

Lung Lesions in Old Mice

Crystals

Eosinophilic crystals of varying sizes are sometimes found focally in the lungs of various strains of mice ([Green, 1942](#); [Yang and Campbell, 1964](#); [Rehm et al., 1985c](#)). The small crystals are usually within the cytoplasm of alveolar macrophages ([Fig. 1](#)), and the larger crystals are free in the alveoli. These crystals may less frequently involve large areas within a single lung, especially in association with lung tumors. Crystal formation was reported to be an autosomal recessive trait in moth-eaten mice ([Ward, 1978](#)).

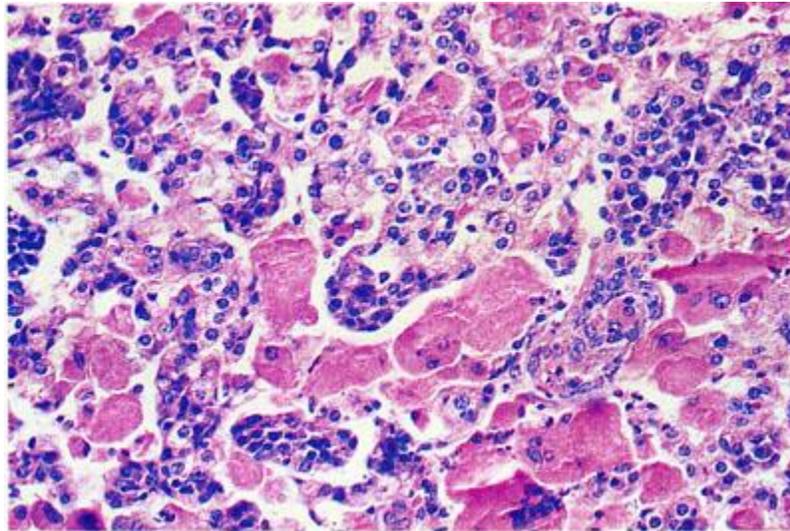


Figure 1. Eosinophilic Crystals - Pulmonary Alveolar Macrophages

Edema and Hemorrhage

Edema and hemorrhage occur spontaneously in the lungs of mice; their etiology is often obscure. Focal areas of hemorrhage can occur during sacrifice, especially after carbon dioxide euthanasia. The edema may be focal or diffuse and is characterized by an eosinophilic homogeneous material in the alveoli. Sometimes the edema is restricted to perivascular locations. Hemorrhage in the lungs is characterized by the presence of erythrocytes free in the alveoli and may occur in conjunction with pulmonary edema.

Chronic Passive Congestion

Chronic passive congestion of the lungs may be secondary to any factor resulting in the restriction of the flow of blood from the pulmonary veins into the left atrium. Left atrial thrombosis predisposes the mouse to chronic passive congestion. The alveolar walls are thickened and may contain increased amounts of collagen. The alveoli may contain macrophages filled with hemosiderin, which stain for iron ([Fig. 2](#)).

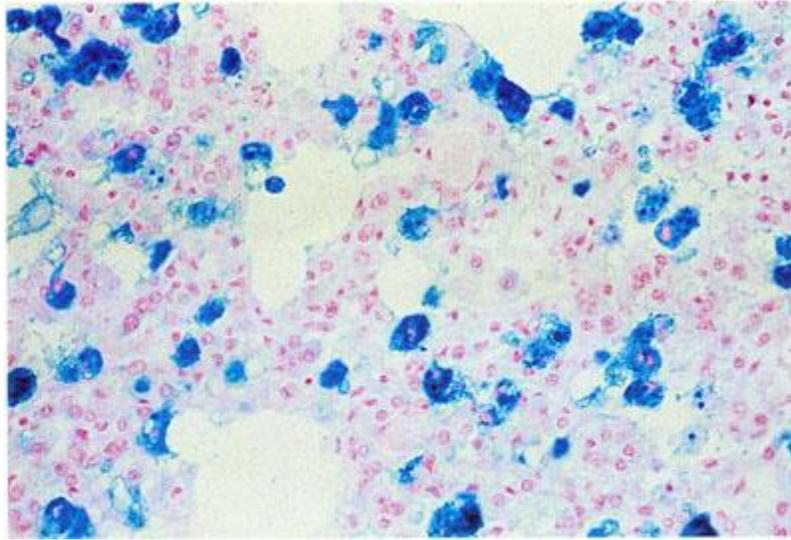


Figure 2. Chronic Passive Congestion (Prussian Blue Stain) - Lung

Lymphoid Aggregates

Perivascular and peribronchial lymphoid aggregates are sometimes seen in the lungs of older mice. The cells are normal in appearance and consist primarily of small lymphocytes ([Fig. 3](#)). The lymphocytic foci may be indicative of a past or latent viral infection. Lymphoid foci are not normally found in lungs of most strains or stocks of germ-free or SPF mice but are the normal bronchial-associated lymphoid tissue (BALT) in rats.

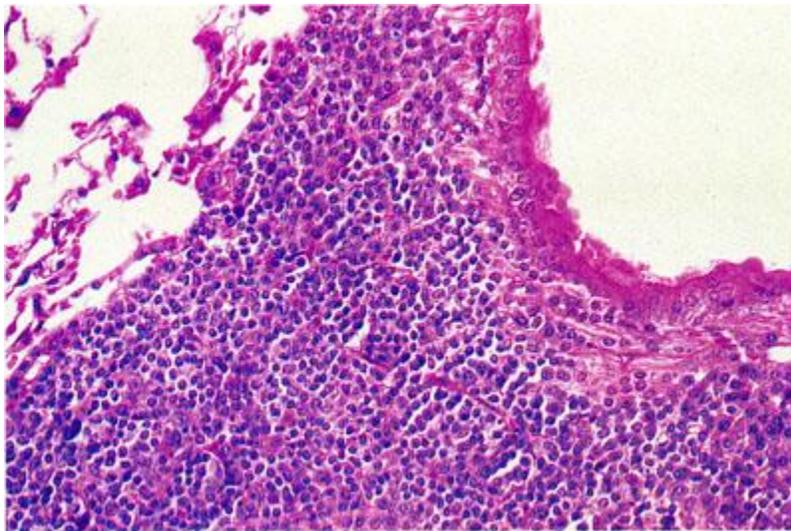


Figure 3. Perivascular and Peribronchial Lymphoid Aggregates - Lung

Atelectasis

Atelectasis is due either to a collapse or a compression of the alveolar spaces and may be focal or involve large areas of lung parenchyma. One of the more common causes of atelectasis in the lungs results from compression

by pulmonary tumors. The affected lung has a distinctly solid appearance due to the collapse of the alveoli ([Fig. 4](#)).

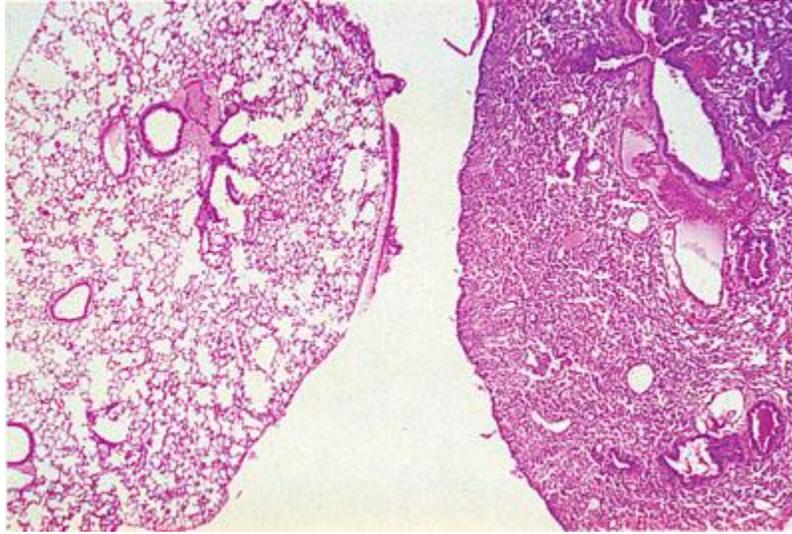


Figure 4. Pulmonary Atelectasis Adjacent to Normal Lung

Macrophage Accumulations

Focal areas of increased numbers of alveolar macrophages may occur in the alveoli of lungs of mice as an incidental finding ([Fig. 5](#)). Large collections of macrophages may also occur adjacent to pulmonary tumors. Some macrophages may contain crystalline structures.

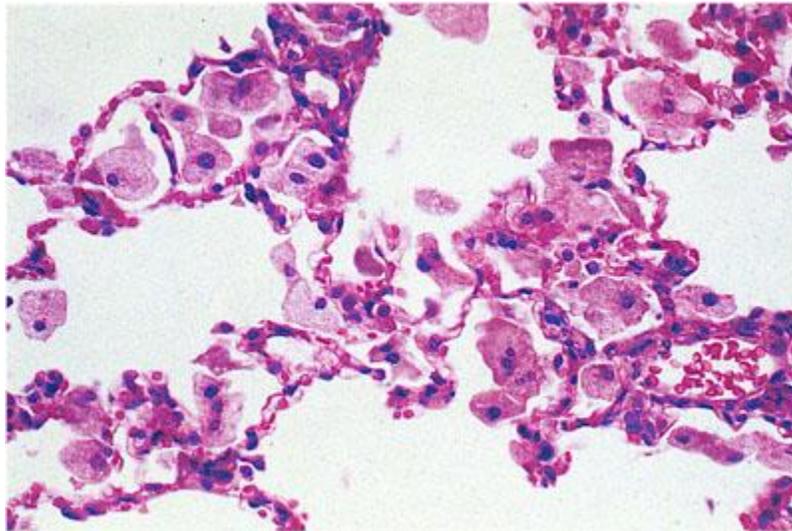


Figure 5. Pulmonary Alveolar Macrophage Accumulations

Pulmonary Tumors

Pulmonary tumors are one of the more common spontaneous lesions in mice, but the incidence varies with strain ([Heath *et al.*, 1982](#)). They have been used as model bioassay systems in mice with a high spontaneous incidence of pulmonary tumors ([Shimpkin and Stoner, 1975](#); [Maronpot *et al.*, 1986](#)). They may occur as single or multiple tumors and may be located subpleurally (peripheral lobular) or in peribronchial locations. Until recently, most pulmonary tumors in mice have been assumed to develop from the Type II pneumocyte ([Stewart *et al.*, 1979](#)). Recently, some investigators have provided morphologic evidence and described pulmonary tumors arising from both the Type II pneumocyte and, in mice injected with ethylnitrosourea, from the Clara cells within bronchiolar epithelium ([Kauffman *et al.*, 1979](#); [Palmer, 1985](#)). Tumors of alveolar Type II cell origin consist of continuous cords of uniform cuboidal cells lining alveolar septa (alveolar or tubular pattern) and filling alveolar spaces as they enlarge to give a solid compact appearance (solid pattern; Figs. [6](#) and [7](#)). [Fig. 8](#) shows an adenoma positive for surfactant apoprotein. Some tumors may arise adjacent to or within bronchioles. Ultrastructurally, the alveolar Type II tumors contain spherical nuclei and characteristic osmiophilic lamellar bodies, large mitochondria and multivesicular bodies (Figs. [9](#) and [10](#)).

The Clara cell tumors as described by [Kauffman *et al.*, \(1979\)](#) consist of columnar epithelial cells arranged in a papillary pattern ([Fig. 11](#)). This tumor is more likely to be malignant and sometimes invades the sternum, thoracic lymph nodes and heart and occasionally metastasizes to liver and lymph nodes ([Fig. 12](#)). These malignant neoplasms sometimes assume a sarcomatous pattern. Ultrastructurally, the neoplastic cells show deep folds in the nuclei, prominent smooth endoplasmic reticulum, elongated mitochondria and complex interdigitations of adjoining cells (Figs. [13](#) and [14](#)). While these two types of lung tumors in mice have been described, it is not clear as yet if all solid tumors are composed of alveolar Type II cells and all papillary tumors originate from Clara cells. Commonly, small lung tumors tend to be more solid and large lung tumors tend to be more papillary and in mixed patterns. Recent studies ([Ward *et al.*, 1985](#); [Rehm *et al.*, 1988](#)) have provided evidence that the morphologic papillary tumors of alleged Clara cell origin are not immunoreactive for Clara cell antigen found in normal Clara cells but are immunoreactive for surfactant apoprotein found in normal alveolar Type II cells. In addition, serial sections of lungs with these papillary tumors clearly demonstrate that they arise as tubular lesions from alveolar walls and not usually from bronchiolar epithelium. These findings suggest that many of the alleged Clara cell tumors are of alveolar Type II cell origin. Thus, pulmonary tumors of mice should be diagnosed by morphologic pattern only.

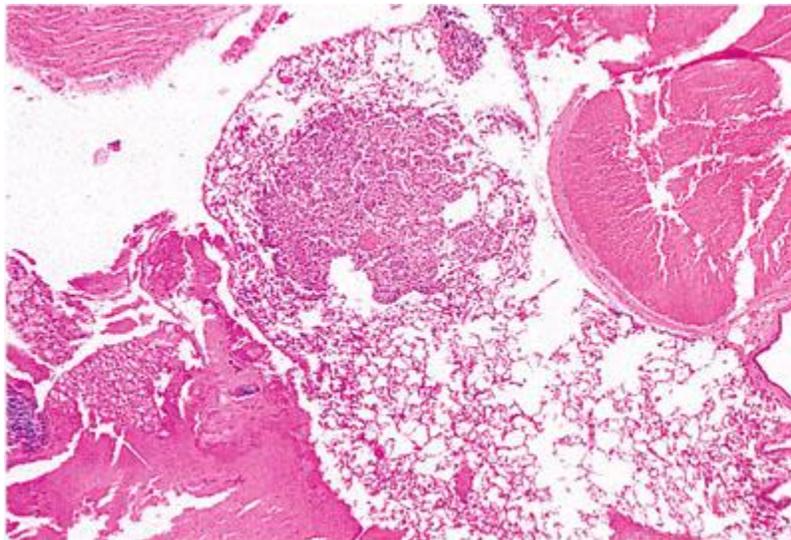


Figure 6. Pulmonary Alveolar Cell Adenoma

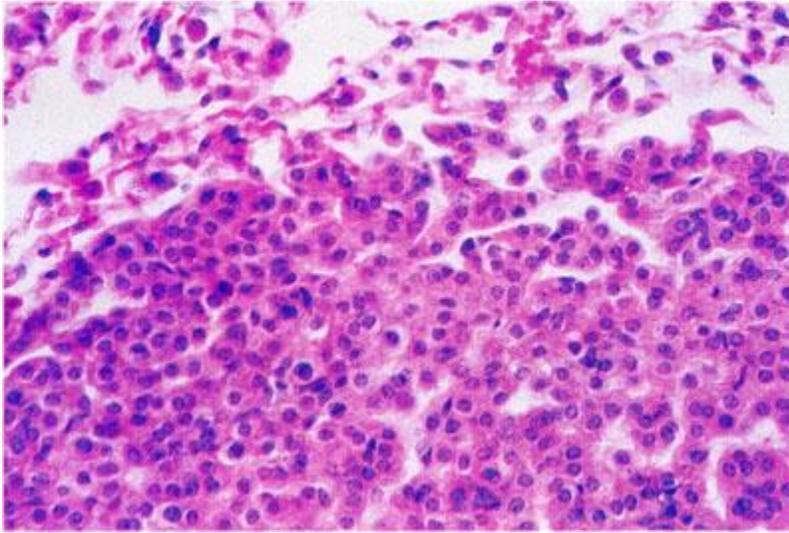


Figure 7. Pulmonary Alveolar Cell Adenoma

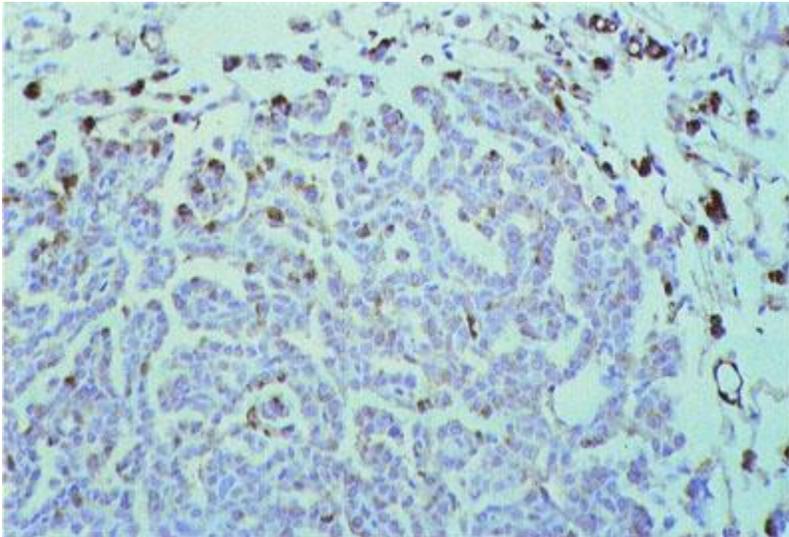


Figure 8. Adenoma - Pulmonary Surfactant Apoprotein - Lung

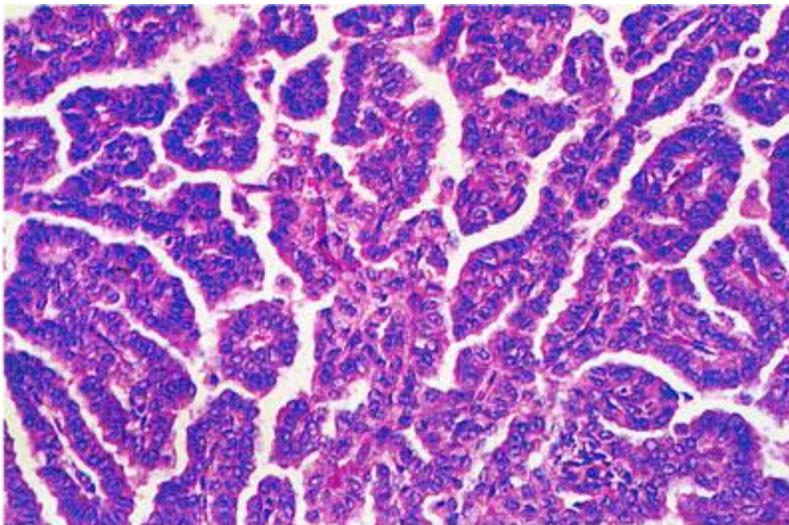


Figure 9. Papillary Adenocarcinoma - Lung

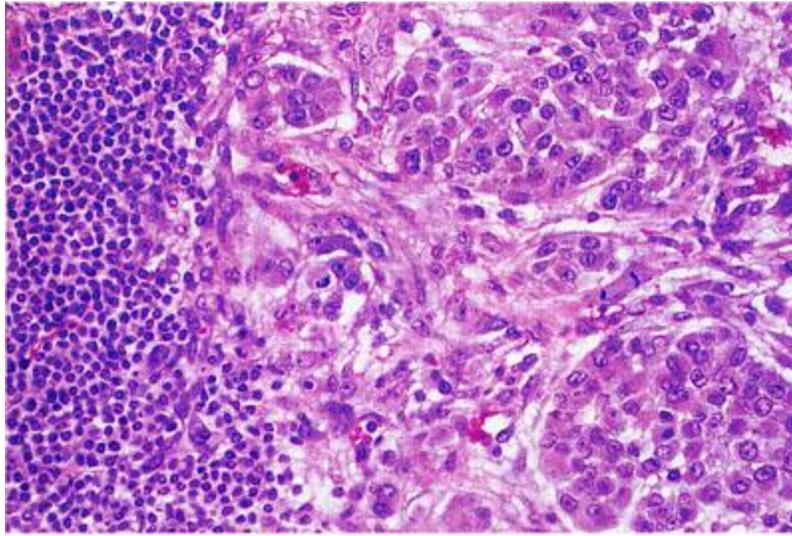


Figure 10. Lymph Node Metastasis of Pulmonary Adenocarcinoma - Lung

Metastatic Tumors

The incidence of pulmonary metastases for various neoplasms in mice was reported by [Frith *et al.* \(1981b\)](#). The most common were osteosarcoma (46.2%), renal adenocarcinoma (20.0%), fibrosarcoma (16.7%) (combined sites), myoepithelioma (10.5%), mammary adenocarcinoma (9.5%), undifferentiated sarcoma (5.6%; combined sites) and hepatocellular carcinoma (4.8%). Other tumors metastasizing to the lungs at an incidence of less than 3% included leiomyosarcoma (combined sites), ovarian granulosa cell tumor, adrenocortical carcinoma, angiosarcoma (combined sites), squamous cell carcinoma (combined sites), Harderian gland adenocarcinoma and urinary bladder transitional cell carcinoma.