committee has prepared a comprehensive program in self-assessment in chest diseases. This examination may be obtained from the ACCP headquarters, 911 Busse Highway, Park Ridge, Illinois 60068. In addition to the subjects published in the test booklet (Volume I), the Committee has prepared the following questions. Answers appear on page 334.

Pulmonary Infarction

A 22-year-old white woman had a three-day history of increasing left lower anterior pleuritic chest pain. She denied cough, fever, chills, or hemoptysis. She had recently traveled throughout the southern and southwestern United States on a trip from Florida to California. She gave a history of intermittent occasional episodes of lower chest pain during the preceding three or four years. She was on no medications, and had not taken birth control pills during the past three years, but had previously. There was no history of other illnesses, operations or trauma. There were no known tuberculosis contacts, or acute respiratory illnesses in her family. Examination showed a pulse of 120/min, temperature 100.6° F, respiratory rate 26, and blood pressure 120/70. There was tenderness to percussion of the left anterior chest; breath sounds were diminished in intensity over this area. A few rales were audible over the left lower lung base posteriorly. Chest x-ray film showed left basilar infiltration and pleural effusion. The hematocrit was 36%; WBC 12,900 (85% Segs, 10L, 4M), and sedimentation rate 54. The alkaline phosphatase was 3.5 (N = 3.0), SGOT 13, SGPT 5, LDH 710, CPK 0.9.

1. Which of the following entities is most likely the diagnosis:
   A. Tuberculosis
   B. Virus pneumonia
   C. Pulmonary infarction
   D. Bacterial pneumonia
2. Which of the following procedures are required to determine whether an infectious pneumonitis is present?
   A. Serological tests
   B. Blood cultures
   C. Thoracentesis
   D. Sputum smears and cultures

Arterial blood gas determination showed a Po_2 of 66 mm Hg, Sat O_2 93%, Pco_2 29 mm Hg, pH 7.45, HCO_3 2/mEq/L. Cold agglutinins were negative, as were blood cultures. Sputum cultures showed normal flora. Sputum smears and concentrates for acid-fast bacteria were negative. An ECG showed sinus tachycardia. The second chest x-ray film showed both right lower and left lower lobe infiltrates and pleural effusions.

3. The diagnosis should be established by which of the following:
   A. Lung puncture, for culture of aspirated fluid
   B. Pulmonary angiography
   C. Perfusion lung scan
   D. Ventilation and perfusion lung scans