Silo Filler's Disease*

Clinical, Physiologic and Pathologic Study of a Patient

ROBERT L. MOSKOWITZ, M.D.,† HAROLD A. LYONS, M.D. *and* HAROLD R. COTTLE, M.D.
Brooklyn, New York

SINCE THE report of Delaney et al. [*1*] in 1956 of two cases of silo filler's disease, nineteen cases have been recorded. The course of these patients has ranged from rapidly fulminating death from respiratory insufficiency to mild or moderate symptoms of respiratory involvement which remitted spontaneously. There has also been described a patient in whom chronic pulmonary insufficiency developed approximately six months after initial exposure [*2*]. Five of the patients described were treated with corticosteroids. Clinical recovery followed their use and was attributed to this therapy. Eight untreated patients died, and three recovered spontaneously [*3–10*].

In the cases of silo filler's disease reported thus far, no functional or anatomic studies have been made during the acute episode and after a course of therapy. The case to be described provides information on these points.

CASE REPORT

On December 25, 1960, a twenty year old white man was hospitalized at the Kings County Hospital Center because of rapidly progressive dyspnea of two weeks' duration. The patient, a Brooklyn resident, was well until three weeks prior to admission when he entered a silo on a farm in upper New York State to get rid of some "spoiling corn silage." The silo had not been opened since the corn had been ensiled six weeks previously. He worked in the closed silo for three hours. While doing so he once noticed a fine yellow vapor arising from some of the silage. He was a little weak and dizzy at the time but continued his work. Thereafter he worked in the silo for fifteen to thirty minutes a day for almost two weeks. During this time the patient became progressively weakened and dyspneic; and toward the end of this period he began to be feverish. During the last week on the farm a hacking dry cough developed. He came home to Brooklyn after two weeks and consulted his physician who examined him and began treating him for pneumonia with tetracycline, 250 mg. four times a day. No roentgenogram or cultures were made. During the next four days his cough became productive of a small amount of yellowish sputum, and his temperature rose to 104°F. each evening, with chills. His dyspnea rapidly became more severe and progressed to being present at rest. On the day before admission his mother noticed that his lips and tongue had become blue. He was now completely incapacitated.

At the age of seven and again at the age of ten he had been hospitalized elsewhere with an illness diagnosed as acute rheumatic fever. Because of this illness he never worked after he finished high school, although he was completely asymptomatic.

The review of systems yielded no abnormalities. He had smoked ten cigarettes a day for the past four years. His parents, sister and two brothers were alive and well.

The patient was an acutely ill, anxious, thin young white man in extreme respiratory distress with marked tachypnea but without orthopnea. His blood pressure was 128/80 mm. Hg, heart rate 132 per minute and regular, respiratory rate 72 per minute and temperature 103°F., rectally. Marked cyanosis of the lips, tongue and mucous membranes of the mouth was present. Small, soft lymph nodes were palpable in each axilla and also scattered in the posterior cervical chains. Expansion of both sides of the thorax, although equal, was marked by intercostal retraction. Respiration was primarily abdominal. Scattered areas of tubular breathing and bronchophony were noted. Scattered rales and expiratory wheezes could be heard in small areas bilaterally. The heart was not enlarged, and its rhythm was regular. The pulmonic second sound was accentuated, and there was a short diastolic high-pitched blowing murmur following the second sound at Erb's point. Visceral enlargement and clubbing of the fingers were absent.

* From the Departments of Medicine and Pathology, State University of New York, Downstate Medical Center, and the Kings County Hospital Center, Brooklyn, New York. This study was supported in part by the U. S. Public Health Service Grant B 1594 (C3) and the U. S. Public Health Service Training Grant H 5485. Manuscript received February 11, 1963.

† Present address: 185 Lexington Avenue, Passaic, New Jersey.

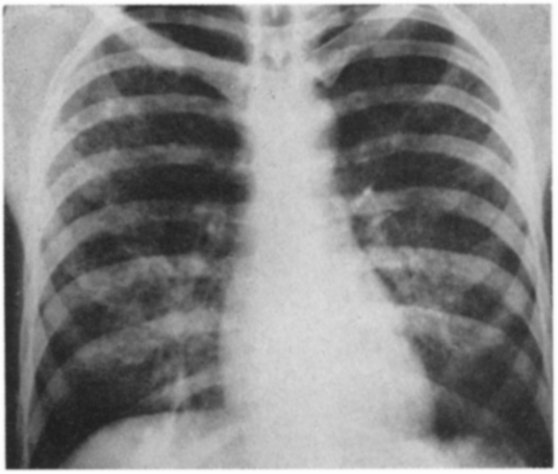

FIG. 1. Initial posteroanterior roentgenogram of chest showing diffuse parenchymal infiltration of a nodular quality throughout both lung fields.

The hemoglobin was 14 gm. per 100 ml., hematocrit 43 vol. per cent, white blood count 23,000 per cu. mm. and the differential count 6 per cent band forms, 78 per cent polymorphonuclear neutrophils and 12 per cent lymphocytes. The (Wintrobe) erythrocyte sedimentation rate was 25 mm. per hour. The urinalysis, result of a test for syphilis (Venereal Disease Research Laboratory titer), blood urea nitrogen, fasting blood sugar, serum total protein, albumin and globulin, calcium, phosphorus, sodium, potassium, chloride and cold agglutinin titers were all within normal limits. Serum carbon dioxide content was 20.5 vol. per cent, and the arterial oxygen saturation was 68 per cent. Examination of the sputum for pathologic organisms and by special stains for fungus and acid-fast organisms, and cytologic examination for tumor cells were all negative on two occasions. Material from the nose and throat and the sputum were cultured and showed growth of normal bacterial flora. Three blood cultures were negative. Results of skin tests for coccidioidomycosis, histoplasmosis and tuberculosis were all negative. Diffuse parenchymal infiltration throughout both lung fields, more dense in the central portions and slightly more extensive on the right side, were seen on the chest roentgenogram. (Fig. 1.) In most areas the infiltrate was of a fine nodular quality. An electrocardiogram indicated sinus tachycardia and a 1.5 mm. elevation of the S-T segment in leads V_4 to V_6; these abnormalities were absent five days later.

Daily treatment with 300 mg. cortisone, given intravenously, was begun. Penicillin and streptomycin were administered during the first forty-eight hours. Nasal oxygen was administered continuously. This regimen was continued for five days, when the dosage of cortisone was reduced to 150 mg. daily and given orally. The dose of cortisone was maintained at the latter level for three weeks and then was further reduced gradually during the next three months, at the end of which time therapy with the drug was discontinued.

An open lung biopsy was performed on the eighteenth day, and a 1 cm. piece of lung parenchyma from the lingula was obtained. The tissue (Fig. 2 and 3) showed a diffuse interstitial infiltration of mononuclear cells, most of which were lymphocytes. Clusters of these cells and macrophages were also present in the alveoli. The most striking observation was the presence in every bronchiole (and only there) of organizing masses of tissue, composed largely of

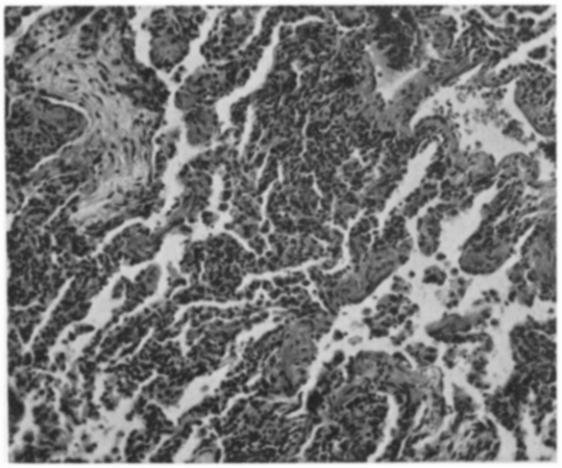

FIG. 2. Organizing bronchiolitis. Biopsy specimen of January 12, 1961, showing bronchioles containing organizing exudate (upper left) and scattered, predominantly mononuclear cells (lower right). A marked degree of chronic interstitial infiltrate is also present.

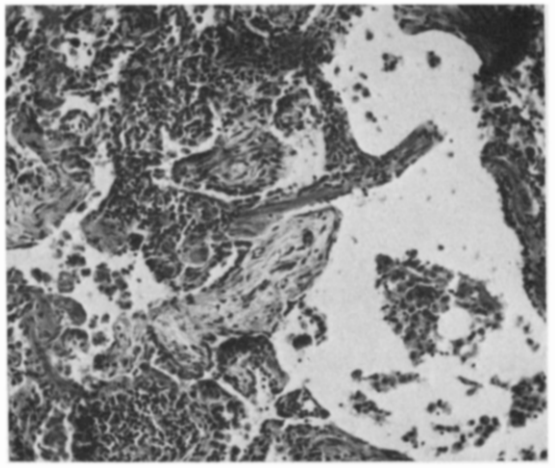

FIG. 3. Organizing bronchiolitis. Biopsy specimen of January 12, 1961, showing masses of inflammatory exudate in an unevenly distended bronchiole varying from simple aggregate (right) to predominantly fibroblastic masses (center and left).

fibroblasts, in a loose matrix within which collagen fibers were present. Bronchiolar epithelium was absent in some areas and appeared to be damaged in others. In some areas there was regenerative hyperplasia of the bronchiolar epithelium. This picture of organizing bronchiolitis, often referred to as bronchiolitis obliterans, is similar to that described in the reported cases of industrial, as well as agricultural, exposure to nitrogen dioxide fumes [*11*], and have been reproduced experimentally [*12*]. The lesion is also similar to that noted following inhalation of other irritant gases, for example, "smoke poisoning."

The patient's dyspnea diminished rapidly, cyanosis became less evident, and the respiratory rate fell to 36 per minute within twenty-four hours. The temperature became almost normal (99.6°F.) within thirty-six hours. At the end of one week, the respiratory rate was below 20 per minute. After the second week an open lung biopsy was performed. The fine nodular quality of the lesion on the chest roentgenogram became indistinct in about ten days, and the infiltration began to show resolution in about two weeks and disappeared completely in six weeks. (Fig. 4.)

The patient continued to improve and was discharged asymptomatic on the thirty-ninth hospital day. He was followed in the outpatient clinic and was readmitted six months after discharge for a second open lung biopsy. His management continues in the clinic, and he remains asymptomatic.

The open lung biopsy performed approximately six months after the start of therapy delivered an 8 cu. cm. specimen from the lower lobe of the left lung which was mechanically compressed by the biopsy technic. Microscopic examination of this specimen showed complete disappearance of exudate from all bronchioles (Fig. 5), and only minimal infiltration of the interstitium (including the interalveolar septums) by lymphocytes. Few macrophages remained in the alveoli. (Fig. 6.) A mild, unevenly distributed collagenous thickening of interalveolar septums was present, and scattered groups of abnormally enlarged air spaces, considered to represent mild centrilobular emphysema, were observed.

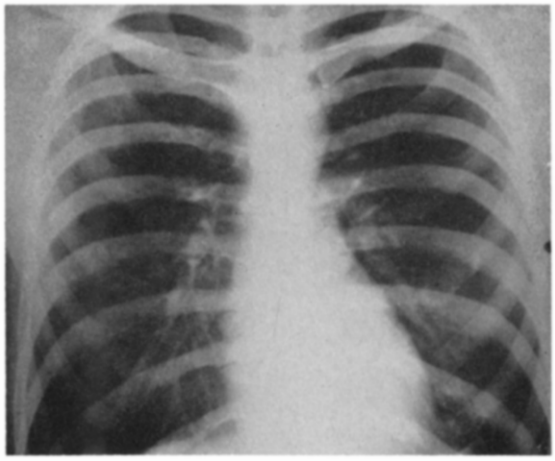

FIG. 4. Posteroanterior roentgenogram of chest (following therapy) showing complete clearing of the infiltration.

The anatomic change over the six month period confirmed the clinically evident healing of the original inflammatory process. It is noteworthy that the type and degree of emphysema present anatomically

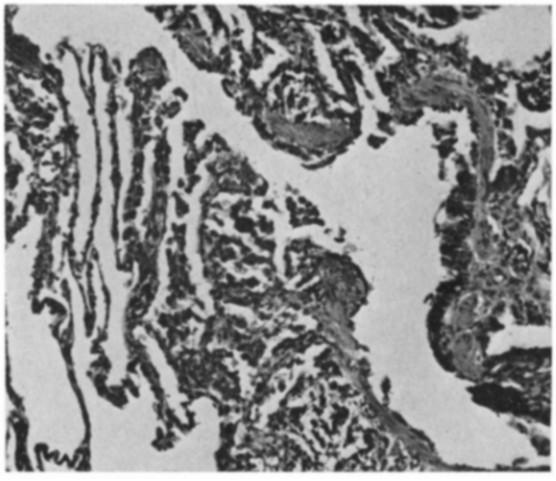

FIG. 5. Healed bronchiolitis. Biopsy specimen of July 18, 1961, showing typical bronchiole and subdivisions exhibiting disappearance of exudate from lumen. A minimal degree of diffuse interstitial lymphocytic infiltration remains, and some groups of air sacs are abnormally large (right) albeit mechanically compressed due to technic of biopsy.

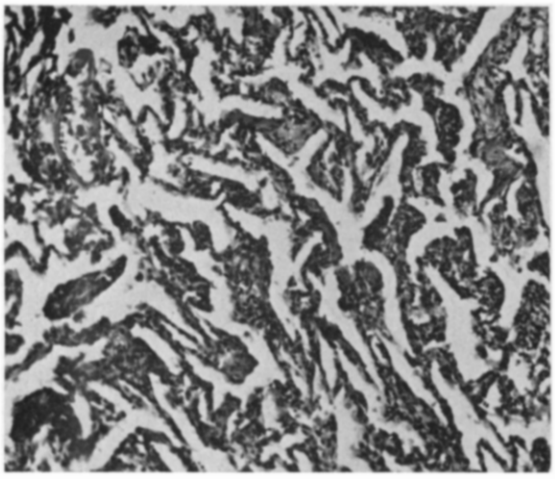

FIG. 6. Healed bronchiolitis. Biopsy specimen of July 18, 1961, showing parenchyma exhibiting (in addition to mechanical compression due to biopsy technic) unevenly distributed minimal septal thickening by collagen and small numbers of lymphocytes. Small numbers of macrophages remain scattered in alveoli.

corresponded so precisely to the implications of the pulmonary function studies, namely, that the disease had resulted in a moderate increase of inefficiently arranged air-filled spaces within the lung, although the previously impaired transit of gases through partially obstructed bronchioles and moderately altered alveolar membranes had become restored to normal.

PULMONARY FUNCTION STUDIES

Methods of Study. Determinations of the total lung capacity and its subdivisions were made using the Godart Pulmonor apparatus. Predicted normal values were based on the formulas of Baldwin et al. [*13*]. Functional residual capacity was meaured by the helium closed circuit method [*14,15*]. Dynamic ventilatory tests, including timed vital capacity, maximum breathing capacity and maximum expiratory flow rates, were carried out by the methods described by Gaensler [*16*], Baldwin [*14*] and March and Lyons [*17*]. Arterial blood was collected by placement of a Cournand needle in the brachial artery. Determinations of arterial blood gases were made by standard Van Slyke pro-

TABLE I

PULMONARY FUNCTION DATA

Pulmonary Function	Normal or Predicted	12/27/60	1/9/61	3/24/61	7/7/61	1/18/62	6/18/62
Inspiratory capacity (L.)*	2.88	1.16	...	2.32	2.22	2.67	2.10
Expiratory reserve capacity (L.)*	1.56	1.24	...	2.11	2.55	2.84	2.65
Vital capacity (L.)†							
With bronchodilators	4.45	2.41	3.50	4.15	4.65	4.25	4.70
Without bronchodilators	...	...	3.57	4.42	4.65	4.30	4.60
Functional residual capacity (L.)*	2.67	1.46	...	4.67	4.73	3.89	4.74
Residual volume (L.)*	1.11	1.21	...	2.57	2.18	1.40	1.91
Total lung capacity (L.)*	5.56	2.62	...	6.99	6.95	6.91	6.84
Timed vital capacity (% of vital capacity)							
Without bronchodilators†							
1 second	75	86	84	89	83	87	84
2 seconds	90	95	96	100	98	99	93
3 seconds	97	99	99	100	100	100	100
With bronchodilators							
1 second	75	92	87	90	88	86	85
2 seconds	90	97	98	99	98	99	98
3 seconds	97	100	100	99	100	100	100
Maximum expiratory flow rate (L./min.)*	500	224	...	392	...	391	392
Maximum inspiratory flow rate (L./min.)*	400	261	...	348	...	261	348
Maximum breathing capacity (L./min.)*	129	...	146	159	...	...	150
Tidal volume (cc.)†	500	555	...	...	630	600	510
Respiratory rate (per minute)	...	30	24	16	14	14	14
Alveolar ventilation (L./min.)*	4.0–5.0	13.7	...	...	6.58	6.30	5.04
Oxygen consumption (cc./min.)†	250	291	...	...	...	250	220
Arterial blood							
O_2 saturation at rest (%)	97	86	...	96	96.8	...	98.5
O_2 saturation with 100% O_2 (%)	99	92	...	96	97.7	...	...
CO_2 at rest (vol. %)	50–70	45.5	...	45.1	60.0	...	47.3
CO_2 with 100% O_2 (vol. %)	...	45.4	...	43.9	...	...	...
pH at rest (mm. Hg)	7.40	7.49	...	7.45	7.48	...	7.37
pH with 100% O_2 (mm. Hg)	7.40	7.44	...	7.47	...	...	...
pCO_2 at rest (mm. Hg)	40	31.2	...	34.2	34.0	...	42.3
pCO_2 with 100% O_2 (mm. Hg)	40	35.0	...	31.8	...	...	...
Hematocrit (vol. %)	...	42	...	44	42	...	...
Lung compliance (L./cm./H_2O)	0.22	...	0.167	...	...	...	...
Diffusion capacity							
CO_2/min./mm. Hg	18–25	3.63	10.81	15.48	26	...	28.9
O_2/min./mm. Hg	25–30	4.46	13.25	19.10	32	...	35.5

* These volumes are expressed as body temperature, pressure and saturation.

† These volumes are expressed as standard temperature, pressure and saturation.

cedures [*18*]. Arterial pH was determined by an Astrup Radiometer electrode at 37°C. [*19*]. Arterial carbon dioxide tensions were calculated by means of the Hastings-Singer nomogram [*20*]. Diffusion capacity was determined by the single breath technic of Forster [*21*]. Normal values for diffusion capacity in this laboratory are between 18 and 35 ml. per mm. Hg per minute.

At the first physiologic study performed two days after admission, a marked reduction in inspiratory capacity (40 per cent of predicted), vital capacity (53 per cent of predicted) and total lung capacity (47 per cent of predicted) was observed. Normal values for ventilatory function (mechanics of breathing) accompanied these changes. Values for pulmonary compliance were low, 0.167 L. per cm. of water. These data indicated a restrictive pattern without evidence of airway obstruction. The ratio of residual volume to total lung capacity was increased to 45 per cent, which is explained by the reduction in total lung capacity with maintenance of an unchanged residual volume [*22*]. Obstructive emphysema was not a cause of this alteration of subdivisions of the lung volume. Arterial oxygen saturation was 87 vol. per cent. Hypoventilation could not be a cause of this desaturation, since carbon dioxide tension was low (31.2 mm. Hg) and associated with an elevation in arterial pH (7.49). Furthermore, the rapid attainment of helium equilibrium (less than three minutes) during determination of the functional residual capacity indicated that there was no impairment of distribution of inspired air. Minimal venous admixture was considered to be present because of failure to attain maximal saturation during inhalation of 100 per cent oxygen (99 instead of 100 vol. per cent). These factors suggested strongly the presence of impairment of diffusion capacity of the lung (alveolar-capillary block), a conclusion supported by the determination of a diffusion capacity of 3.63 ml. per mm. Hg per minute (normal is 18 to 25 ml. per mm. Hg per minute). (Table I.)

Subsequent respiratory function studies, performed while therapy was continued with corticosteroids, indicated disappearance of the restrictive pattern of breathing and attainment of normal arterial blood gas values and normal pulmonary diffusion capacity.

A significant increase in functional residual capacity (from 1.46 to 4.74 L.) was present eighteen months after admission. This increase began three months after admission and suggested the presence of pulmonary hyperinflation. The normal dynamic test results on these occasions indicated the absence of any appreciable airway obstruction. (Table I.)

COMMENTS

In 1956 Lowry and Schuman reported four cases of silo filler's disease [*3*] and set forth the main features of the syndrome and its clinical characteristics. Typically, there is a history of exposure to irritating gas (nitrogen oxide) in a silo within hours to days after filling has begun. Cough, dyspnea and weakness are noted shortly after exposure. For a period of two to three weeks after exposure, symptoms are relatively mild or only slightly progressive. Then follow chills, fever, cyanosis, increased cough and rapidly increasing dyspnea. The only abnormalities on auscultation of the lungs are numerous fine and medium moist rales and sibilant asthmatic-type rales. Roentgenogram of the chest shows a nodular infiltrate throughout both lungs with perhaps some confluence of lesions in severe cases. Treatment with antibiotics is without effect. The administration of oxygen and bronchodilators gives little or no help. If death does not occur, the recovery phase begins three and a half to six weeks after exposure.

Grayson [*5*] has noted, as is evident upon review of published reports, that there is a spectrum of clinical syndromes which result from exposure to nitrogen dioxide (silo gas). A more severe exposure (300 to 500 parts per million of air) can result in a fulminating course with death from pulmonary edema and/or chemical bronchopneumonia within hours to days [*1,4,5*]. Other cases [*3,6,7*], as well as our own, represent the subacute course. Two cases have been described [*2,8*] in which chronic pulmonary insufficiency (not unlike that of pulmonary emphysema) ensued, resulting probably from a shorter single exposure or from brief multiple exposures.

The present case conforms in most aspects to the previously described "subacute" syndrome, with one important difference. When the exact time of exposure could be traced in the previously reported cases, it was found that exposure occurred in the first few days to one week after the silo had been filled. Most textbooks and articles [*3,9,10,13*] emphasize this

time of maximum occupational hazard. The patient described herein entered a silo six weeks after the silo was filled. The period of danger, therefore, can be longer than that considered previously, and this circumstance should be made known to farmers and agricultural workers.

Pulmonary function studies show that the initial defect is mainly one of diffusion and should be considered in the differential diagnosis of acute alveolar-capillary block. Pulmonary diffusion capacity became normal when the patient was treated with cortisone, in confirmation of corticosteroid therapy as the treatment of choice for this chemical pneumonitis. The lung biopsy specimen taken after treatment as well as the pulmonary function studies suggest that some residual pulmonary hyperinflation (emphysema) may be the sequel even to a successfully treated case without residual clinical symptoms. The follow-up period has not been long enough to suggest whether or not this slight abnormality will progress or remain stationary.

SUMMARY

A case of silo filler's disease is reported, resulting from exposure to silage six weeks after it was stored. Pulmonary function studies and lung biopsy specimens were obtained in the acute stage and during the period of convalescence. Pulmonary function studies showed the acute disturbance to be one of impaired diffusion of oxygen across the alveolar-capillary membrane. The initial lung biopsy showed a bronchiolitis. Following therapy with corticosteroids the alveolar diffusion capacity became normal, but the pulmonary function studies as well as the biopsy indicated that a mild degree of pulmonary hyperinflation resulted.

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