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Furrier's lung

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As is known, the inhalation of animal hairs can provoke immunological reactions in the respiratory tract affecting the naso-tracheo-bronchial sector and giving rise to asthma-like syndromes. Another form of disease, found in furriers with long exposure to 'hair dust', is described. It is characterized by a granulomatous interstitial pneumonia, of the tuberculoid type, very similar to that described in other diseases related to the inhalation of organic dusts, both vegetable and animal, such as 'farmer's lung' and 'bird fancier's lung'. This new disease—which we experimentally reproduced—can be diagnosed from the occupational history together with the finding on lung biopsy of hair shafts within granulomatous lesions (birefringence and histochemical reactions). As in other diseases of this type, a host factor of probable immunological nature is suggested. Attention is drawn to the need to protect workers in the furrier's trade.

Animal hairs have antigenic properties and can produce immunological reactions in the respiratory tract. These are mostly specific sensitizations affecting predominantly the nose and the bronchi and presenting quite frequently as asthma (Vallery-Radot, Wolfromm, Charpin, and Halpern, 1963; Sherman, 1968). These sensitizations can be set off either by direct contact with the animals (farmers, animal handlers, shearers, etc.) or by manipulation of their furs (mattresses, carpets, 'mohair' and furs) (Vallery-Radot *et al.*, 1963; Crofton and Douglas, 1969).

Lately it has been noticed that organic dusts, of both animal and vegetable origin, can give rise to another type of reaction, presumably of an immunological nature, which specifically affects the interstitium of the lung, producing a granulomatous process which leads to an irreversible pulmonary fibrosis (Emanuel, Lawton, and Wenzel, 1962; Pepys, Longbottom, and Jenkins, 1964; Seal, Hapke, Thomas, Meek, and Hayes, 1968; Jamison and Hopkins, 1940–41; Cancella, 1955; Horta and Cancella, 1956–57; Pimentel and Marques, 1969; Nash, Vogelpoel, and Becker, 1967; Cohen, Merigan, Kosek, and Eldridge, 1967).

This paper demonstrates that prolonged inhalation of dusts containing animal hairs can also produce changes in the interalveolar septa characterized by the presence of follicles and leading to diffuse pulmonary fibrosis. These findings were noted whilst studying some patients who had pulmonary resections for alleged tuberculosis, but in whom tubercle bacilli were never demonstrated, either in the patient's sputum or in the operative specimens. We later produced these interstitial lesions experimentally in the guinea-pig by the inhalation of animal hair.

CASE REPORT

A 34-year-old white woman had worked as a furrier for 18 years when, in April 1962, she became aware of weakness, general malaise, and considerable loss of weight. A chest radiograph showed a rounded shadow with indefinite limits near the right hilum. Tubercle bacilli were repeatedly searched for in the patient's sputum, always with negative results. However, the patient was treated with streptomycin, isoniazid, and para-aminosalicylic acid for nine months with some subjective improvement but with no change in the chest film. Right lower lobectomy was proposed and the patient was admitted to the Thoracic Surgery Centre of Sanatorio D. Carlos I (I.A.N.T.) in December 1962. Still no tubercle bacilli could be demonstrated, but the chest radiographs taken at this time showed a right hilar opacity (Fig. 1) considered to be tuberculous. Bronchoscopy showed a little congestion of the mucosa of the right bronchial tree with some reduction in the calibre of the right lower lobe bronchus due to oedema. There were no changes in the blood picture, and sedimentation rates never went above 7 mm./hour (Westergren). Ventilatory tests showed a restrictive type insufficiency. Examination of the resected lobe showed that the apical segment of the right lower lobe was firmer than usual and greyish-yellow in colour.

The cut surface of the lungs showed narrow strands of fibrous tissue, small focal areas of necrosis resembling caseation, and numerous greyish nodules. These nodules were 1 to 2 mm. in diameter and were either isolated or grouped together, particularly in

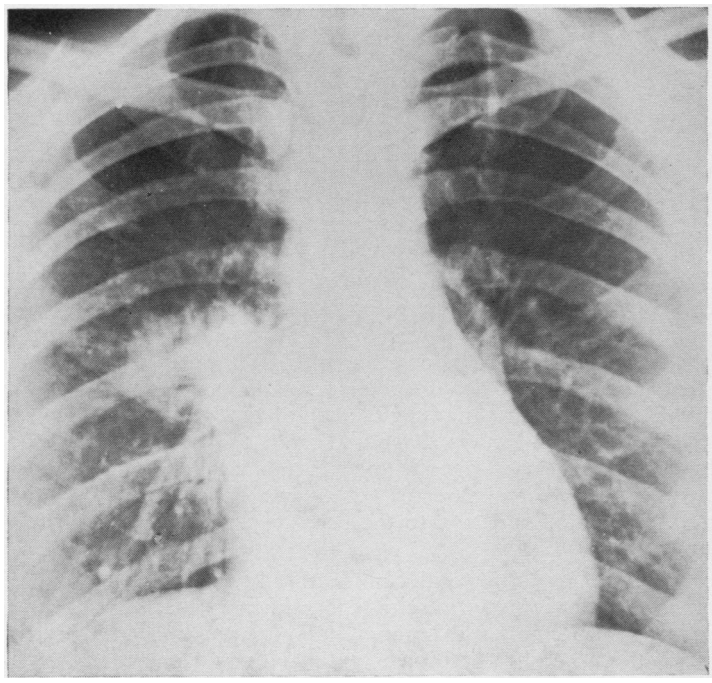


FIG. 1. *Chest radiograph showing a round, poorly defined shadow in the right hilum. Slightly increased pulmonary markings.*

areas of fibrosis. The surrounding lung was normal in appearance. No tubercle bacilli could be demonstrated in direct smears or following culture or the inoculation of guinea-pigs. Histological examination of the abnormal area of lung revealed follicles reminiscent of tuberculosis or sarcoidosis. These follicles included giant cells of Langhans or foreign-body type, generally surrounded by a rim of lymphocytes (Fig. 2). Associated with isolated or conglomerated follicles were focal areas of necrosis with surrounding granulation tissue infiltrated with eosinophils. There was no palisading of epithelioid cells around these necrotic foci (Fig. 3) which often showed calcification. Many of the follicles were centrilobular, being situated near a respiratory bronchiole. The majority of the giant cells contained multiple slits, some of which occupied the entire diameter of the cell (Figs 4a and b). In many places the alveolar septa were thickened by a cellular exudate of lymphocytes, histiocytes, and plasma cells. Special stains revealed an excess of reticulin fibres in the alveolar septa and granulomas. In some places this was associated with the deposition of collagen which frequently showed hyalinization. Although there was no obvious proliferation of alveolar lining cells, the alveoli contained many granular pneumocytes. Numerous follicles of the type described above were seen in the mucosa and submucosa of segmental and subsegmental bronchi which also showed infiltration by eosinophils.

The patient was re-examined six years after operation, and stated that she had been making fur coats and stoles, especially of fox and astrakhan, and that for the last three years she had been wheezing and having progressive dyspnoea on medium effort. A chest radiograph showed a more evident pulmonary reticulation than before and numerous nodules, especially in the left lower lobe (Fig. 5a and b). Results of ventilatory tests were similar to the previous ones and there was a significant reduction in the transfer of CO.

METHODS

EXAMINATION OF 'FUR DUST'

The following samples of fur dust inhaled by the patient were examined:

(a) fox and astrakhan furs used daily in the patient's work;

(b) other furs manipulated in the workshop (wild cat, leopard, seal, lamb, mink, and others);

(c) dust formed while making up pieces of fox and astrakhan;

(d) dust accumulated on the patient's worktable.

These samples were smeared, using glycerine as a vehicle, and embedded in paraffin, sectioned and stained with haematoxylin-eosin, Sakaguchi (mod. Baker) for arginine (Pearse, 1968), and performic acid-alcian blue and performic acid-Schiff methods for

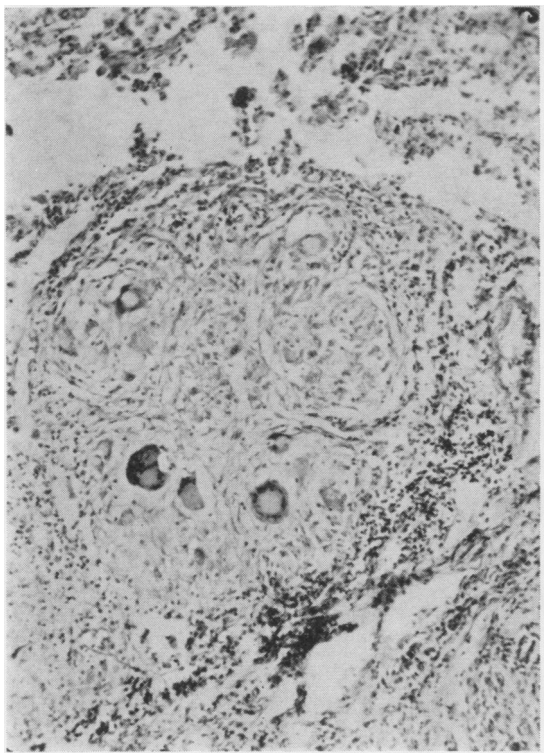


FIG. 2. *Follicles consisting of epithelioid cells, giant cells of Langhans and foreign body type and a rim of lymphocytes (Haematoxylin and eosin.* × 50).

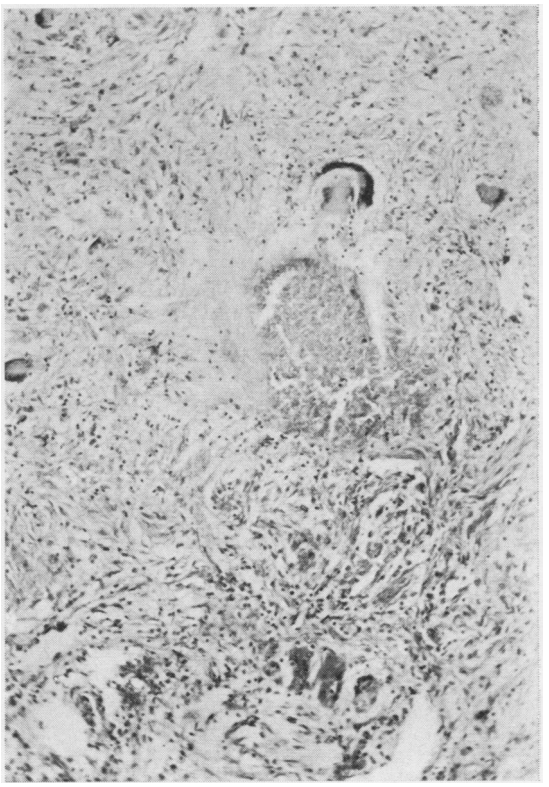


FIG. 3. *Necrotic focus within a granuloma showing similarities to caseation. There is no palisading of epithelioid cells (H. and E.* × 50).

SS groups (Pearse, 1968). In their study, conventional, fluorescent, and polarized light microscopy were used.

HISTOLOGICAL STUDY OF THE PATIENT'S LUNG

Fresh lung sections, fixed in 10% neutral formalin and stained by haematoxylin-eosin and performic acid-alcian blue method for SS groups, were examined with conventional, phase contrast and polarized microscopy. On paraffin sections of lung tissue, previously fixed in 10% neutral formalin, the following staining methods were tried: haematoxylin-eosin, Wilder for reticulin fibres, Weigert's resorcin-fuchsin for elastic fibres, von Kossa PAS, van Gieson, Ziehl-Neelsen, performic acid-alcian blue for groups SS, performic acid-Schiff for groups SS, and Sakaguchi (mod. Baker) for arginine. In this study conventional light, phase contrast and polarization microscopes were used. In the analyses of the inclusions found in the granulomas the following methods were used:

1. 'Formamid degradation' of pieces of lung after dehydration and extraction of the lipids, by the technique described by Thomas, Baumann, and Einbrodt (1951) and used routinely for the identification of mineral (Wettstein, 1966) and vegetable (Rüttner, Spycher, and Engeler, 1968) substances in the lung;

2. Micro-incineration, according to Rüttner and de Quervain (1947);

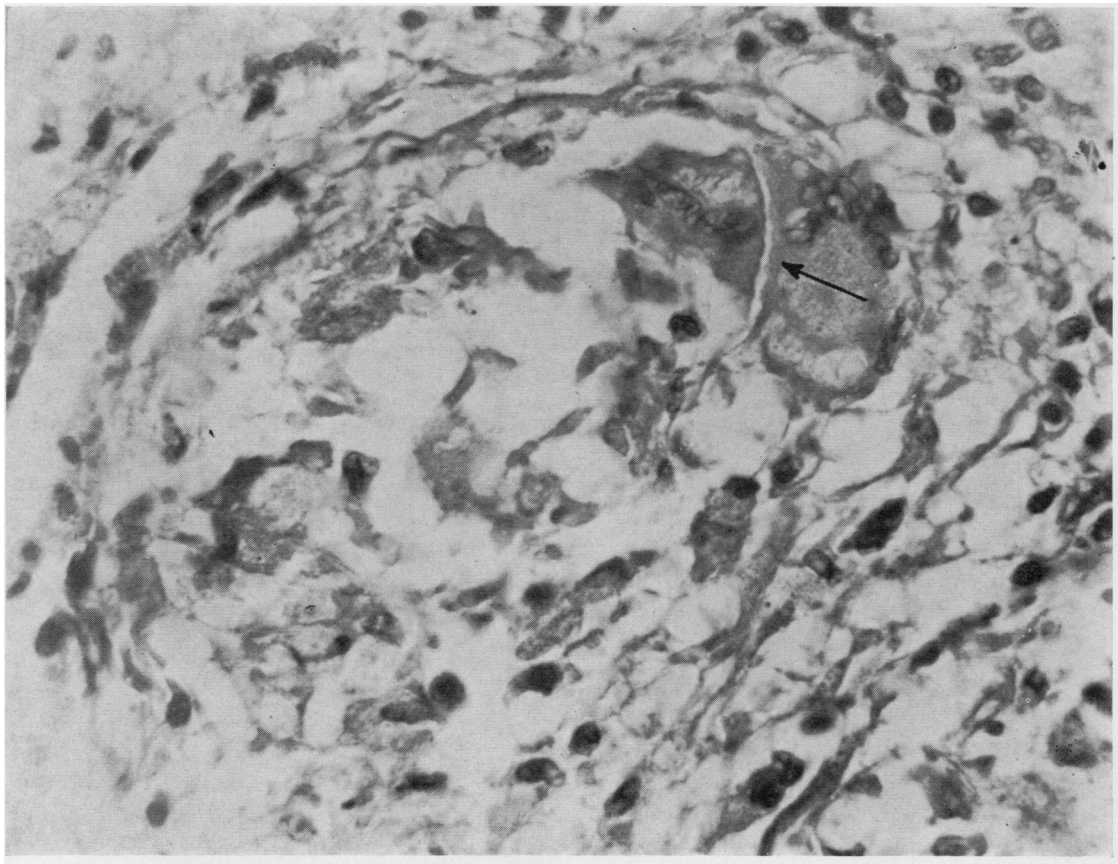
3. 'Formamid degradation' of histological sections of the lesions to identify the foreign bodies 'in situ' (Einbrodt, 1957);

4. Staining of sections after 'formamid degradation' by the performic acid-alcian blue method;

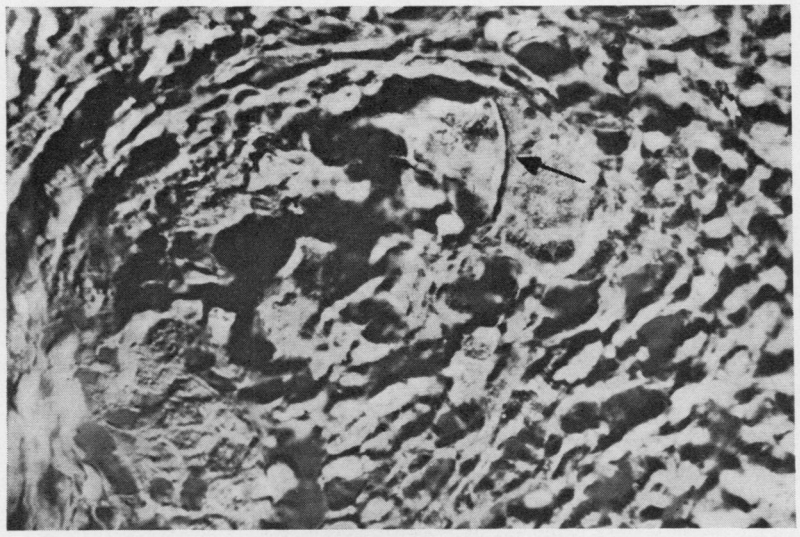
5. A comparative study with conventional light and polarization microscopes of the material found in the lesions and the dusts inhaled by the patient.

ANIMAL EXPERIMENTATION

Four groups of six guinea-pigs were used, three being submitted to the inhalation of fox hair and the remainder acting as controls. In each of the three groups a different method was used for the inhalation: (1) the guinea-pigs were placed in the workshop where the patient worked; (2) badly ventilated cages were used through which the dust, made up of finely cut fox hair, was made to pass by means of a



(a)



(b)

FIG. 4. *(a) A foreign body type giant-cell containing a hair (arrow) which extends through the entire cell into the surrounding tissue (H. and E. × 550). (b) The same photomicrograph using the 'bas-relief' effect (Thiery, 1949). Note the relief of the cellular inclusion and its large size (arrow).*

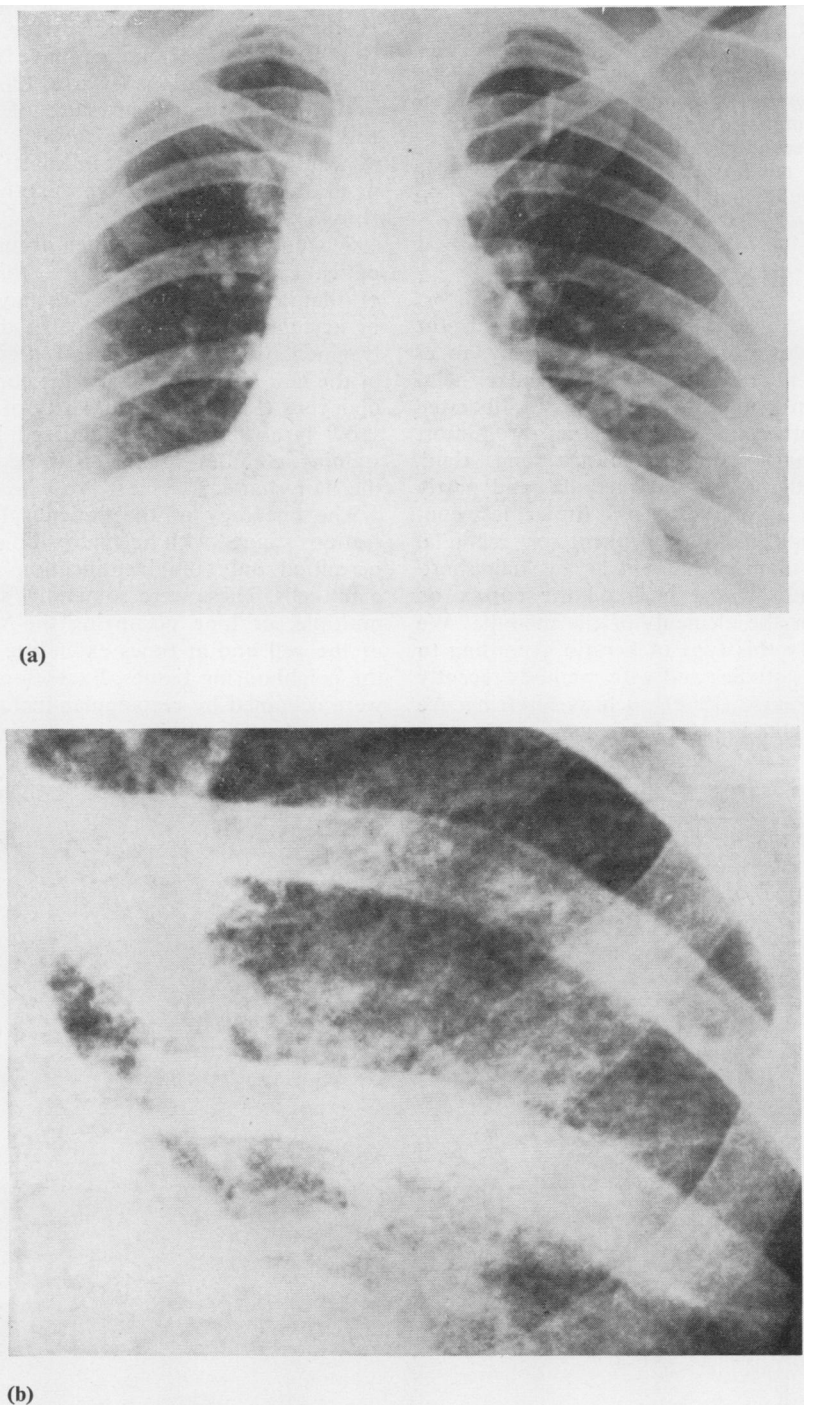


FIG. 5. *(a) Chest radiograph seven years after lobar resection. (b) Detail of left lobe (increased lung markings with micronodular lesions).*

fan for two hours three times a day; (3) the guinea-pigs were given repeated intratracheal injections of a saline suspension of the hairs. The experiments were started on 2 January 1969 and ended on 2 November of the same year. Radiographs were taken of the lungs of the animal at the beginning of the experiment, at the second month, and at the end of the experiment. In the histological study of the animal lungs the same techniques were used as for the patient's lung.

RESULTS

The different varieties of furs with which the patient worked were studied histologically, so as to help in the interpretation of the cellular inclusions found in the patient. The hairs liberated during the processing of the furs are almost exclusively 'shafts' and are partly long, rigid, pigmented, with or without medulla, and partly 'lanugo', made up of shorter and firmer, less consistent filaments without pigment or medulla. Keratin is the main constituent of the 'hair shaft' and exists both in the cells of the cortex or cuticula and in the elements of the medulla. We tried to identify this type of keratin according to Mercer's (1961) studies and with methods recently suggested by Pearse (1968), such as birefringence by polarized light (Fig. 6), Sakaguchi reaction for arginine, and the performic acid-alcian blue and performic acid-Schiff methods for SS groups. The results were the same as have been described under these conditions (Pearse, 1968).

As to the special structure of some of these furs, only the fox hairs showed a characteristic deposition of the pigment in 'shafts' which enabled us to distinguish them from the other hairs studied (Fig. 7).

A study of the dust which accumulated on the patient's worktable showed that this was made up of filaments and irregular, rectangular, rounded or acicular particles, due to the dissociation and fragmentation of the keratinized cellular elements of the hair shafts, especially the cortical and cuticular cells (Fig. 8). The majority of these particles show birefringence by polarized light and have staining affinities similar to those mentioned for the hair shafts.

The histology of the patient's lung, based on sections stained with haematoxylin-eosin, generally permitted only the identification of slits in the giant cells. These were sometimes small and often multiple, or long occupying the whole diameter of the cell and at times extending beyond it into the neighbouring tissues. Exceptionally, these slits were occupied by rectangular inclusions of different lengths (Fig. 9). These were simple or multiple

FIG. 6. *Paraffin section of a sample of fox hairs seen with partially crossed Nicol prisms. Birefringence.* (*H. and E.* × 75.)

FIG. 7. *Microscopic structure of a fox hair. Note characteristic deposition of the pigment in 'steps' (H and E.* × 300).

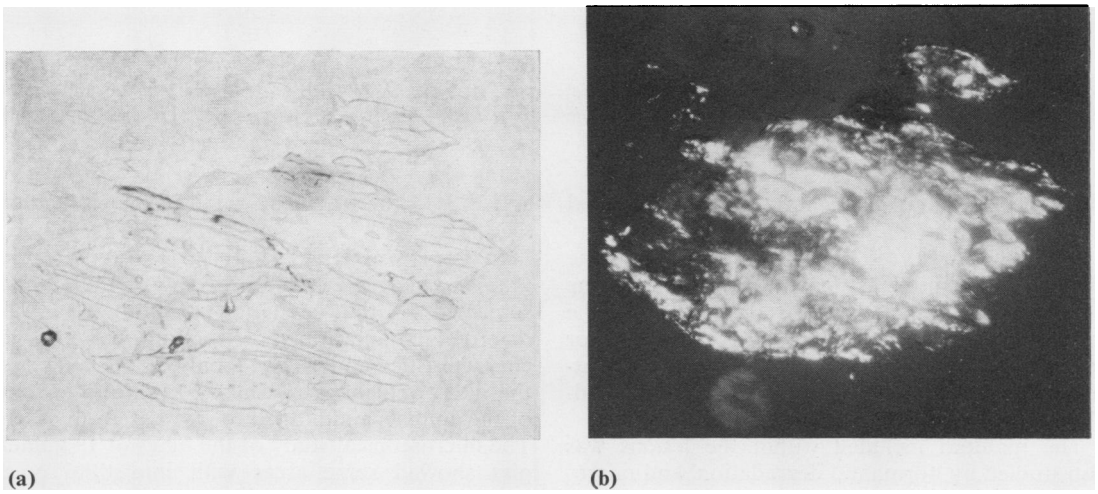


FIG. 8. (*a*) *Microscopic appearance of dust from the patient's worktable.* (*b*) *Same with polarized light. Birefringence of filaments and particles.* (× 75.)

and grouped in clusters. These inclusions were frequently partly intracellular and partly extracellular, sometimes quite long (Fig. 10).

Contrast phase microscopy (Fig. 11), and especially polarized light examination, showed that the slits contained inclusions, and that these were more numerous in the fresh preparation than in the paraffin-embedded material. The inclusions were made up of fine, often long filaments, but the majority were irregular, rectangular, ovoid or acicular particles. The inclusions were quite numerous and were found not only in the giant-cells but also in the epithelioid cells, in the necrotic foci, and in the thickness of the mucosa and sub-

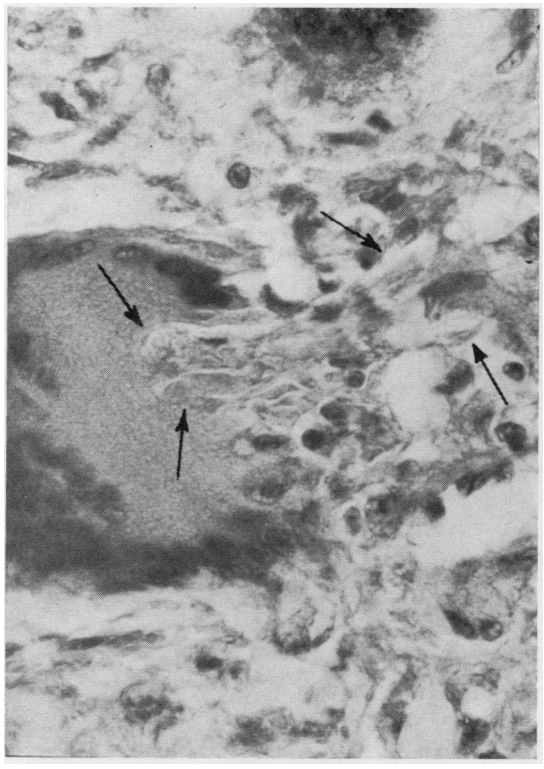


FIG. 9. *Giant cell containing a rectangular 'bundle' of inclusions within it. Note that part of these are outside the cell (arrows) (H. and E.* × 650).

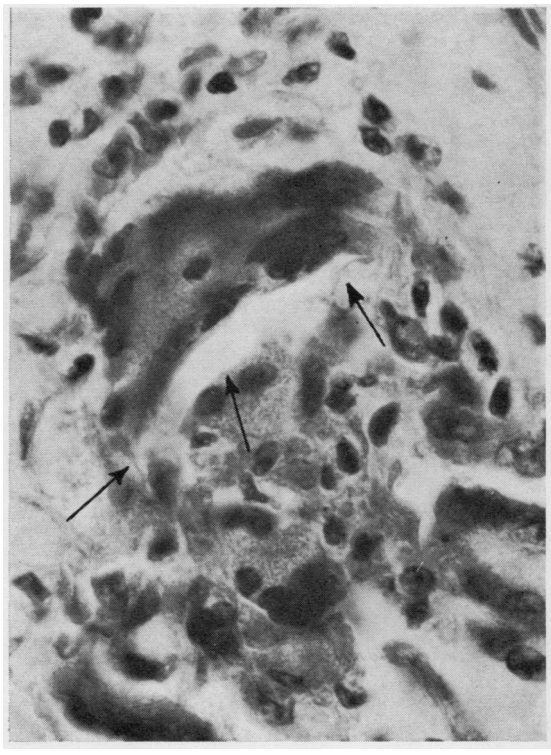


FIG. 10. *Another view of a cellular inclusion presenting as a long ribbon within a giant cell (H. and E.* × 580).

mucosa of various segmental and subsegmental bronchi found in the section.

For the study of the inclusions, the same methods were used as for the hair shafts. The results were similar to those described for the samples of felts and dust, and we saw, for example, inclusions within a foreign body giant-cell, stained dark blue by the performic acid-alcian blue method for the SS groups.

The material included within the lesions was also studied by 'formamid degradation' and micro-incineration of lung tissue. The results of these studies were confirmatory and permitted the same conclusions as those of the former studies. However, the micro-incineration of the histological sections was particularly interesting, as it not only allowed us to form an idea of the abundance of the inclusions in a limited portion of the lesion (Fig. 12) but also made it possible to identify the shaft of a fox hair within it. Figure 7 shows the microscopical appearance of one of these hairs with its typical step-like distribution of pigment and Fig. 13 the fragment found in the incinerated section.

In the experimental study no abnormal radiographic changes were seen in any of the animals subjected to the inhalation of fur dusts. The macroscopic appearance of the lung was also not characteristic, and showed only a thickening of the interalveolar septa, which was diffuse in some of the animals and limited to small areas in others. The microscopical study of the lungs of 19 guinea-pigs showed some areas with interstitial pneumonia made up of lymphocytes, histiocytes, and plasma cells, there being no changes in other areas.

The use of polarized light and of the staining methods described allowed us to identify hair dust in some of the granular pneumocytes within the alveoli of the majority of the animals.

In three of the guinea-pigs we found some sarcoid type septal granulomas containing a variable number of giant-cells, very similar to those found in the patient's lung. Numerous birefringent

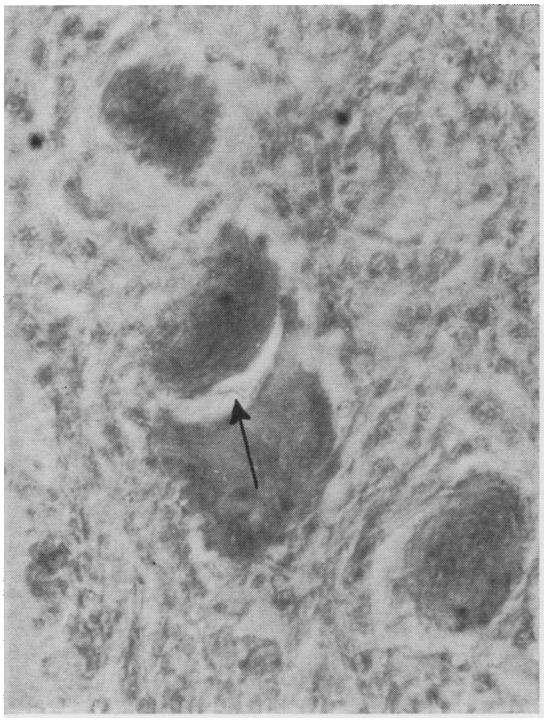


FIG. 11. *Another inclusion seen with phase contrast (arrows)* (× 580).

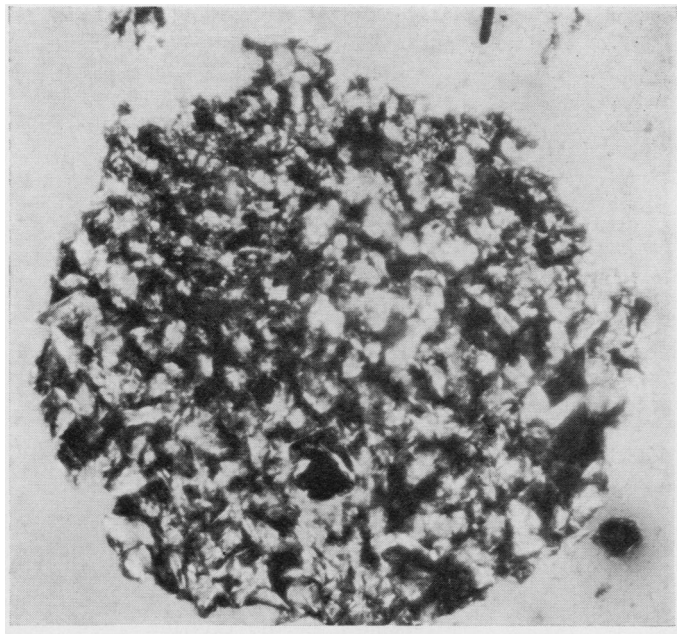
particles were seen within these granulomas whose staining characteristics were similar to those found in the hairs, in the dusts, and in the patient's lung. These three guinea-pigs came from the group of six exposed for 304 days in the furrier's workshop.

DISCUSSION

This patient had worked as a furrier for 13 years, making coats and stoles especially of fox and astrakhan fur. Her complaints were rather vague and consisted of weakness, malaise, and loss of weight. Her chest radiograph showed a segmental, para-hilar opacity which was considered to be tuberculous, although tubercle bacilli could never be demonstrated. The patient had antituberculosis chemotherapy, but no radiological improvement resulted, and so a right lower lobectomy was done. Microscopical examination of the resected lobe showed a necrotic epithelioid granuloma, compatible with the diagnosis of tuberculosis, and as such it was filed. However, no tubercle bacilli could be found in the lesions.

The case was later reviewed and we believe the data obtained are sufficiently demonstrative of a disease intimately related to the inhalation of hair dust which is similar to other diseases produced by vegetable, animal, and chemical dusts, sometimes related to fungi, such as farmer's lung (Pepys *et al.*, 1964; Seal *et al.*, 1968), bagassosis (Jamison and Hopkins, 1940–41), maple-bark disease (Emanuel *et al.*, 1962), sequoiosis (Cohen *et al.*, 1967), bird fancier's lung (Nash *et al.*, 1967), suberosis (Cancella, 1955, 1959; Horta and Cancella, 1956–57; Avila and Villar, 1968), malt handler's 'extrinsic allergic-alveolitis' (Filip and Barbořík, 1966; Riddle and Grant, 1967; Riddle, Channell, Blyth, Weir, Lloyd, Amos, and Grant, 1968), vineyard sprayer's lung (Pimentel and Marques, 1969), and coffee worker's lung (van Toorn, 1970). These findings suggest that inhalation of animal hair leads not only to sensitization which affects the nose and bronchial tree, often revealed as an asthma-like syndrome, but also to an interstitial granulomatous process which damages the interalveolar septa and culminates in diffuse irreversible pulmonary fibrosis. The eosinophilic infiltration of the mucosa and submucosa of the bronchi in the reported case, similar to that found in allergic asthma, leads us to postulate that these are not two different manifestations due to a common antigen but that they are probably intimately related. We also believe that the development of either of these pictures depends on the dose and concentration of the agent to which the patient is exposed (Villar, 1968). Similar asthma-like symptoms have been described in maple-bark disease, which is a granulomatous-type pneumonitis, very similar to furrier's lung and has been related to the inhalation of *Coniosporum corticale* (Towey, Sweany, and Huron, 1932; Emanuel *et al.*, 1962). With pulmonary aspergillosis an asthma-like syndrome has also been described (Hinson, Moon, and Plummer, 1952; Pepys, Riddell, Citron, Clayton, and Short, 1959; Longbottom and Pepys, 1964; Pepys, 1969) along with an 'allergic alveolitis' (Riddle and Grant, 1967) related to the massive inhalation of fungus spores, characterized by a tuberculoid granuloma (Filip and Barbořík, 1966) similar to the one we have described. Finally, contact with some species of birds can give rise not only to bird fancier's lung but also to hypersensitivity reactions of immediate type, characterized by rhinitis and asthma which may be related to antigens found in the feathers (Carrego, 1969).

The identification of cellular inclusions within the lung, and of bronchial lesions as well as hair dust, was based on the experimental reproduction of the disease and on the verification that the



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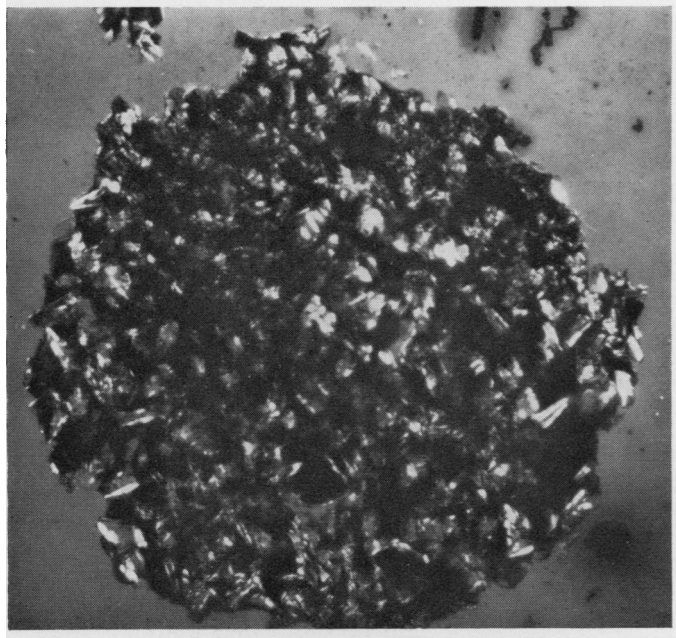

(b)

FIG. 12. *(a) Lung section incinerated by the method of Rüttner and de Quervain* (1947). *(b) With polarized light (numerous birefringent inclusions)* (× 60).

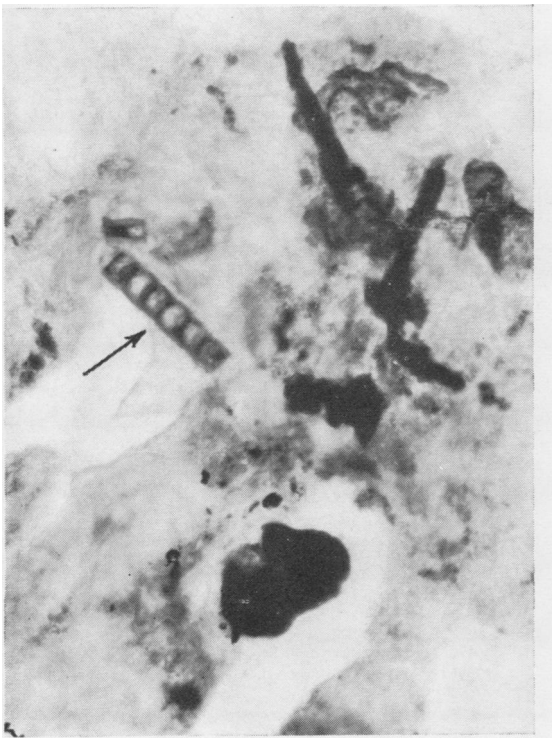

FIG. 13. *Detail of part of a section studied by micro-incineration. Note the presence of a fox hair (arrow) and compare with Fig.* 8 (× 195).

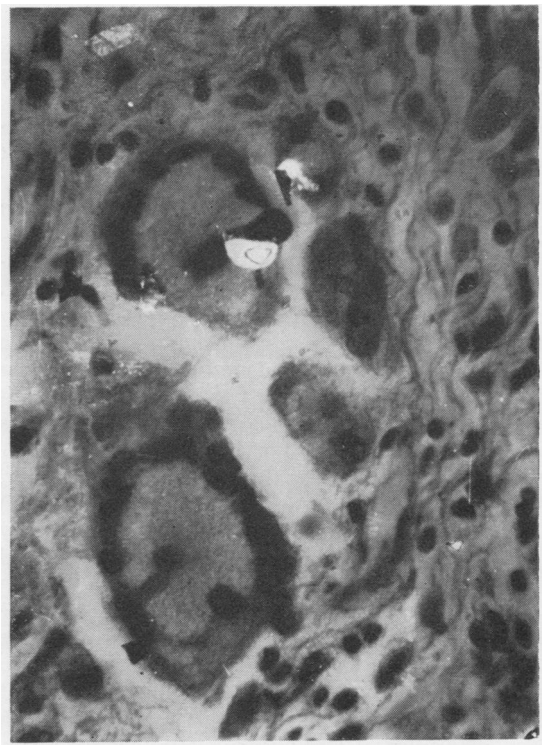

FIG. 14. *A small fragment of fox hair. Shaft within a giant cell, seen with partially crossed Nicol prisms (H. and E.* × 200).

accumulated material had the same physical and histochemical characteristics as the keratin in the hair shafts. These cellular inclusions are made up mainly of fine particles due to dissociation and fragmentation of the keratinized cells of the cortical and cuticule of the hairs. However, they may sometimes contain fragments of the entire thickness of the hair shaft, which may even permit identification of the variety to which they belong (Figs 13 and 14).

The penetration of hair dust into the lung seems to take place not only through the alveolar wall, as proved by their presence within the large alveolar cells, but also directly through the bronchial wall, as seems to be shown by the large number of granulomas found in this structure. This penetration should be facilitated by the rigidity of the keratinized particles of the hairs and the bronchial movements. The diagnosis of furrier's lung does not seem difficult if there is a history of inhalation of hair dust and if granulomas with numerous birefringent particles, giving the usual histochemical reactions of keratin, can be demonstrated on lung biopsy. The necrotic foci which can be found in the granulomas are similar to those referred to in other diseases of this type (Seal *et al.*, 1968; Pimentel, 1969a), although, in this case, they have an unusual extension (Fig. 3). We believe they represent a terminal phase of the evolution of some follicles and are not an expression of the activity of the disease, as seems to be the case in tuberculosis. The eosinophilic affinity of this necrosis, the presence of hair dust within it and the absence of epithelioid cell borders make it possible to distinguish it from real caseation.

As a complement to the study of this case of furrier's lung we reviewed 1,000 pulmonary resection specimens filed at the Sanatorio D. Carlos I and found two similar cases. One had worked as a furrier for 22 years and had had an unconfirmed history of tuberculosis for eight years before having her right middle lobe resected. The patient had recurrent bouts of haemoptysis in the latter months and her chest radiograph showed a large cavity which was considered to be tuberculous.

The microscopical lesions of the resected lobe were identical to those in our patient reported here, the only difference being the degree of the healing process and the presence of bronchiectatic cavities, one of which was radiologically interpreted as a tuberculous lung cavity. The other case was that of a woman who had worked as a furrier for 12 years, and who 10 years later suffered from properly confirmed fibro-cavitary tuberculosis. After failure of chemotherapy, pulmonary resection was done and examination of the specimen showed, along with an 'active' tuberculous cavity (histologically confirmed and containing tubercle bacilli), the presence of a sarcoid type granuloma with numerous giant-cells containing an appreciable number of inclusions made up of particles of hair shafts. We think that the lesions of furrier's lung, as is the case with silicosis (Gardner, Midleton, and Orenstein, 1930; Amsler, 1957) and suberosis (Pimentel, 1969b), may not only predispose to tuberculosis but also make clinical healing more difficult.

We have not yet had the chance to examine a large number of furriers to determine the incidence of the disease, but the data we have so far seem to show that only a limited number of these workers are affected. This fact, along with our experimental findings, suggests that, as seems to happen with other diseases of this type (Pepys, 1969; Pimentel and Marques, 1969), the establishment of the disease requires a host factor of a probable immunological nature. Further studies are necessary not only to confirm this important aspect of the disease but also to evaluate the possibility of fungi playing a part.

Finally, we wish to call attention to the long-drawn-out and silent course the disease may follow and to the need to protect people working in the fur industry.

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