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Glucose Oxidase Induced Granulomatous Lung Disease

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While the exact etiology of allergic granulomatous lung disease has not been established, various fungi or fungus products have received the most attention. A worker exposed to an intense inhaled inoculum of glucose oxidase, a glycoprotein extract of *Aspergillus niger*, is presented who developed a clinical and pathologic picture similar to farmer's lung.

Granulomatous diseases of the lung are known to have many etiologies, among which have been the association with numerous organic antigens, usually containing and presumably derived from a wide variety of animal or fungal substances. Their clinical, pathologic, radiologic, and immunologic features have been the subject of several recent reviews.¹⁻⁴ The various proposed etiologies have been enumerated by Williams.⁵ Although an exact etiology has not been established, an allergic reaction to some fungus or fungus antigen in the organic material to which these people are exposed has received the most attention. Precipitins to various fungal agents have been demonstrated; often more than one antibody-antigen serum reaction is noted, thus complicating the etiologic picture. We are reporting a patient who worked in close contact with one purified protein extract of the fungus *Aspergillus niger*, who developed a granulomatous pulmonary disease that in many ways resembles farmer's lung.

CASE REPORT

This 29 year-old Negro man was first seen in the Michael Reese Hospital emergency room on May 5, 1967, complaining of bilateral pleuritic chest pain, progressive dyspnea, cough productive of only small amounts of whitish sputum, a low grade fever and a 20 pound weight loss over a five month period. The patient had been employed in the extraction and purification of glucose oxidase from *Aspergillus niger* for two years before admission. While initially his duties included redissolving the impure wet precipitate. In September, 1966, the manufacturing process was changed so that he then emptied bags filled with the dry, light-

weight, powder-like purified product. The fine material easily passed through a protective mask and was inhaled in large amounts. In December, 1966, symptoms of cough, chest pain, and dyspnea began and by April, 1967, became so severe that the patient was forced to leave work. A chest roentgenogram performed elsewhere on April 4, 1967, showed a fine interstitial infiltrate and bilateral hilar adenopathy.

The patient was treated symptomatically. At the time he was first seen here in May, 1967, his symptoms had become more severe and included anorexia and palpitations. The past history was remarkable only that he had worked with sandmolds five years before. A mobile unit tuberculosis screening film in January, 1967, was normal. The patient was born in Chicago, and had never lived on a farm, nor handled farm products.

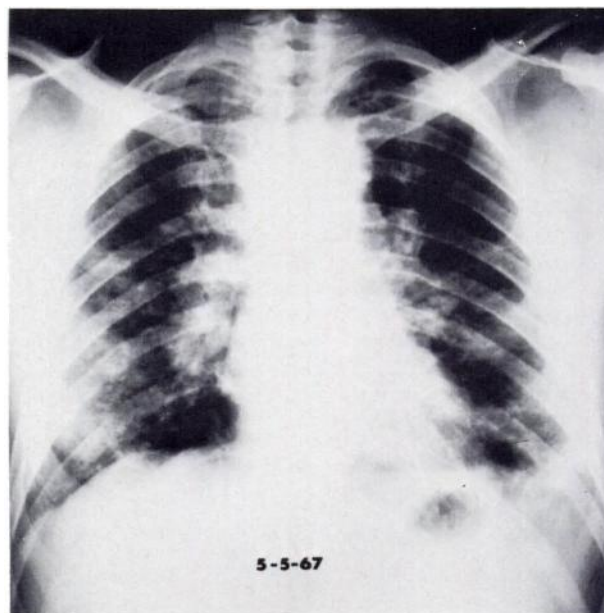


FIGURE 1. Roentgenogram early in course showing bilateral hilar adenopathy, and dense bilateral reticulonodular infiltrates.

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Table 1—Summary of serial pulmonary function data on the patient demonstrating a combined restrictive and diffusion defect. The greatest improvement occurred in the first four months of steroid therapy.

	5/9/67			9/19/67		1/19/68	
	Predicted	Calculated	Percent Predicted	Calculated	Percent Predicted	Calculated	Percent Predicted
M.V.V., L./min.	163	83	50.9	172.5	106	166	103
V.C., liters	4.460	1.67	38	2.985	67	3.07	67
T.L.C., liters	6.220	2.63	42	3.635	58	3.9	62
R.V., liters	1.780	.87	49	.650	37	.94	55
Insp. Cap., liters	3.020	1.33	44	1.922	63		
ERV, liters	1.420	.43	30	1.063	75	1.10	77
FRC, liters	3.480	1.3		1.760		2.0	57
FEV _{1.0} (L)	3.720	1.65	42	2.530	68	2.510	66
FEV ₁ /v.c.	75%		99		83.6		82
MMF L./sec.	1.79	2.8		2.96			2.5
RV/TC	30%		33		17.9		24
Dco	30.6		15		22		25.4
D _L /VA			5.7		6.05		6.5

Physical examination revealed a muscular man in mild respiratory distress. The blood pressure was 120/80, pulse 110/min, respirations 24/min and temperature 100.2°F. Examination of the eyes, ears, nose and throat was negative. There was no uveitis, conjunctivitis or significant adenopathy. Examination of the chest revealed dullness to percussion in both lower lung fields posteriorly, decreased breath sounds below the right scapula, and fine inspiratory rales heard widely over both lungs. The liver was 2 cm below the right costal margin and the total span was 10 cm; the spleen was not palpable. There was no clubbing, cyanosis, arthritis or skin rash.

The initial chest film here (Fig 1) showed a small right pleural effusion, bilateral hilar adenopathy, and dense bilateral reticulonodular pulmonary infiltrates. The blood count showed a hemoglobin of 12.5 gm per 100 ml, white count of 15,000/mm³ with 40 percent polymorphonuclear leukocytes, 22 percent lymphocytes, 30 percent eosinophils, and 8 percent monocytes. Sputum and pleural fluid cultures for bacteria, acid-fast bacilli, and fungi were negative. Bronchoscopy showed an inflamed bronchial mucosa. Bronchial biopsy showed nonspecific inflammatory changes. The pleural fluid protein was 3.2 gm/100 ml, and the cell count was 3,200 WBC/mm³, with 62 percent eosinophils, 30 percent lymphocytes, and 8 percent polymorphonuclear leukocytes. Cytology of the pleural fluid and sputum was negative for malignant cells. Conjunctival biopsy was negative. Mediastinoscopy demonstrated enlarged paratracheal and hilar nodes. Skin tests for coccidioidomycosis, blastomycosis, and PPD second strength (100 units) were negative. Histoplasmin skin test was positive with 10 mm of induration. Complement fixation tests for the above fungi were negative.

Initial and subsequent pulmonary function data are summarized in Table 1. A right thoracotomy and open lung biopsy were performed on May 25, 1967. The lung at surgery was firm and leather-like; white tubercles could be seen in the lung parenchyma; there was marked pleural thickening and 100 ml of serous pleural effusion. Cultures and stains of the lung tissue and nodes including special stains for bacteria, fungi, and acid-fast bacilli were negative.

The patient was given prednisone, 40 mg per day, and over the next six months gradually tapered to 20 mg per day. On this therapy the pulmonary infiltrates showed marked clearing, but hilar adenopathy remains (Fig 2). The

pulmonary function studies have shown a progressive improvement in both lung volumes and carbon monoxide diffusion capacity, (Table 1) and the patient is asymptomatic while maintained on low steroid doses; symptoms of dyspnea on discontinuing therapy have dictated their continuance.

PATHOLOGIC DESCRIPTION

There was dense and extensive nodular infiltrate throughout the lung section. This was concentrated along the bronchi and beneath the pleura where the nodules became confluent, although many scattered foci were found in the lung parenchyma itself (Fig 3). The vessels appeared to be involved only incidentally. The granulomas were all approximately of the same size and were made up of masses of macrophages with Langhan's or foreign body type giant cells in the center. Careful search failed to reveal either

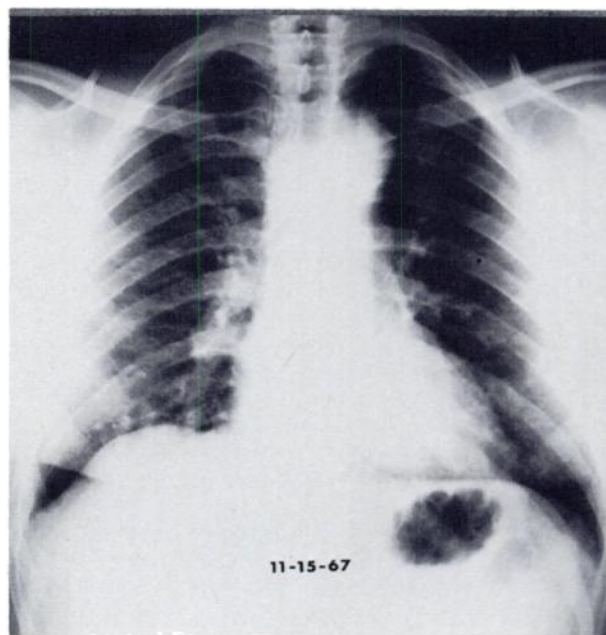


FIGURE 2. Chest roentgenogram after five months of steroid therapy showing clearing of the effusion and decrease in intraparenchymal infiltrates, but residual of bilateral hilar adenopathy.

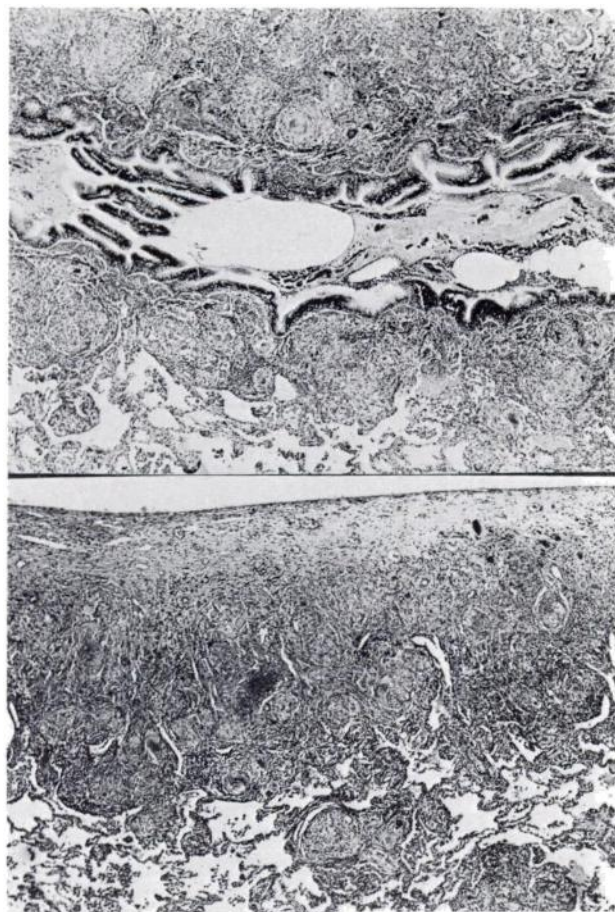


FIGURE 3 (upper). Low power view of the granulomatous inflammation of the lung. The lesions are confluent along the bronchi. FIGURE 4 (lower). Low power view of the granulomatous inflammation along the visceral pleura. The gray smudge just left of center is an area of necrosis. This area was virtually the only necrotic focus observed in any of the sections.

Schaumann or asteroid bodies. These granulomas were surrounded by an inflammatory infiltrate consisting of many lymphocytes and a relatively large number of eosinophils with occasional plasma cells. A rare granuloma showed some central fibrinoid necrosis (Fig 4).

Both visceral and parietal pleura showed moderate fibrosis with confluent granulomas beneath. The fibrous tissue was diffusely infiltrated with a moderate number of lymphocytes, plasma cells and eosinophils, and an organized layer of fibrin on the serosa.

The paratracheal lymph nodes that were removed by mediastinoscopy microscopically showed the architecture to be distorted by the presence of numerous granulomas that varied in size and were usually confluent, although smaller isolated ones were seen (Fig 5 and 6). These nodules were made up of masses of large, plump macrophages similar to those seen in the lung. In the lymph node, however, giant cells were uncommon and when found, were always at the periphery of the granulomas. Neither Schaumann bodies nor asteroid bodies were present. These granulomata too were surrounded by infiltrate similar to that found in the lung. This infiltrate could not be sharply delineated from the lymph node parenchyma. Acid-fast and fungal stains were negative, and no birefringent crystals were seen.

The glucose oxidase handled by the patient was examined and cultured by us and found to contain viable *Aspergillus niger*.

DISCUSSION

Glucose oxidase is a glycoprotein found almost exclusively in plant life. It has been isolated from molds, red algae, citrus fruits, and bacteria. The only known animal source is the honey bee.⁶ For commercial purposes glucose oxidase is extracted from the fungus *Aspergillus niger*,⁷ and is used in a method for glucose determinations in biologic fluids.⁸ Our patient's symptoms began three months after he began handling a purified glucose oxidase preparation that was fine enough to pass through a protective mask. The patient has no other recent environmental exposure to a possible pulmonary allergen or toxin.

To our knowledge, glucose oxidase has not been previously reported as causing a granulomatous lung disease, and while the patient stated that other employees in his plant would on occasion develop sneezing and tearing from the product, no one else

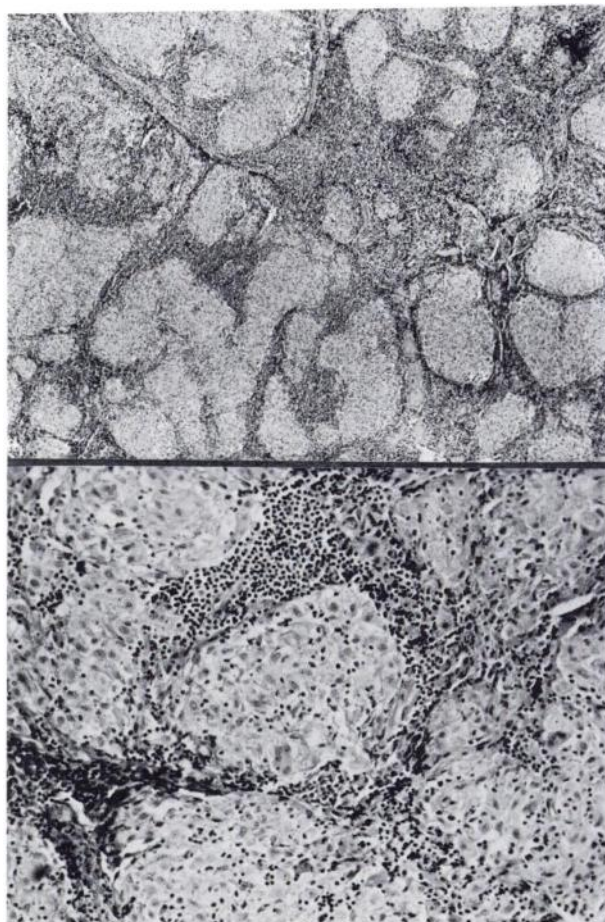


FIGURE 5 (upper). High power view of the granulomas in the lymph node. FIGURE 6 (lower). Low power view of the numerous, sharply-defined noncaseous granulomas in the mediastinal lymph node.

developed lung disease. This was confirmed by a roentgenographic survey of other employees who handled the material.

Despite the presence of *Aspergillus niger* in the material, the failure to culture the organism from either sputum, pleural fluid, mediastinal lymph nodes, or lung tissue or to demonstrate it histologically, excludes aspergillosis as the clinical entity. The presence of a high eosinophil count in the peripheral blood and pleural fluid and numerous eosinophils within the tissue sections support an allergic etiology. Liebow and Carrington⁹ have reviewed the ever-enlarging clinical and pathologic spectrum of this entity, and have compiled a classification. The case presented here could be grouped with the sarcoid-like lesions: however, it does not duplicate all of the classic features of farmer's lung, specifically in regard to the extensive tissue and blood eosinophilia present in our case. Pepys has described a pulmonary hypersensitivity disease secondary to *Aspergillus fumigatus* which can present either with an asthmatic picture, or one with eosinophilia and asthma, and he has shown precipitin antibodies to the organism in these cases. The disease must be distinguished, however, from invasion of the pulmonary tissue by the aspergillus organism where precipitin antibodies can also be demonstrated.^{10,11} This is best done by appropriate histologic examination of tissue and culture of sputum and tissue, as well as the roentgenologic features of invasive disease in which the aspergilloma may be present. The patient was skin-tested with *Aspergillus niger* material by both the immediate and delayed hypersensitivity methods; both were negative. The limitations to skin testing in these disorders are well known.¹²

Two other diseases that can produce this picture are sarcoidosis and berylliosis. The intense pleural thickening with fibrinous exudate and pleural effusion as well as the absence of Schaumann and asteroid bodies militate against sarcoidosis. The lesions are less sharply delineated in both lung and lymph nodes than in the classic picture of sarcoidosis. Our patient had no known exposure to beryllium.

Rankin and his associates have recently reviewed the occupational diseases that appear to be related to the inhalation of organic antigens.⁴ While numerous fungi and other organic products have been implicated in causing this clinicopathologic entity, no single etiologic organism has been proven. The patients do not have fungal infiltration of the lung. Serologic studies frequently show one or more precipitin lines to various partially purified antigen preparations. The exact biochemical classification of the antigens is unknown, but undoubtedly are com-

binations of various proteins. A cause and effect relationship between these protein products and the symptom-complex as well as aggravation of the pulmonary functional abnormalities have been duplicated using purified extracts of these environmental antigens.^{13,14}

This patient is unique in that instead of being exposed to numerous antigens as is the farmer, wool sorter, or lumberman, his industrial occupation limited him to a heavy bronchopulmonary exposure to one apparently antigenic protein of one fungus in a large inhalable inoculum.

The restrictive ventilatory abnormality and diffusion defects without significant obstruction is characteristic of the allergic granulomatous lung diseases. The excellent response to steroids with improvement in both lung volumes and carbon monoxide diffusion capacity is additional evidence for immune phenomena. This response was favorable apparently because therapy was initiated before fibrosis took place.

Bishop and co-workers³ attempted unsuccessfully to demonstrate complement-fixation antibodies to aspergillus species in patients with farmer's lung. No specific precipitin tests were performed on our patient, although ideally they are indicated. Since the exact nature of the protein was known, and since he had had prolonged direct skin contact and inhalation exposure to it, the presence of specific circulating antibodies would only confirm this extensive contact.

REFERENCES

- 1 RANKIN, J., JAESCHKE, W.H., CALLIES, Q.C., AND DICKIE, H.A.: Farmer's lung, *Ann. Intern. Med.*, 57:606, 1962.
- 2 EMANUEL, D.A., WENZEL, F.J., BOWERMAN, C.I., AND LAWTON, B.R.: Farmer's lung, *Amer. J. Med.*, 37:392, 1964.
- 3 BISHOP, J.M., MELNICK, S.C., AND RAINE, J.: Farmer's lung, *Quar. J. Med.*, 32:257, 1963.
- 4 RANKIN, J., KOBAYASHI, M., BARBEE, R., AND DICKIE, H.: Pulmonary granulomatosis due to inhaled organic antigens, *Med. Clin. N. Amer.*, 51:495, 1967.
- 5 WILLIAMS, J.V.: Inhalation and skin tests with extracts of hay and fungi in patients with farmer's lung, *Thorax*, 18:182, 1963.
- 6 SCHEPARTZ, A.I., AND SUBERS, M.H.: The glucose oxidase of honey, *Biochim. Biophys. Acta*, 85:228, 1964.
- 7 SWOBODA, B.E.P., AND MASSEY, V.: Purification and properties of the glucose oxidase from *Aspergillus niger*, *J. Biol. Chem.*, 240:2209, 1965.
- 8 ROBIN, M., AND SAIFER, A.: Determination of glucose in biologic fluids with an automated enzymatic procedure, *Clin. Chem.*, 11:840, 1965.
- 9 LIEBOW, A.M., AND CARRINGTON, C.B.: Hypersensitivity reactions involving the lung, *Trans. Coll. Physicians Phila.*, 34:47, 1966.
- 10 PEPYS, J.: Pulmonary hypersensitivity disease due to inhaled organic antigens, *Postgrad. Med. J.*, 42:698, 1966.

- 11 LONGBOTTOM, J.L., AND PEPYS, J.: Pulmonary aspergillosis: Diagnostic and immunologic significance of antigens and C substance in *Aspergillus fumigatus*, *J. Path. Bact.*, 8:141, 1964.
- 12 HINSHAW, H.C., AND GARLAND, L.H.: *Diseases of the Chest*, ed. 2, Philadelphia: W. B. Saunders Company, p. 703.
- 13 BARBEE, R.A., DICKIE, H.A., AND RANKIN, J.: Pathogenicity of specific glycopeptide antigen in farmer's lung, *Proc. Soc. Exp. Biol. Med.*, 118:546, 1965.
- 14 KOBAYSKI, M., STAHMANN, M.A., RANKIN, J., AND DICKIE, H.A.: Antigens in moldy hay as the cause of farmer's lung, *Proc. Soc. Exp. Biol. Med.*, 113:472, 1963.

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DOMINANT LEIT MOTIF: THE WILL TO LIVE

There is a deep relation between the attitude that is taken toward the historic past and the conception that is formed of death, and this relation is expressed in the disposal of the dead. The Egyptian denied mortality. The Egyptians embalmed even their history in chronological dates and figures. From pre-Solonian Greece nothing has been handed down, not a year-date, not a true name, not a tangible event—with the consequence that later history (which alone we know) assumes undue importance—but for Egypt we possess, from the third

millennium, and even earlier, the names and even the exact reign-dates of many of the kings, and the New Empire must have had a complete knowledge of them. Today, pathetic symbols of the will to endure, the bodies of the great Pharaohs lie in our museums, their faces still recognizable.

Spengler, O.: *The Decline of the West* (English abridged edition prepared by Helps, A., from the translation by Atkinson, C. F.), Knopf, New York, 1962

THE CURSE OF GREATNESS

The public career of Cicero (106–43 BC) as a lawyer and holder of offices up to his consulship in 63 BC has been called that of a trimmer, a man who tried to run with the hares of reform while hunting with the hounds of plunder. Cicero apparently hoped to do a bit of good here and another bit there, as opportunity afforded, with the idea of reforming the state from within. If mental endowment had been enough for this task, Cicero certainly was the man who could have succeeded. He was the greatest orator Rome ever produced; most scholars agree that his only peer in all history was the Athenian Demosthenes. Throughout his life he did much to foster love of Greek literature and art, and even though he was no more able than any other Roman to

add anything to Greek philosophy, he did manage to blend Greek ideas with the practical needs of the Roman situation into a polished, resigned attitude toward life. In 43 BC the partisans of Caesar's nephew Octavian decided that the danger of oratorical blasts against them and their schemes required proscription of Cicero. Accordingly he was murdered and his head and his hands were nailed to the orator's rostrum in the Forum—a sardonic end for greatest orator and philosopher Rome ever produced.

Stevens, M.: *Mind Through the Ages*, Doubleday, Doran & Co., New York, 1940

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