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Experimental Infective Pneumoconiosis: Effect of Asbestos Dust and *Candida albicans* Infection on the Lungs of Rhesus Monkeys

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The combined effect of *Candida albicans*, a facultative pathogen in the normal physiological condition in the throat of miners, and amosite dust produces after intratracheal inoculation extensive collagenous fibrosis at 330 days in rhesus monkeys. The lesions produced by amosite dust alone comprise fine reticulin fibrosis around bronchioles and blood vessels and moderate interstitial fibrosis. The *C. albicans* infection alone caused acute inflammatory reaction in the early stages while at the termination of experiment (330 days) the only evidence of pulmonary candidiasis was a few small fibrotic foci of compactly arranged reticulin fibers.

In workers suffering from pulmonary asbestosis radiological studies have revealed large opacities in the lung (Sluis-Cremer and Wagner, 1964; Bristol, 1967; Solomon, 1969). The areas corresponding to the opacities were made up of diffuse hyaline fibrosis which consisted of foci of concentric collagenization (Solomon *et al.*, 1971). To what extent a chronic low grade infection plays a part in the pathogenesis of these lesions remains obscure. The feasibility of such an interaction seems possible in view of the earlier studies in which one of us observed that the combined action of an inert dust and chronic low-grade tubercle bacilli infection produced massive fibrosis in the lungs of guinea pigs (Zaidi *et al.*, 1955a,b,c). Further, Zaidi (1969) has reviewed the role of infection in pulmonary massive fibrosis. In the present experiments, therefore, this aspect has been investigated with asbestos dust and with a low-virulence organism, *Candida albicans*, which is capable of setting up a mild infective stimulus in the lung. Amosite variety of asbestos dust has been used because of its greater susceptibility to infection in animals than other varieties of asbestos (Wagner, 1963). The animals used in this study are Rhesus monkeys which may have a similar immunological response to that of man and, therefore, be the best suited primate for experimental asbestosis.

MATERIALS AND METHODS

Indian amosite asbestos used in this investigation was supplied by the Director, Geology and Mining, Uttar Pradesh Government, India. A coarse fiber dust was prepared by crushing the asbestos flakes so that the resulting fibers passed through a 200-mesh B.S. sieve. The desired size of fibrous dust was then prepared which had fiber length less than 30 μm (Zaidi, 1969). The composition of amosite dust is given in Table 1.

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TABLE 1
CHEMICAL ANALYSIS OF AMOSITE DUST

SiO_2	50.46%
Al_2O_3	1.33%
Fe_2O_3	25.16%
CaO	1.06%
MgO	17.03%
MnO	0.03%
K_2O	0.13%
Na_2O	0.16%
Loss on ignition	4.97%
Ni	77 ppm
Zn	141 ppm
Pb	nil

The dust suspension for inoculating the monkeys was prepared by suspending amosite dust in normal saline. It was then sterilized by autoclaving for 20 min at 15 lb pressure.

The organism *Candida albicans* (Robin) Berkh. was obtained from Antibiotics Division of Central Drug Research Institute, Lucknow, India. The suspension for inoculating the monkeys was prepared from a 48–72-hr-old culture grown on Sabouraud's agar medium. A weighed amount of organism, scraped from the surface of the plates was then shaken with 0.85% sterile normal saline in a bottle containing glass beads for 5 min. Suitable dilutions of the suspension were then made in sterile normal saline.

A series of preliminary experiments were performed by intratracheal inoculation in monkeys with varying doses of amosite dust alone, organism alone and amosite and organism and the animals were observed over a period of 15 days. There was no mortality in various groups of monkeys receiving the organism alone which ranged from 500 μg to 1.5 mg per animal. When the amount of amosite dust ranged from 750 mg to 1.5 g per animal, none of the animals died. Increased mortality was observed in the combined group of monkeys when the dose of amosite was raised from 1 g to 1.25 g and organisms from 1 mg to 1.25 mg per animal. However, with 1 g of amosite together with 1 mg of organisms (corresponding to 16.2×10^6 organisms) none of the animals died during the course of 15 days and onwards and it was, therefore, decided to use these doses.

A total of 80 rhesus monkeys (*Macaca mulatta*) of average body weight of 4 kg were obtained locally and observed for a period of 4–5 wk. The animals were fed bread, soaked grains, fruit and carrot. All animals were tuberculin tested with 0.1 ml of 1:9 dilution of concentrated tuberculin injected intradermally in the upper eyelid. Only two of the animals showed positive reaction which were discarded. Seventy-eight monkeys were then injected intratracheally, by the technique described by Zaidi (1969), organisms alone, amosite dust alone and amosite and organism into the following three groups:

	No. of animals	
Group I	26	Organism alone—1 mg in 10 ml sterile normal saline per animal.

Group II	26	Amosite dust—1 g in 10 ml sterile normal saline per animal.
Group III	26	Amosite dust—1 g and 1 mg organism in 10 ml sterile normal saline per animal.

One animal from each group was sacrificed under pentobarbital sodium anaesthesia and autopsied immediately after the inoculation. Other animals were sacrificed at intervals of 24 hr and 7, 15, 30, 60, 90, 120, 150, 210, 270, 300, and 330 days post-inoculation and autopsied.

In order to obtain the viable count of the organisms from the lungs the cardiac lobe was removed, dried with a piece of blotting paper and accurately weighed. The lobe was then crushed in a Potter-Elvehjem type all-glass homogenizer and diluted with sterile normal saline so that 1 ml of suspension contained 100 mg of lung tissue. The suspension was serially diluted ten-fold with sterile normal saline and 0.2 ml of each dilution inoculated on Sabouraud's agar plates and incubated at 37 ± 2°C. The colonies from each dilution obtained at 24 and 48 hr were counted and results expressed as number of organisms per gram of the lung.

The remaining lobes of the lungs were gently distended to normal size with 10% formol saline. After preliminary fixation blocks were selected along the long axis of both the lungs at the level of the hilum. The fixation was completed with fresh fixative, blocks embedded in paraffin and cut at 5 μm. Multiple sections from each block were stained with haematoxylin and eosin, silver impregnation for reticulum and collagen (Gordon and Sweets, 1936). Alcian blue–Periodic Acid Schiffs stain, Periodic Acid Schiffs–Haematoxylin for organisms and Perls' method for the demonstration of asbestos bodies (Winner and Hurley, 1964; McManus and Mowry, 1965). Pathological grading of the fibrosis was assessed according to Belt and King (1945).

RESULTS

Macroscopic Findings

The gross examination of the lungs in animal of group I, 24 hr after inoculation revealed congestion which persisted up to 30 days. Thin adhesions were noted at 120 days in the animals of group II. In group III the first evidence of gross change occurred at 60 days which comprised many thin adhesions between the lobes of lungs and parietal pleura. The adhesions in both the groups II and III became thicker and denser when examined at 270 and 300 days. At 330 days well-marked bilateral adhesions and white areas of fibrosis were also present in both pleural sacs. The dense adhesions sometimes involved the whole of the lung (Fig. 1). Two animals of group I which died on 40th and 172nd day post-inoculation showed small abscesses. Similar abscesses were also encountered in one animal of group II, 270 days post-inoculation.

Microscopic Findings

Group I. Immediately after the intratracheal inoculation of organisms accumulation of mucus in the lumen of bronchi together with a few desquamated epi-

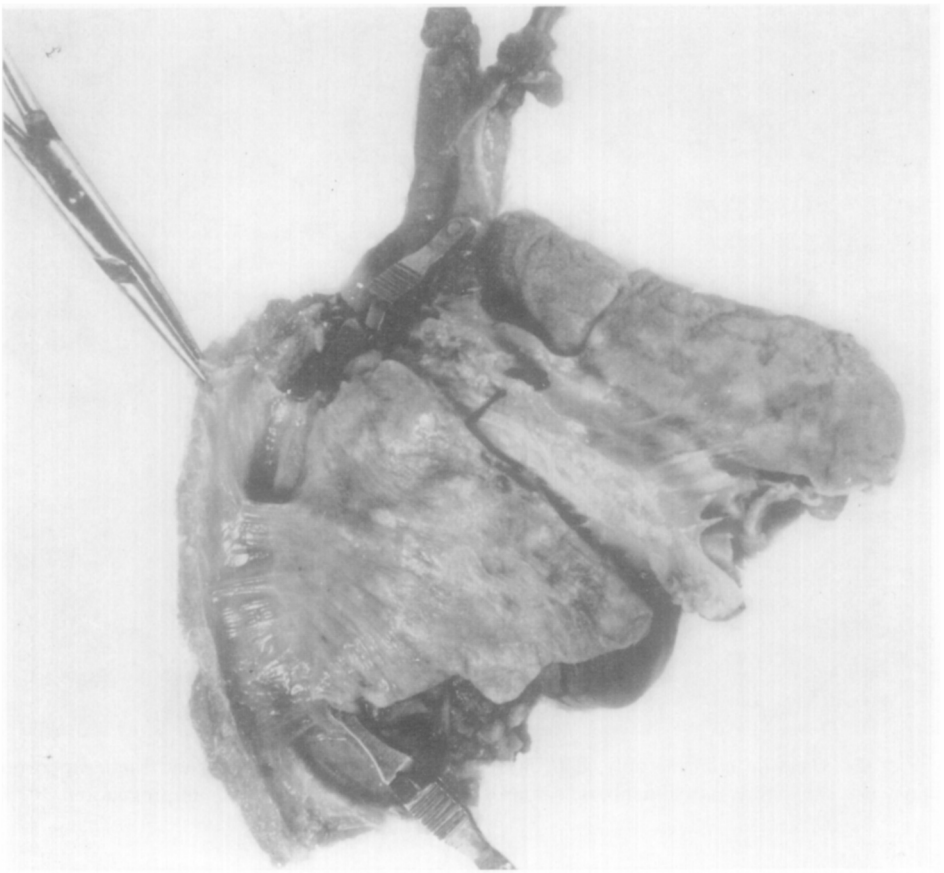

FIG. 1. Amosite dust and *Candida albicans*. 330 days. Dense pleural adhesions.

thelial cells occurred. The PAS-positive organisms were present in the lumen of the bronchus, bronchiole, alveolar duct and also in some of the alveoli. By 24 hr congestion and acute inflammatory reaction developed. The alveoli surrounding the bronchioles also contained polymorphonuclear leucocytes. By the seventh day alveolar septa became edematous and in the alveolar lumen along with macrophages large number of PAS-positive organisms were seen. At 15 days post-inoculation besides macrophages and organisms, at places the alveoli were also filled with lymphocytes, epithelioid cells and plasma cells. Increased cellularity was also observed in the thickened pleura.

At 30 days aggregates of macrophages were encountered around blood vessels and bronchioles and the adjacent lung parenchyma showed slight to moderate degree of emphysema. The alveoli contained large number of macrophages but the organism could not be properly seen with histochemical staining. At 60 days the reaction did not markedly differ from that seen at 30 days. However, at 90 days the macrophage activity around bronchioles and alveolar duct became marked which progressed considerably at 150 days. At places, by 300 days the bronchial epithelium became slightly hyperplastic and a few small fibrotic areas consisting of compactly arranged reticulin fibers were encountered. At 330 days

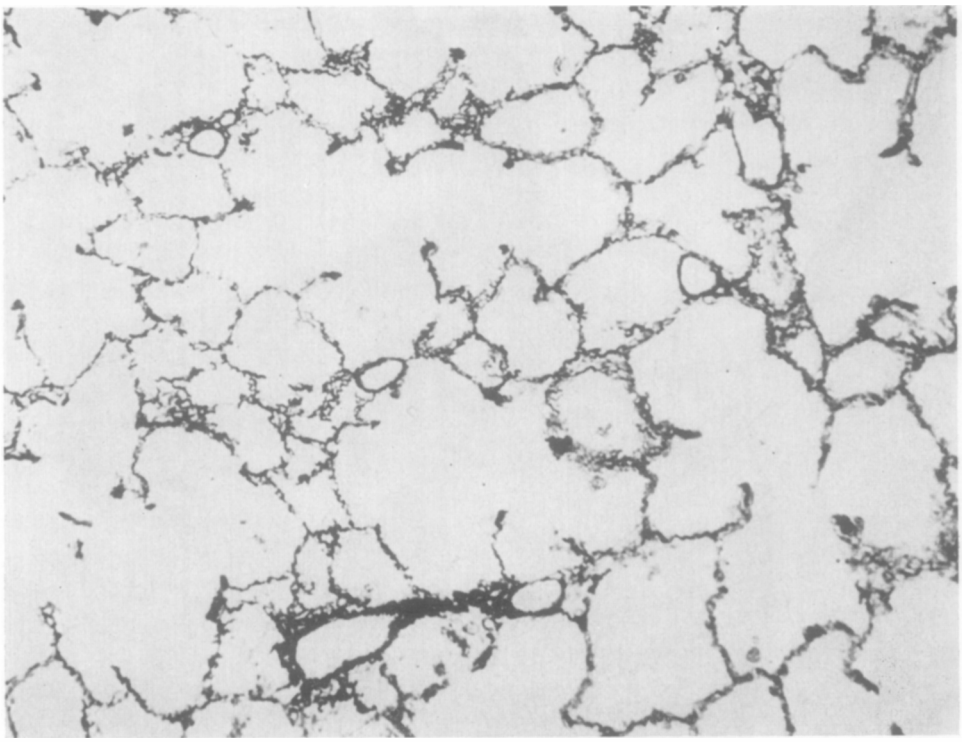

FIG. 2. *Candida albicans* only, 330 days. The alveolar septa are thin and their supporting framework show tiny reticulin fibers, some of them are branched. Silver impregnation. ×190.

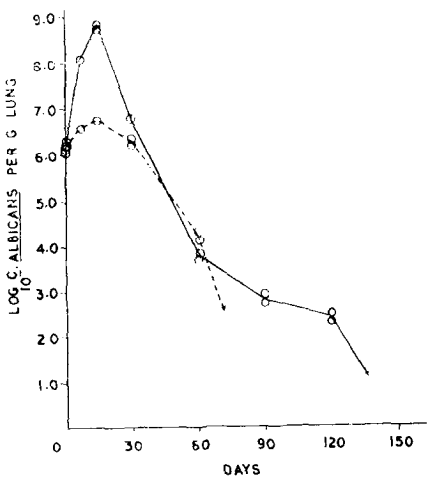

FIG. 3. Viable counts of *Candida albicans* from lungs of monkeys given an intratracheal injection of 1 mg of *C. albicans* alone (– – –) or with 1 g of amosite dust (——).

the few isolated fibrotic foci persisted but most of the lung tissue regained its normal architecture (Fig. 2).

The viable counts of the organisms from the cardiac lobe are shown in Fig. 3. The counts did not reveal the presence of organisms from 90 days onwards, but organisms persisted in presence of amosite dust (see group III).

Group II. With the intratracheal injection of amosite dust the lungs revealed, on immediate autopsy, masses of dust fibers either adhering or blocking a number of bronchi, bronchioles, alveolar ducts and a few alveoli. Except for a mild desquamative changes in the bronchi and bronchioles, no other changes were encountered. By 24 hr there appeared generalized edema and acute inflammatory reaction and dust became uniformly distributed throughout the alveoli. The bronchioles also contained the inflammatory exudate.

By the seventh day edema and congestion had cleared and the dust was now confined to the alveoli surrounding the bronchioles and also around the alveolar duct. Increased blue reaction revealed the presence of a few asbestos bodies corresponding to deposits of dust. By 15 days the peribronchiolar area and the area around alveolar duct showed increased cellularity which on silver impregnation revealed thin reticulin fibers.

At 30 days the reaction did not markedly differ from that seen at 15 days except that the dust collected in definite areas which contained few reticulin fibers. At this interval, in one animal few areas of necrosis containing polymorphonuclear cells were seen. By 60 days large areas of fibrosis having thick compactly

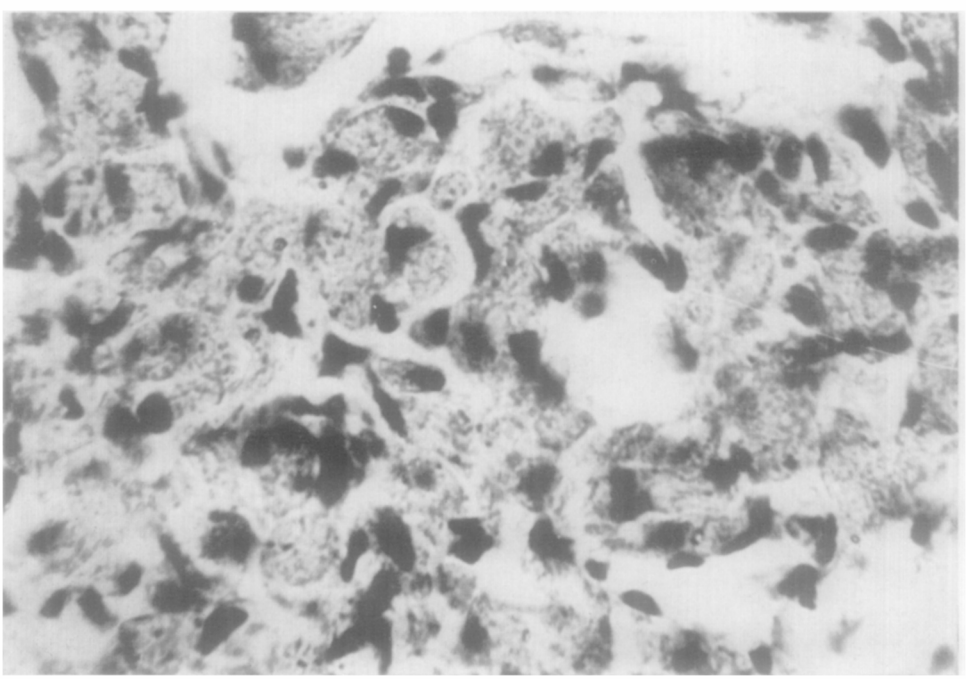

FIG. 4. Amosite dust alone, 90 days. Reaction zone consists of giant cells and macrophages containing dust fibers. Haematoxylin and eosin. ×654.

arranged reticulin fibers were encountered corresponding to the deposits of dust. The blood vessels showed at its periphery increased deposit of iron pigment.

The collagen fibers appeared at the periphery of focal areas by 90 days. A few multinucleated giant cells were also present which contained asbestos fibers (Fig. 4). Asbestos bodies were found in the muscular coat of the blood vessels and bronchioles. A few small blood vessels showed characteristic proliferation of vascular intima with partial occlusion of the lumen. However, by 120 days the fibrotic reaction had not considerably progressed and the lesions contained only few reticulin fibers (Fig. 5). Besides these lesions, few necrotic areas were also seen.

The lesions composed mostly of dust laden macrophages and situated mostly in para- and perivascular areas by 150 days, and fibroblastic proliferation and thickening of interalveolar septa. At 210 days the lesions had more fibrosis at the periphery, and few collagen fibers pierced into the dust cell areas irregularly. There was marked emphysema of the adjacent alveoli.

By 270 days the dust cell aggregates developed large number of clefts resulting from the collapse of alveolar ducts and alveoli. In addition, focal fibrosis also developed. The alveolar capillaries showed, in general, obliteration of their lumen. The fibrotic reaction at 300 days, did not differ much from that seen at 270 days except that the multifocal areas around blood vessels became more collagenous. At places marked emphysema was encountered. Besides, collagenous interlobular adhesions pleural adhesions were well marked. At this time interval only in one animal small foci of necrotic area was observed.

The focal areas around bronchioles and blood vessels by 330 days had attained

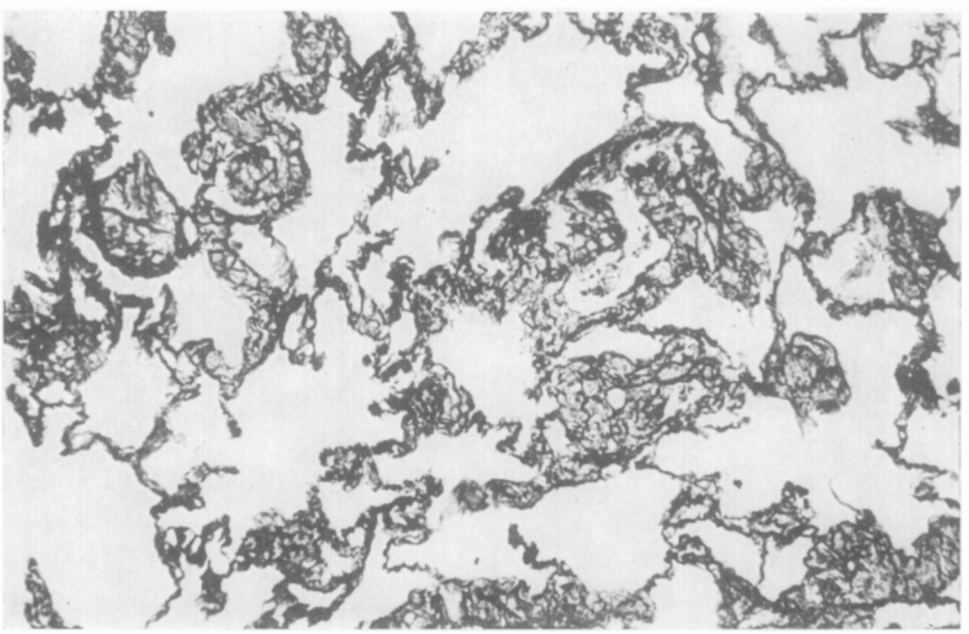

FIG. 5. Amosite dust alone, 120 days. Focal areas of dust collection having few reticulin fibers. Silver impregnation. ×190.

marked fibrosis (Fig. 6). The smaller blood vessels showed intimal proliferation. In addition, collagenous interlobular adhesions became prominent and numerous asbestos bodies of various size and shape were present.

The viable counts of the cardiac lobe of the lung were performed which were negative at all periods.

Group III. Soon after the intratracheal inoculation of amosite dust together with organisms there appeared irregular distribution of dust and organism (PAS-positive) in the various segments of bronchi, bronchioles, alveolar duct and alveoli. The lumen of the alveoli was either filled completely with the dust or it formed a lining on the surface of alveolar membrane. By 24 hr there was marked congestion, acute inflammatory reaction and widespread edema. Bronchi and bronchioles contained inflammatory exudate in their lumen along with dust fibers, organisms and desquamated epithelial cells. However, by the seventh day congestion and edema subsided and alveolar macrophages were seen around bronchioles and alveolar duct. Some of the alveoli were filled with macrophages containing organism (PAS-positive) and dust fibers. Dust fibers were also encountered in the interalveolar septa. No characteristic asbestos bodies were seen.

The dust-laden macrophages interposed by loosely arranged reticulin fibers around bronchioles and alveolar ducts became more circumscribed by 15 days.

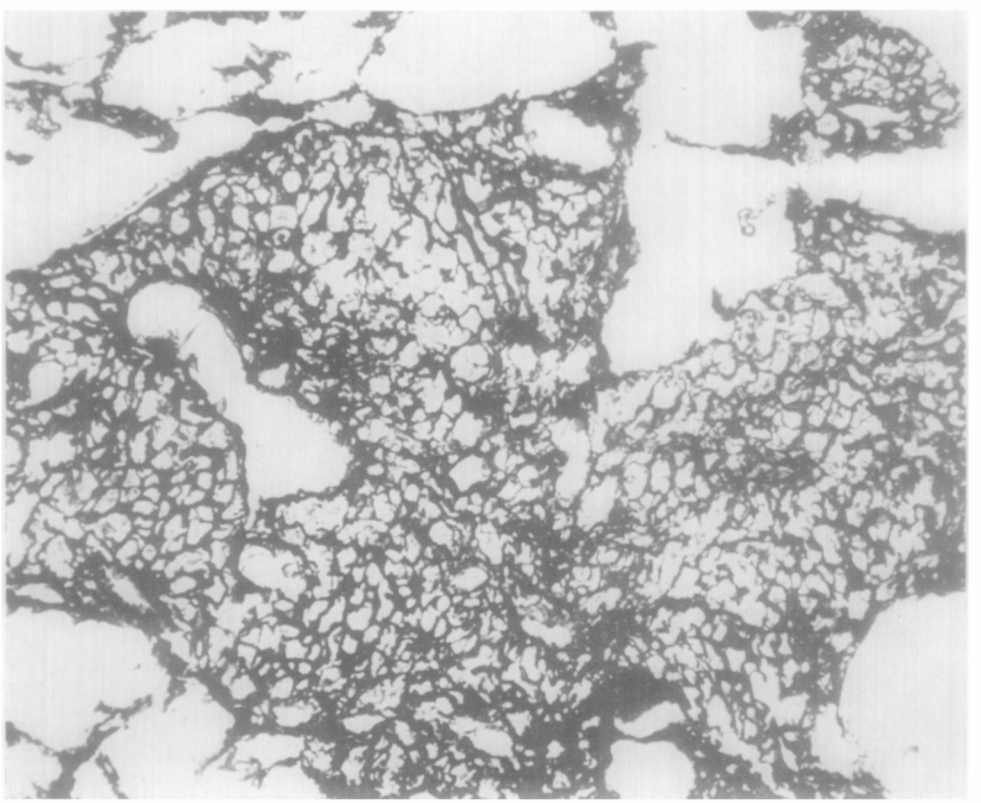

FIG. 6. Amosite dust alone, 330 days. Focal area showing thick collagen fibers and a network of reticulin fibers. Silver impregnation. ×190.

A few intensely stained asbestos bodies were encountered. At 30 days active proliferation of fibroblasts started in the dust aggregates. The short dust fibers packed the swollen macrophages and the longer ones were seen free. At places the dust mass in the alveoli was surrounded by a number of nuclei giving the appearance of giant cells. Some of the fibers had penetrated the alveolar wall and reached the interstitium of the parenchyma. The bronchial epithelium showed marked degree of desquamative changes. Histochemical staining revealed faint PAS-positive reaction for the organisms. Thick compactly arranged reticulin fibers were, however, observed around bronchiole and alveolar duct.

By 60 days peribronchiolitis, marked deformity and distortion of bronchioles and aggregates of dust laden macrophages around small blood vessels were seen. In these areas deposit of iron pigment and laying of fibrous tissue was also observed. At 90 days the fibrosis further progressed and thick collagen fibers in the focal areas, around bronchioles, alveolar duct and blood vessels appeared. At these intervals few areas of necrosis were also seen. The presence of organisms could not be demonstrated histochemically.

The fibrotic areas at 120 days became large and showed a tendency to coalesce and these diffused areas showed increased laying down of collagen (Fig. 7).

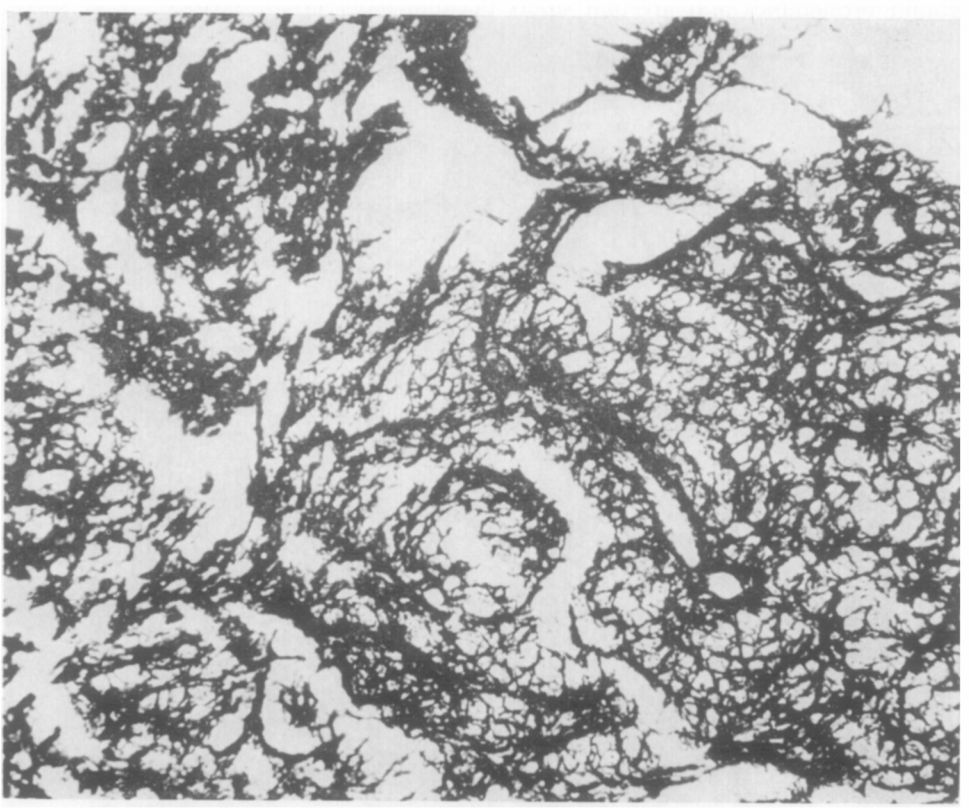

FIG. 7. Amosite dust and *Candida albicans*, 120 days. Stromal reaction with branched argyrophylic fibers and thick collagen fibers. Silver impregnation. ×190.

Small blood vessels in the fibrotic areas got obliterated while larger blood vessels showed thickening of their muscular coat. Short fibers were packed in the swollen macrophages and long ones even penetrated the alveolar wall.

At 150 days the reaction did not markedly differ from that seen at 120 days except the fibrosis became diffused. The interalveolar septa continued to be thickened. However, at 210 days fibrosis further advanced and, in addition, collagenous interlobular adhesions became quite distinct. The fibrotic lesions were progressive around bronchioles, blood vessels and alveolar duct. By 300 days fibrosis composed of thick collagen fibers appeared. Such fibrous areas continued to exhibit increased fibroblastic activity and numerous asbestos bodies of different size and shape were present (Fig. 8).

At 330 days the reaction did not differ from that seen at 300 days. Diffuse fibrosis composed of collagen and thick reticulin fibers was observed (Fig. 9). Thickened interalveolar septa were present and well-developed collagenous interlobular adhesions seen. In the fibrosed area some of larger blood vessels revealed fibrocellular proliferation of intima. In one animal there was a small area of necrosis with nuclear remnants.

The viable counts of organism at 120 days revealed their presence (see Fig. 3). At 150 days post-inoculation and later the count became negative.

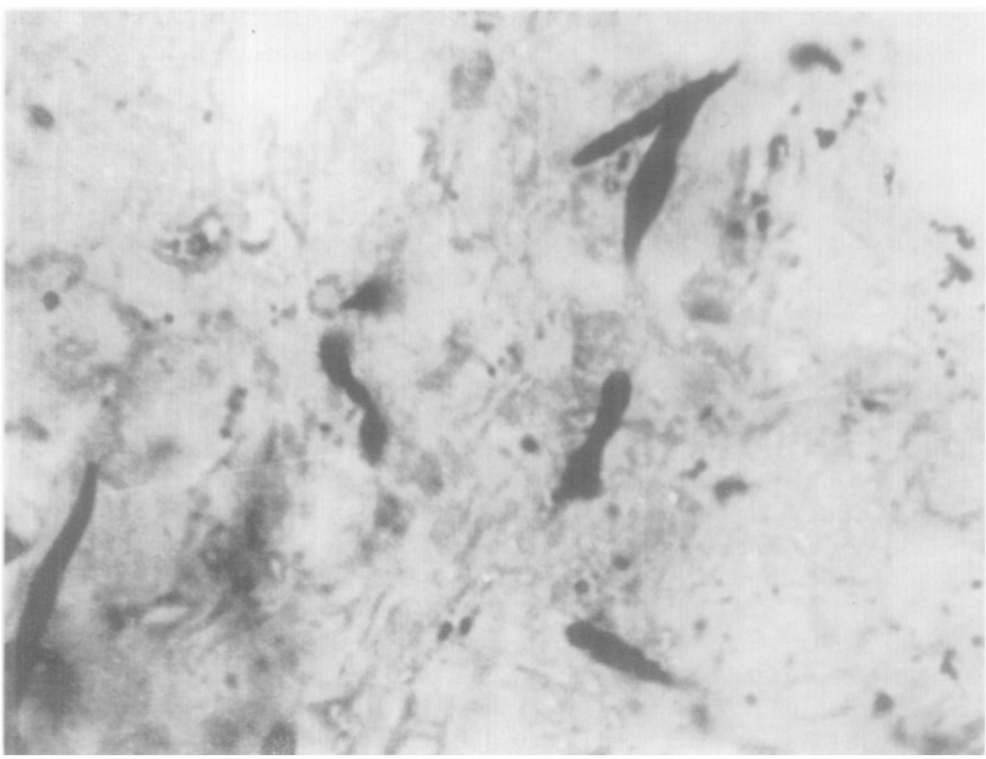

FIG. 8. Amosite dust and *Candida albicans*, 300 days. Asbestos bodies of various shapes in the area of dust cell reaction. Perl's stain. ×1275.

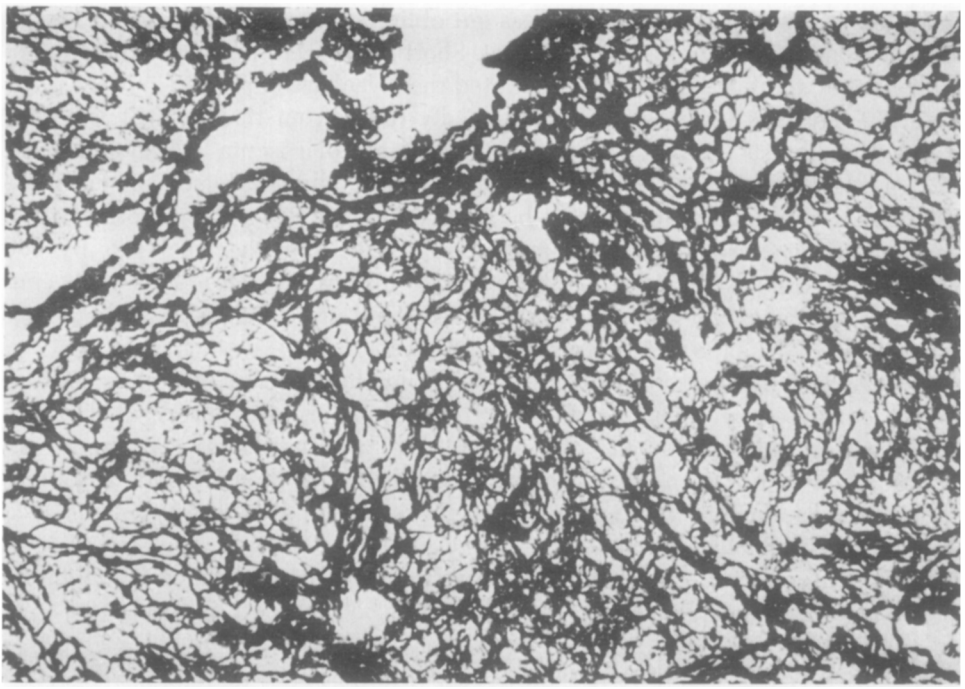

FIG. 9. Amosite dust and *Candida albicans*, 330 days. Lesions consist mostly of collagen and thick reticulin fibers. Silver impregnation. ×190.

DISCUSSION

Wagner (1960, 1963) reported experimental asbestosis in primates. He observed diffuse interstitial fibrosis and areas of moderate fibrosis in the region of respiratory bronchioles with inhaled amosite dust in vervet monkeys. In our studies, on rhesus monkeys, severe lesions were noted by 330 days post-inoculation of amosite dust. They comprised of dense fibrosis in the form of thick collagen fibers around bronchioles and blood vessels and moderate interstitial fibrosis. As regards the distribution of lesions these results confirm the findings of Wagner (1960). The severity of lesions in our experiments may be due to a different technique of dust administration (intratracheal injection), large amount of dust administered or a species difference.

Experimental pulmonary candidiasis has been reported in rabbits (Kurotchkin and Lim, 1933; Schattenberg and Flinn, 1939; Zettergren, 1950; Evans and Winner, 1954; Felisati *et al.*, 1959), in guinea-pigs (Urso and Capocaccia, 1952; Vogel and Krehl, 1957), and in mice (Urso, 1950; Hurley, 1962), but no detailed reports are available in primates. In our experiments in the lungs of rhesus monkeys which received *Candida albicans* infection alone, widespread congestion, edema and acute inflammatory reaction were noted in early stages. Zettergren (1950) stated that the pulmonary lesions were the result of an endotoxic effect of the disintegrated fungal cells. In our investigation an increase was observed in viable count of the organism in the lung up to 15 days and a subsequent decline when the infection got cleared off and the pulmonary tissue assumed its normal ap-

pearance. At the termination of experiment (330 days) the only evidence of pulmonary candidiasis in rhesus monkeys was a few small fibrotic foci of compactly arranged reticulin fibers encountered around bronchioles. Whether this fibrogenic reaction originated from the live organism or their metabolites even after the negative viable counts were obtained is not clear.

Zaidi *et al.* (1955a,b,c) noted production of massive pulmonary fibrosis in guinea-pigs as a result of tubercle bacilli and nonfibrogenic dust like coal mine dust. Earlier extensive pulmonary fibrosis was reported in the animals infected with tubercle bacilli and dusted with asbestos dust (Gardner and Cummings, 1931). In our experiments the lesions produced by the combined action of amosite dust and *C. albicans* at 330 days consisted of extensive collagenous fibrosis along with thick collagenous pleural adhesions. The extensive fibrosis seen in the combined group was altogether different from that observed with amosite dust or *C. albicans* alone. The exact mechanism related to the production of extensive pulmonary fibrosis in the combined group may be due to a synergistic effect of dust and *C. albicans* or to a product of the metabolism of candida which provided a continued stimulus, or by way of some immunological mechanism cannot be clearly understood from these experiments and requires further investigations.

From the above investigations, it may however be concluded that the pulmonary extensive fibrosis in the presence of dust is not only related to tubercle bacilli as reported earlier by Zaidi *et al.* (1955a,b,c) but also to other infections like *C. albicans* which are often found in upper respiratory tract. How far the organism, which often remains as a facultative pathogen in the normal physiological condition, under low vitality and dusty environment gains the upper hand and accentuates the fine fibrosis of asbestosis remains to be investigated.

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