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MORPHOLOGICAL RESEMBLANCE OF PULMONARY ADENOMATOSIS (JAAGSIEKTE) IN SHEEP AND CERTAIN CASES OF CANCER OF THE LUNG IN MAN

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In 1915 Mitchell (18) gave an extensive description of "Jaagsiekte" or "Jagziekte," a serious infectious endemic disease of sheep known in South Africa since about 1893. Both rams and ewes belonging to various races of sheep were said to be more or less susceptible, though lambs seemed to remain free. In more recent publications, however, lambs are also said to become victims of the disease.

Jaagsiekte can be introduced into areas previously free from it by sick animals, and healthy sheep contract the disease in stables formerly used by sheep suffering from it, which proves its infectious character. The course is chronic, the onset is insidious, and the disease may be present long before clinical symptoms can be recognized, which causes considerable difficulty in experimental work in endemic regions. The main symptoms are a progressive dyspnea with an abundant catarrhal exudate from the nose, cough, loss of appetite, emaciation and general weakness with very little fever, leading eventually to cachexia and death.

At autopsy the lungs show chronic inflammatory changes with development of much connective tissue and proliferation of alveolar epithelium, which will be further discussed below. Mitchell's description will not be used as a basis for this discussion since an intercurrent form of pneumonia was apparently present among the animals which he studied.

The histopathology of the lung lesions has been restudied by Cowdry (4), who considers the connective-tissue changes as primary. In sheep from endemic regions in Africa, even though they showed no symptoms, some increase of connective tissue with accumulation of macrophages and lymphocytes could be demonstrated. No such increase of connective tissue was found in the lungs of animals in non-endemic areas in America. In the connective tissue some foreign bodies and bacteria are present.

The first sign of irregular epithelial growth is an increase and enlargement of the cells lining the alveolar sacs. These cells may remain adherent to the alveolar wall or may assume a papillomatous arrangement, filling up the lumen. This proliferation of alveolar cells may occur entirely independent of the bronchi, as observed in serial sections. The enlarged cells stain abnormally, the nucleus staining much more intensely than that of the ordinary alveolar cell. In the end, the alveolar wall is lined with a layer of cubical or cylindrical cells (Fig. 1), showing a tendency to the development of papillomatous growths. Leukocytes may enter the alveolar sacs in the initial stages, but when the metaplasia of the alveolar cells is complete their number is again reduced. The interalveolar connective tissue contains then only very few capillaries.

The lining of the smallest bronchi may take part in this process, with folding of the epithelium and a filling up of the lumen as a result. This metaplastic bronchial epithelium also is often very atypical in structure.

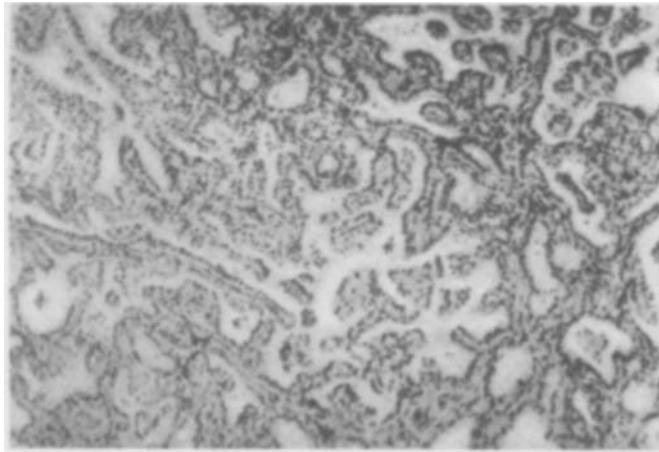


FIG. 1. JAAGSIEKTE: EPITHELIAL GROWTH INVESTING THE ALVEOLAR LUMEN
(From Cowdry: *J. Exper. Med.* 42: Plate XVII following p. 345, 1925.)

The total aspect of the lung begins to resemble that of a tumor, either an adenoma or an adenocarcinoma. Mitoses remain scarce, however, and metastases are never found even in the nodes at the hilus.

Similar lung lesions are found in other diseases of sheep. Cowdry and others compared the changes in Jaagsiekte with those described by M'Fadyean (17), in England, in verminous pneumonia of sheep (Fig. 2), a condition in which nematodes are present in the lungs. In Cowdry's South African cases of Jaagsiekte there were no worms at all and apparently worms play no rôle in the disease. In recent conceptions of the etiology of verminous pneumonia, the presence of worms is also looked upon as incidental.

In attempts to throw light upon the etiology of Jaagsiekte not only worms, but also protozoa, spirochetes, and bacteria have been ruled out as factors of importance. The condition is today regarded as a virus disease, although the nature of the virus remains obscure and no attempt at experimental infection of sheep has so far succeeded with any regularity.

In 1927 Cowdry and Marsh (5) restudied Jaagsiekte and compared it with the so-called Montana progressive pneumonia of sheep, another disease of unknown origin. Morphologically they seemed identical.

Studying the influence of coal tar applications on the frequency of lung tumors in mice at the Leeuwenhoekhuis in Amsterdam in 1927 (2), I was struck by the similarity of these tumors in certain phases of their development (Figs. 3 and 4) to the lesions described by Cowdry in sheep. In mice the lesions are more localized, but here also there occurs an epithelial proliferation in areas of interstitial pneumonia, which leads in certain cases to the same alveolar lining of tumor cells, or at least of cells resembling tumor cells, as in Jaagsiekte. Eventually the epithelial proliferations obtain more definite autonomy and the inflammation recedes so that the tumor character is accentuated.

De Kock (6) in 1929, in a new series of histologic investigations, paid special attention to the following questions: (1) Do sheep in infected areas show

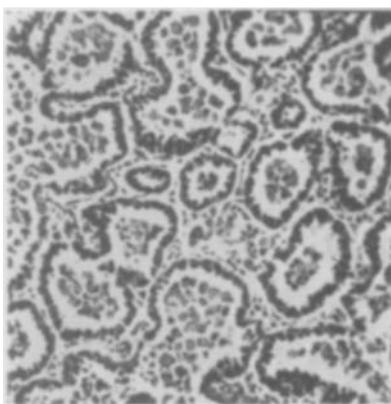


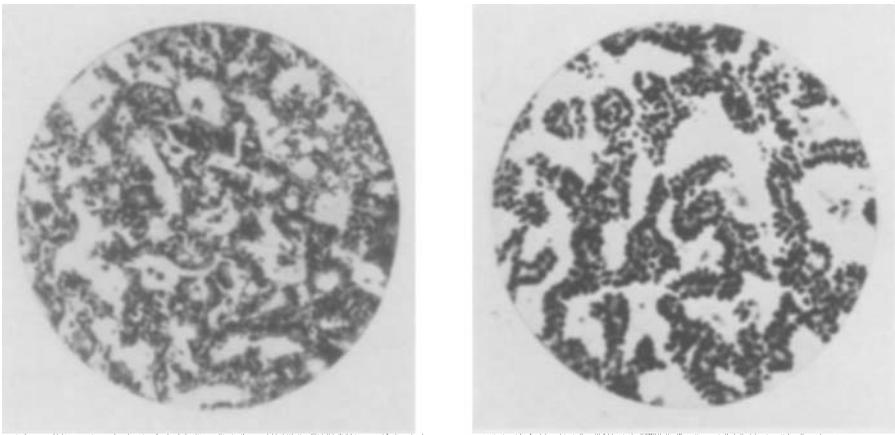
FIG. 2. TUMOR-LIKE LESION IN SHEEP LUNG
(From M'Fadyean: J. Comp. Path. & Therap. 33: 1, 1920.)

the primary interstitial lesions described by Cowdry? (2) Are the epithelial proliferations primary and must they be considered as tumor growth? (3) What is the significance of certain concentrations of lymphoid cells, to which Mitchell gives special attention? His conclusions were (1) that Cowdry's interstitial lesions may be absent and are not essential; (2) that the epithelial changes are primary in character, that they are often complicated in later stages by pneumonia, and that they represent a tumor process comparable to pulmonary growths in mice; (3) that Mitchell's lymphoid infiltrations have no significance, but are due to a concomitant but separate disease of the lungs. In other respects de Kock confirmed Cowdry's descriptions but mentioned, also, involvement of the bronchioli in the papilliferous-adenomatous proliferations.

After 1929 little reference to Jaagsiekte is found in the readily available medical and veterinary literature. In 1934, however, a disease of sheep with high mortality was reported from Iceland. It had not previously been observed there and it spread to such an extent as to become a serious problem.

It has been studied and reported on by Niels Dungal and his collaborators (7-9). The disease was introduced by a ram imported from Germany, from which it was contracted by two sheep on the same farm. Thence it spread to other flocks which were herded, in the autumn, with those from the farm where the disease had first appeared. Dungal and his coworkers identify this disease (Figs. 5 and 6) with the South African Jaagsiekte. Epithelial proliferation of the alveolar epithelium was pronounced and Dungal uses the term "epizootic adenomatosis of the lungs." The presence of nematodes (*Muellerius capillaris*) in the lungs of sheep in Iceland is of no etiological importance, as has been shown more especially by Taylor (24).

The lungs in the Iceland strain of epizootic adenomatosis are large, with confluent grayish non-protruding patches, which eventually involve nearly the entire organ. The diseased tissue is friable and resembles soft carcinomatous tissue, though the older lesions tend to become firmer. On close observation



FIGS. 3 AND 4. TUMOR FORMATION IN THE LUNG OF THE MOUSE, INCIPIENT (LEFT) AND MORE ADVANCED (RIGHT)

(From Bonne: *Ztschr. f. Krebsforsch.* 25: 13 and 14, 1927.)

tiny patches may be discovered in those parts that seem healthy on first appearance; these patches become fewer and fewer with increasing distance from the diseased portion of the lung. The hilus nodes are slightly enlarged. There are no metastases. Other organs do not show lesions, except for occasional enlargement of the heart.

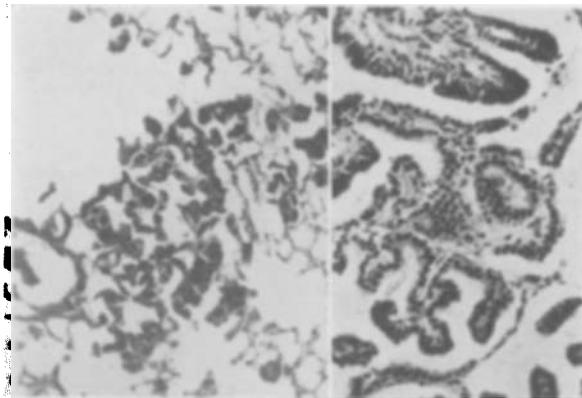
Microscopically, papilliferous adenomatous proliferations are found, the alveolar septa acting as a stroma for the cells. In the lung tissue between the adenomatous patches the alveoli are filled with mononuclear cells, sometimes in large, sometimes in small numbers. Microorganisms could not be demonstrated. Injection of suspensions of diseased lung tissue or filtrates thereof failed to reproduce the disease in sheep, rabbits, or mice. Only one positive result was obtained in a sheep by intrapulmonary injection of a tissue suspension.

The sudden appearance of the disease in Iceland and its epizootic course indicate an infectious agent, possibly a filtrable virus.

In summarizing these observations, we may say that in widely different parts of the world there exists a disease, or a group of closely related diseases, causing a certain amount of interstitial fibrous tissue reaction and tumor-like proliferation of the lung epithelium in sheep, and known by several local names—Jaagsiekte, epizootic adenomatosis, progressive pneumonia, etc.

It is little realized that similar changes are to be found in the lungs of sheep suffering from sheep pox. Roux (20), according to Cowdry and Marsh (5), has described these briefly. Eber (10) reported a pulmonary adenomatosis of sheep in Saxony in 1899, without worms, and, as is apparent from his pictures, analogous in character. Aynaud (1) in 1926 described a similar condition from France, associated with worms. In one case he observed metastasis in the hilus glands.

Similar epithelial proliferations occur in guinea-pigs. Spronck (21), of Utrecht, described them in 1907 and Grumbach (12), of Zurich, in 1926.



FIGS. 5 AND 6. ADENOMATOSIS OF SHEEP LUNG (JAAGSIEKTE), SHOWING (RIGHT) FORMATION OF PAPILLAE

(From Dungal: Proc. Roy. Soc. Med. 31: 500 and 501, 1938.)

Spronck found solitary or multiple nodules in the lungs, the smallest a few millimeters in diameter; the largest occupying nearly the entire lung. No growth was observed in the pleura or mediastinum. The nodules showed epithelial tubes with high cylindrical epithelium that might become flattened. Their lumen contained mucoid masses. Spronck regarded this tissue as neoplastic but he found no metastases. He referred to Sternberg's description of similar cases which in the latter's opinion were congenital anomalies (22). Spronck, however, speaks of a bronchioma destruens, a tumor arising from the bronchial epithelium. No parasites were present.

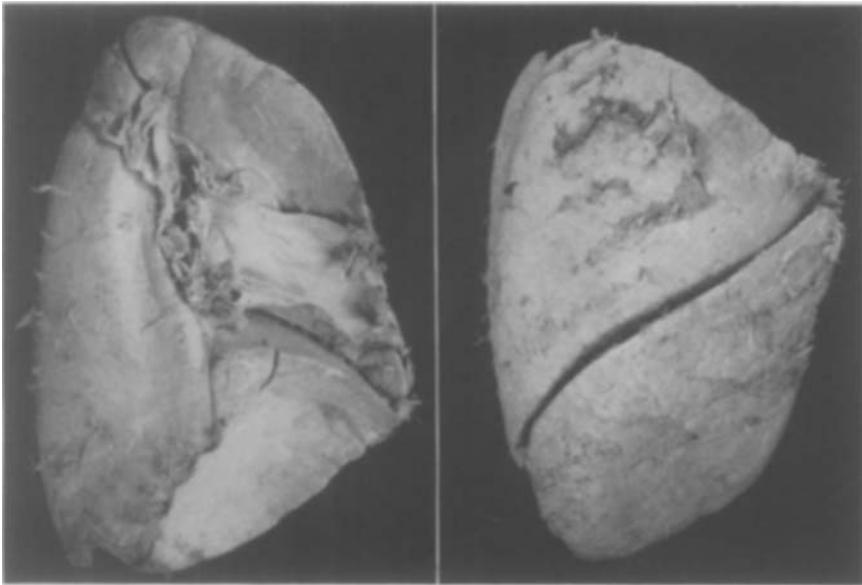
Grumbach's lesions occurred in guinea-pigs injected with *Corynebacteria* isolated from a case of lymphogranuloma, but the etiological importance of the bacteria is doubtful. Both bronchial and alveolar epithelium took part in the proliferations, and Grumbach noticed the resemblance to the South African Jaagsiekte. In both Spronck's and Grumbach's cases there was a considerable production of mucus by the tumor cells; in cases of Jaagsiekte the tumor cells produce mucus more rarely, although it may be present in abundance as the result of a concomitant bronchitis.

Straub (23) has recently described tumor-like epithelial proliferation of the bronchiolar epithelium in mice infected with the virus of influenza. In these animals, however, the epithelial new growth usually had a stratified character, whereas in the lesions of Jaagsiekte it is always cubical or cylindrical.

Theiler (25) mentions Jaagsiekte in horses, due in his opinion to the presence of a poisonous plant, *Crotalaria dura*, in their food.

Dungal (8) has searched the literature for reports of adenomatosis of the lungs in man, and mentions cases recorded by Oberndorfer (19), Helly (13), and Löhlein (16).

In Oberndorfer's patient, twenty-one years old, both lungs were uniformly dark red with small patches of a lighter colored tissue, about 0.5 cm. in diameter. Only the left apex was free and contained air. Microscopic examination showed the picture of a hemorrhagic pneumonia; the alveoli were filled



FIGS. 7 AND 8. LEFT LUNG OF CHINESE PATIENT: LATERAL AND MEDIAN VIEWS

with blood, leukocytes, and alveolar epithelium. Organization had already begun. The lighter patches interest us more especially; here there was replacement of the alveolar cells by papillomatous cubical or cylindrical epithelium and desquamated cubical cells, with leukocytes, edema, and some mucus in the lumina. Oberndorfer considers this to be an acute mutation of the alveolar epithelium with blastomatous affinities, developing out of a hemorrhagic pneumonia.

Briese (3) saw a similar case in Chemnitz. He found a mucus-producing papillomatous adenocarcinoma, without any recognizable primary starting point, entirely replacing both lungs. The bronchi were free, but metastases were present in the bronchial and prevertebral nodes. There were no pleural adhesions. The lobular lung structure was maintained. Löhlein's and Helly's cases showed a more local character, an abundant mucus production and less resemblance to Jaagsiekte.

In this paper I shall describe the lung lesions in a case in which autopsy was performed in the School of Medicine at Batavia (K. S. 5187).

A thirty-year-old Chinese patient had a fever of four weeks' duration some nine months before his death, with a cough, which failed to disappear after the temperature returned to normal. The sputum contained much mucus but no blood. The chest became painful and in the later months there were dyspnea and emaciation. The family history was negative. X-ray examination showed massive darkening of the left lung and exudation in the right lung. The blood picture was normal, and the Wassermann reaction negative. No tubercle bacilli were found. The patient died in an extremely emaciated condition.

At autopsy the total weight of the patient was 37 kg., while the lungs weighed 2700 gm. They were large and retained their shape after removal. The only lesions were found in the lungs. The left one was completely (Figs. 7 and 8), and the right one almost completely replaced by a diffusely growing homogeneous tumor. Only the right apex remained free; the hilus nodes were uninvolved. There were only very slight adhesions to the thoracic wall

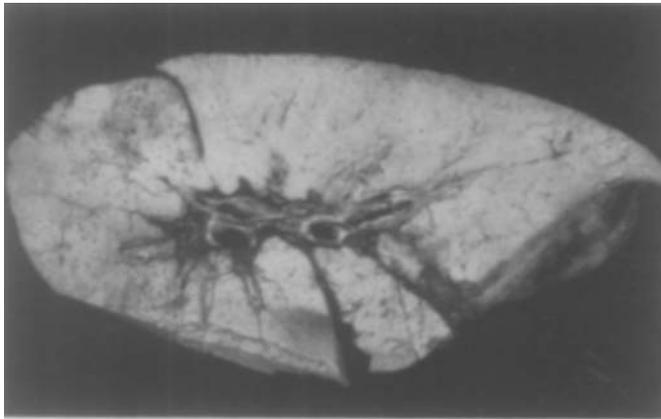


FIG. 9. RIGHT LUNG OF CHINESE PATIENT: CUT SURFACE

and between the lobes. The tumor tissue was of a light rose color, friable, and rather moist. A small quantity of foamy pus was present in some of the bronchi. In its homogeneous diffuse aspect the lesion resembled the hepatization stage of lobar pneumonia (Fig. 9) but the lungs were a little firmer on touch than in that disease. No necrotic areas were visible macroscopically.

Microscopic examination shows normal lung structure only at the apex of the right lung. In the other parts diffuse changes are present: replacement of the alveolar epithelium by cubical and cylindrical cells, with dark staining nucleus and protoplasm, resembling tumor cells (Fig. 10). Budding and papillomatous protrusions into the alveolar lumen is a common phenomenon. Mitoses are numerous. There is no destruction of the interalveolar septa nor any other distinct sign of destructive change, and only traces of invasive growth are seen. It is true that the papillomatous epithelial proliferation passing through the pores from alveolus to alveolus may widen these pores so that a group of adjacent alveoli are gradually changed into a single alveolar space, but outright destruction of alveolar walls practically never occurs. There is some invasion of the pleural connective tissue in places by small groups of tumor-like cells, but there are no tumor masses protruding from the pleura and invading the thoracic walls. A small amount of fluid with some desquamated tumor-like cells and a few leukocytes fill some of the alveolar lumina. Necrosis is practically absent.

There is no distinct thickening of connective tissue and no interstitial cellular infiltration of much importance; only the peribronchial connective tissue contains a few inflammatory cells.

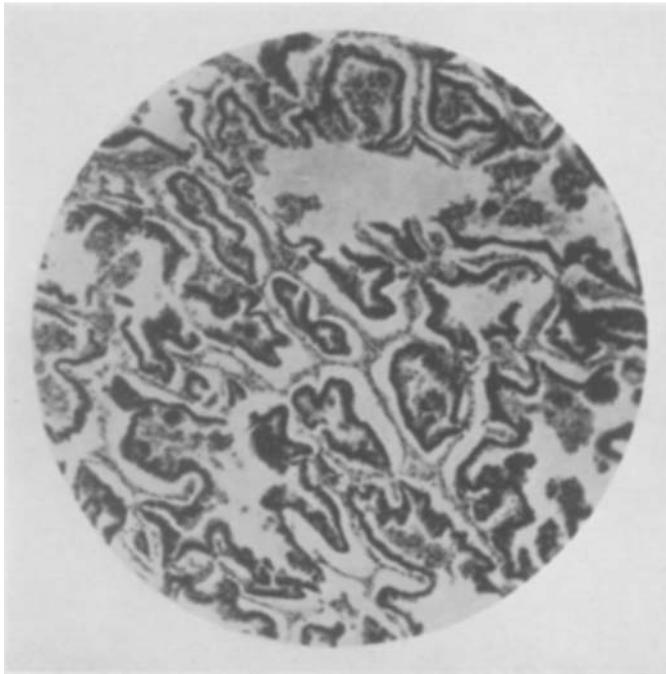
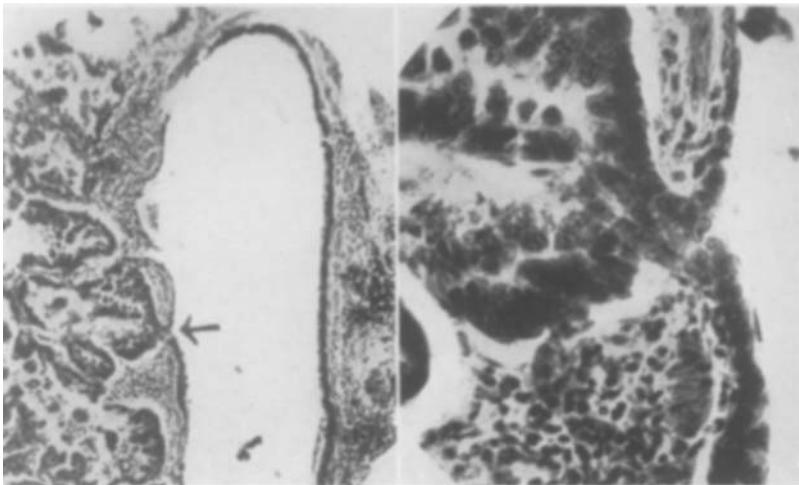


FIG. 10. SECTION OF LUNG SHOWING REPLACEMENT OF ALVEOLAR EPITHELIUM BY CUBICAL AND CYLINDRICAL CELLS, RESEMBLING TUMOR CELLS



FIGS. 11 AND 12. BRONCHIOLAR WALL SHOWING ADJACENT TUMOR-LIKE TISSUE

The photomicrograph to the right is a higher magnification of the area indicated by the arrow, showing the continuation of the alveolar cells on the wall of the bronchiole.

The above mentioned epithelial changes are not restricted to the alveoli; they are present also in the terminal bronchioles. There is an uninterrupted continuation of the lining with tumor-like cells of the alveoli and smallest bronchioli. Figs. 11 and 12 illustrate this continuity. The bronchiolar wall shown in Fig. 11 is in other places lined with normal bronchiolar epithelium. The larger bronchi retain their normal epithelium, but some of them show changes due to ordinary bronchitis.

The mode of progress of the disease can be observed in the right lung. Small patches surrounding a terminal or respiratory bronchiole showing epithelial metaplasia or tumor formation precede the solid mass of pathological tissue invading the right upper lobe. In the right apex the position of the blood vessels seems to be independent, although their position, parallel to the bronchi, often brings them into contact with these patches. No thrombi are visible.

We shall consider now the peculiar change in character of the respiratory cells of the alveoli and respiratory bronchi. It is clear that this respiratory epithelium represents the seat of the disease. What has happened is more than an ordinary metaplasia. The newly formed epithelium shows signs of active growth, *e.g.* numerous mitoses and epithelial budding. The morphological resemblance to the epithelial proliferations in Jaagsiekte is very close, and we meet with similar difficulties in defining the character of the epithelial change.

The epidemic course of Jaagsiekte in South Africa and Iceland being most easily explained by the action of a virus, the possibility of a virus as the etiological agent in our case has to be taken into consideration. No similar cases were discovered, however, in the surroundings of our patient, nor was he known to have been in contact with any cases in sheep or goats. Among Eastern populations it is difficult, however, to collect reliable data.

DISCUSSION

Originally this peculiar disease of the lungs was classified in my laboratory as a tumor, a pulmonary carcinoma. There are, however, several objections to this diagnosis. It is strange, first, that a carcinoma replacing practically all the tissue of both lungs did not give rise to any metastases in the hilar nodes; second, that only very slight adhesions were present between the lungs and thoracic wall and between the lobes of the lungs; third, that the alveolar walls should form the stroma of the tumor; fourth, that necrosis is almost completely absent, and fifth that no definite signs of destruction of either bronchi or pleura could be found. This means that invasive and destructive growth is practically absent. Only at certain spots in the pleura does tumor invasion seem to be undeniably present.

If carcinoma is an unsuitable term to designate this remarkable condition, the term carcinosis may be suggested. Diffuse proliferation of connective tissue is designated as fibrosis instead of fibroma, because definite tumor formation is absent. In the case described there existed a diffuse process of epithelial proliferation, which was certainly more than a simple metaplasia, and which killed the patient, although invasive and destructive growth was not visible. On account of its malignancy, the term carcinosis seems preferable to adenosis.

More important than the name it deserves is the resemblance of the disease to Jaagsiekte. There exists apparently a group of morphologically closely related diseases producing in the lungs of several species of animals, *e.g.* sheep, guinea-pigs and mice, as well as of man, a diffuse new growth of alveolar and bronchiolar cells. In at least one representative of this group, Jaagsiekte in sheep, the infectious character of the disease seems to be beyond doubt and a virus appears to be the cause. This suggests the possibility that certain diffuse

human cancers of the lung, here described as carcinosis, may also be of virus origin.

Can we bridge the gap between this carcinosis of the lung and the ordinary type of pulmonary cancer? The peculiar phenomenon of the walls of the alveolar sacs serving as stroma for the tumor is also observed in certain types of lung cancer described as *alvéolite cancéreuse* or Alveolarcarcinom. Kaufmann (14) describes these lesions as a diffuse form of lung carcinoma. He states that large portions of the lungs are involved by masses of cancer tissue, which are composed of lobular, frequently confluent, whitish-gray or reddish-gray transparent areas. Mucoïd material can be scraped from the surface. Occasionally, also, cloudy necrotic areas resembling cheesy pneumonia can be found, which suggest a multicentric diffuse exudation. The larger lymph channels and the bronchi may remain free from the exudate. "There is often found in these cases a true carcinoma of the lung with cylindrical or cubical epithelium, papillary structures and gelatinous degeneration. The lung alveoli form the stroma of the carcinoma, which is often of the alveolar type."

Ewing (11) also mentions this diffuse type of lung carcinoma and accepts it in certain cases as a sequel of pneumonia. Letulle (15) gives a picture of a similar case in which no production of mucus was apparent. In some cases metastases were present.

Metastasizing alveolar carcinoma may therefore be the connecting link between the carcinosis here described and the ordinary type of lung carcinoma. If the alveolar (or bronchiolar) new growth has a more definite invasive character, it kills the patient by destruction and necrosis, leading to hemorrhage and bacterial infection, and metastasis will be present at the time of death; if the invasive character of the alveolar cells is less distinct, the disease spreads diffusely through both lungs and kills by replacement of lung tissue till practically all respiratory epithelium has disappeared.

CONCLUSIONS

In the human lung a diffuse tumor-like condition, here described as carcinosis, may occasionally be found. Morphologically this closely resembles certain lung diseases of animals, of which Jaagsiekte in sheep is the best known representative. In these diseases the alveolar cells and sometimes the bronchiolar cells are replaced by darkly staining cells in which mitoses are frequent. These cells line the alveolar sacs and often protrude into their lumen, forming papillomatous buds. There is practically no invasive growth and metastases are absent. The possibility of a virus origin of these diseases is discussed. A detailed description is given of a case of general pulmonary carcinosis in a Chinese.

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