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BENIGN CLEAR CELL ("SUGAR") TUMORS OF THE LUNG†

There exist in the lung primary benign tumors that at first glance resemble metastases from hypernephroid tumors of the kidney. To date only an abstract of the first report dealing with the first four examples and a brief descriptive note have been published.[1,2] From a more recent study of twelve of these tumors, criteria have emerged that enable the differentiation from other neoplasms to be made on the basis of routine histological preparations. Correct identification should spare the patient uncomfortable and costly diagnostic procedures, and should provide the solace of a good prognosis. Indeed, it was the fact that extensive diagnostic procedures proved to be without result after they had been undertaken on the basis of a mistaken diagnosis that soon led to a more accurate definition of these tumors. Both cellular and stromal characteristics identify these benign neoplasms. The cells contain immense quantities of glycogen, while fat is essentially absent. Mitoses are exceedingly rare. There is no necrosis and the blood supply is by way of abundant large, thin-walled channels.

Clinical and radiographic features

Some clinical and anatomical features are recorded in Table 1. There is an almost equal sex distribution, five of the twelve patients being male. Nine of the patients ranged in age from 45 to 59 years when they came to surgery. The oldest was a woman of 64 and two of the patients were men aged 28 and 29 respectively.

None of the patients had complaints that could clearly be related to the tumors. There was no hemoptysis nor production of sputum. The lesions were detected in what were essentially routine chest films in 8 of the 12 patients. One of these (Case 8) had had multiple bladder tumors which had been treated successfully. Another (Case 9) had cystitis, and a ureteral stone was demonstrated. In one patient (Case 2) a shadow was noted in the right lower lobe in 1945 and interpreted as postpneumonic scarring. This persisted following several additional episodes of pneumonia, the last of which was 2½ months before the right lower lobectomy was performed in

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1960. Two patients had chest pain. One (Case 3) complained of pain in the chest wall, but on the side contralateral to the tumor. Epigastric distress and chest pain were the complaints for the investigation of which roentgenograms were made in Case 12. One woman (Case 5) complained of low back pain. Thus it may be concluded that these tumors are essentially silent.

There were no significant findings upon physical examination. None of the tumors could be visualized bronchoscopically.

Radiographically the tumors were rounded or ovoid, smoothly contoured, peripheral parenchymal masses (Figs. 1-3). Only one gave a suggestion of notching (Fig. 4). They appeared to be homogeneous, without evidence of cavitation or calcification. There was no specific lobar distribution (Table 1).

Only fragmentary information is available on the rate of development of the lesions. In Case 4 the lesion was said to have been "considerably smaller" six months before it was removed, but this suggestion of rapid growth must be unusual. A pulmonary density corresponding to that of the tumor may have been present 15 years before it was resected in Case 2. Review of chest films in Case 8 indicated the presence of the tumor two, and possibly five, years before its resection, and the interval was three years in Case 8 and eight years in Case 7.

In none of the patients was there evidence of a primary tumor elsewhere than in the lung, except in Case 8 whose bladder papillomas have been mentioned. These had been treated by local irradiation, and there was no evidence of a bladder tumor at the time the chest shadow was discovered. The tumor in the lungs bore no resemblance to that in the bladder. Six of the patients had intravenous pyelography; two of these six also had retrograde pyelograms, three had renal aortograms, and one had a bilateral surgical exploration of the kidney in unproductive attempts to find a primary source for the intrapulmonary clear cell tumor. In Case 6 the kidney was thought to be enlarged but intravenous and retrograde pyelograms and a renal aortogram were negative. Another patient (Case 9) was thought to have a renal calculus, but there was no evidence of renal tumor. Thus the urological workup was essentially negative in demonstrating an intrarenal neoplasm in all six patients in whom it was performed.

Lobectomy was performed in five patients, wedge resection in two, and simple enucleation of the tumor in three, where the tumor was described to "shell-out" easily during the operation. Precise information was not available regarding operative procedure in two of the patients.

There was no evidence of recurrence in five patients for whom chest films were available at varying periods after operation—in one instance seven years, in another three years, and in three patients two years after operation. One of these patients had had simple enucleation of the lesion

TABLE 1. BENIGN CLEAR CELL TUMORS OF LUNG: CLINICAL AND ANATOMICAL DATA

Case no.	*Age*	*Sex*	*Position of tumor*	*Size of tumor*	*Time of radiographic detection to operation*	*Negative chest films postoperatively*	*Remarks*
1	28	M	RLL	2 cm.		7 years	Pyelograms
2	51	F	RLL	2.5 × 2 × 2 cm.	15 years (?)	3 years	
3	50	F	RUL	1.5 cm.		2 years	
4	29	M	RUL	2.5 × 3 cm.	6 months	2 years	
5	59	F	LLL	2.5 × 3 cm.	3 years	2 years	Pyelograms Renal arteriograms
6	59	M	LUL	2 cm.			Pyelograms Renal arteriograms Bilateral exploration
7	55	M	LUL	1.5 cm.	8 years		
8	64	F	LLL	2 cm.	2 years; ?5 years		Pyelograms Renal arteriograms Bladder tumors
9	45	F	RLL	6.5 × 6 × 2 cm.			Pyelograms: Renal calculus No tumor
10	46	F	LLL	2.5 × 2.5 × 2 cm.			
11	57	F	RUL	2.5 × 2.5 × 1.5 cm.			
12	45	M	LLL	2 cm.			Pyelograms: "Bifid kidney" rt. No tumor

(Case 5). These observations confirm the anatomical evidence of benignancy of the lesion.

Gross appearance

All of the tumors were rounded or ovoid masses varying between 1.5 and 3 cm. in diameter at the time of resection, except for one (Case 9) which measured 6.5 × 6.2 cm. The cut surface was translucent and varied in color from pale pink to dark red, grey, or brown. In no instance was there evidence of necrosis. None had the yellow color of some of the hypernephroid tumors of the kidney. While not distinctly encapsulated, these masses were described as soft and separating with greatest ease from the parenchyma (Fig. 5). There was no evidence of involvement of a bronchus or major vessel. Most of the tumors were considered to be in the peripheral portion of the parenchyma, and although frequently within 2 cm. of the pleura, in no instance involved that membrane.

Microscopic features

The microscopic appearance in H & E sections was distinctive and rather uniform. The "clear cells" were arranged in masses and cords for the most part supported by very little connective tissue (Fig. 6). By appropriate staining and chemical analysis these cells were found to contain large quantities of glycogen. There was a rich blood supply in the form of large and thin-walled vessels (Figs. 7 & 8). It is this type of blood supply that at once provides the clue that the tumor is primary in the lung rather than a metastatic hypernephroid tumor, which in considerable part is supplied by thick-walled arteries.

In these tumors the sinusoidal vessels were very large in some fields and less conspicuous in others. In no instance was a muscular coat discernible. A distinct endothelial layer was in evidence with continuity into small capillaries that penetrated among the tumor cells. Only in one case was there penetration of the walls of vessels by tumor cells (Figs. 8 & 9).

Hyaline changes in the walls of what are essentially sinusoidal vessels, usually with some extension about capillaries (Fig. 10), was evident in all but two of the tumors, and was extensive in three (Cases 2, 5, and 7). In one case large quantities of extracellular amorphous acidophilic proteinaceous material (Fig. 11) staining faintly with the PAS stain was found (Case 9), and smaller quantities were observed in tissue from Cases 1, 2, 5, and 6. This material was partially calcified (Fig. 12) in Cases 1, 5, and 9. In the last mentioned, there were distinct psammoma bodies (Fig. 13).

For the most part the cells were plump and rounded or polygonal and had distinct cell boundaries (Fig. 7). In many fields, however, they were rather

elongated and even spindle-shaped, especially in the near vicinity of the large sinusoidal vessels (Fig. 14). In fact, in four of the tumors the spindle-shaped elements predominated. The cytoplasm of the cells on closer view was not quite "clear," but contained scattered acidophilic granules, the latter being quite prominent and closely placed in certain fields. The impression in general was not that of vacuolization. Some cells were much larger than others and granules in linear arrangement appeared to radiate from the nucleus ("spider cells") (Fig. 15). Other cells were rounded or polygonal with rather homogeneous acidophilic cytoplasm, and resembled neurons ("neuroid cells") (Fig. 16). In certain of these the resemblance was heightened by the presence of finely granular brown pigment that did not stain for iron and that had the characteristics of "lipochrome." This material was found, however, in occasional cells of all types (Fig. 17), but only in Cases 1, 2, and 11. Multinucleated cells occurred in all of the tumors and in two cases were frequent and prominent in some fields. Such cells also were sometimes of large size (Fig. 18) and resembled Touton giant cells. In these cells the nuclei were usually smaller than in others and often also hyperchromatic.

In general the nuclei were quite variable in size, but with prominent nuclear membranes. Only one mitosis was found (Case 8) out of many hundreds of fields examined in all of the tumors (Fig. 19). A feature of some nuclei was the presence of one, or sometimes several clustered, rounded, granular, acidophilic "inclusions." Some of these appeared to be limited by membranes but without peripheral condensation of chromatin or the presence of an intervening clear zone as in viral inclusions (Fig. 20). Many of these "inclusions," therefore, probably represented interdigitation of cytoplasm with complexly contoured nuclei. However, others represented intranuclear glycogen masses similar to those found in hepatic cell nuclei in diabetes, as demonstrated by an even more intense staining by the PAS method than the cytoplasm.

An astonishing feature in tissue rapidly fixed and dehydrated for embedding in paraffin was the enormous quantity of PAS-positive material (Figs. 7 & 21). This material also stained intensely with Best's carmine. The glycogen was easily leached out in aqueous solutions including 10% formol. There was considerable loss of staining after exposing the sections to diastase. The composition of the material was established by chemical analysis in one case (Case 4), made in the course of a study of the chemical composition of lung tumors by Dr. Bruno Gerstl,[8] then at the Oakland VA Hospital. The analysis revealed 10,657 μ-moles of glycogen-derived hexose/100 grams of wet tissue. It is for this reason that the term "sugar tumor" was colloquially applied. Glycolipids were absent and other carbohydrates

TABLE 2. CARBOHYDRATE CONTENT OF PULMONARY TISSUE AND TUMORS
(μ-moles hexose/100 g. wet tissue)

Tissue	*Glycogen*	*Glycolipids*	*Other carbohydrates*
Benign "clear-cell"	10,656.5	0	48.0
Large cell adenoma	—	142.6	—
Mucoid adenoma	3.4	128.0	173.1
Undifferentiated	21.1	230.1	244.0
Oat cell	25.1	70.4	149.2
Lung (control)	24.4	164.3	—
Lung (control)	25.7	184.0	87.5

were present in lesser concentration than in other lung tumors or in normal control lung tissue (Table 2).

The Alcian technique revealed small quantities of stainable material, and many cells were shown to contain considerable quantities of materials staining by the colloidal iron technique. In Wilder and Laidlaw reticulum stains the fibers were shown to embrace individual cells for the most part (Figs. 9 & 22).

Even microscopically there was no evidence of a defined capsule, yet the tumor cells were delimited from the parenchyma along a sharp, continuous line (Fig. 23) without extensive intrusion into interalveolar or interlobular septa, nor into lymphatics. Certain alveoli or larger air spaces were seen at the boundary, and the lining cells of these structures were often cuboidal, as is frequently the case when alveoli are immobilized.

Small acinar structures lined by cuboidal or low columnar cells (Fig. 24), sometimes mucin producing, were found, especially near the periphery, of seven of the twelve tumors. Such structures are common in some slides of many slowly growing tumors within the lung, such as sclerosing hemangiomas and fibromas, and they occur even in nodules of "metastasizing leiomyoma." The process is one of entrapment by non-destructive extension into septa among the distal air spaces, and occasionally it can be glimpsed in progress at the periphery of such lesions.

DISCUSSION

It would be of interest to discover a cell in normal tissue that would correspond to the component elements of the tumor. As a first step an attempt was made to find cells replete with glycogen in the periphery of the lung. Normal lungs were therefore fixed by introducing absolute alcohol into a main bronchus and immersing them in the same fluid. Tissue blocks were then cut and put through additional dehydration directly into xylol and

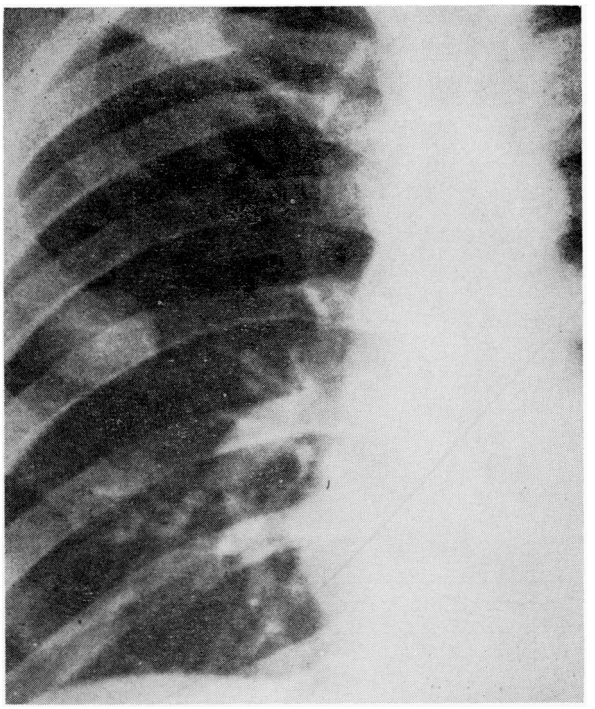

FIG. 1. Roentgenogram, Case 4. Coin lesion showing slightly flattened shape of the tumor, which measured 2.5 × 3 cm. after resection.

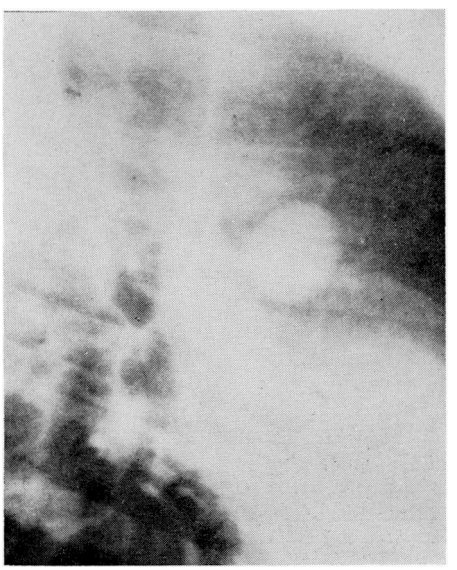

FIG. 2. Roentgenogram, Case 4. Lateral roentgenogram demonstrating position of the tumor in the anterior segment of the right upper lobe.

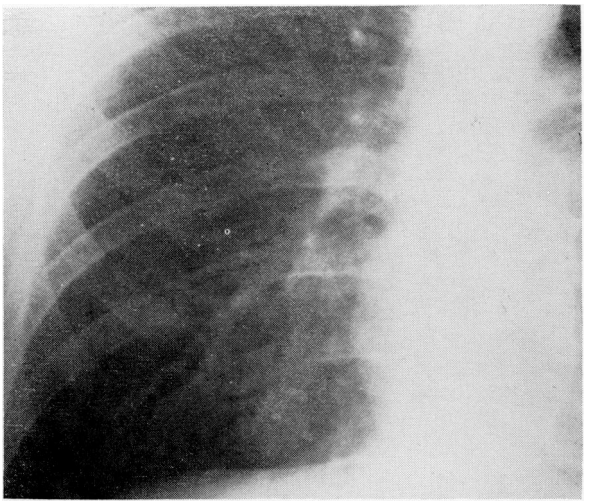

FIG. 3. Roentgenogram, Case 1. A rounded, sharply defined shadow is visible in the right lower lobe. The spherical nodule was 2 cm. in diameter.

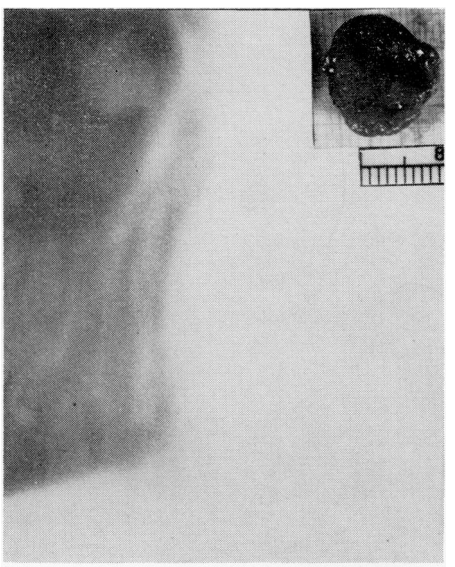

FIG. 4. Tomogram, Case 3, showing a homogeneous density with a notch on its medial aspect (compare with Fig. 5).

FIG. 5. (Inset). The resected nodule, which was approximately 1.5 cm. in diameter, shows gentle indentations. The cut surface is tan and translucent. Some of the sinusoidal vessels can be discerned.

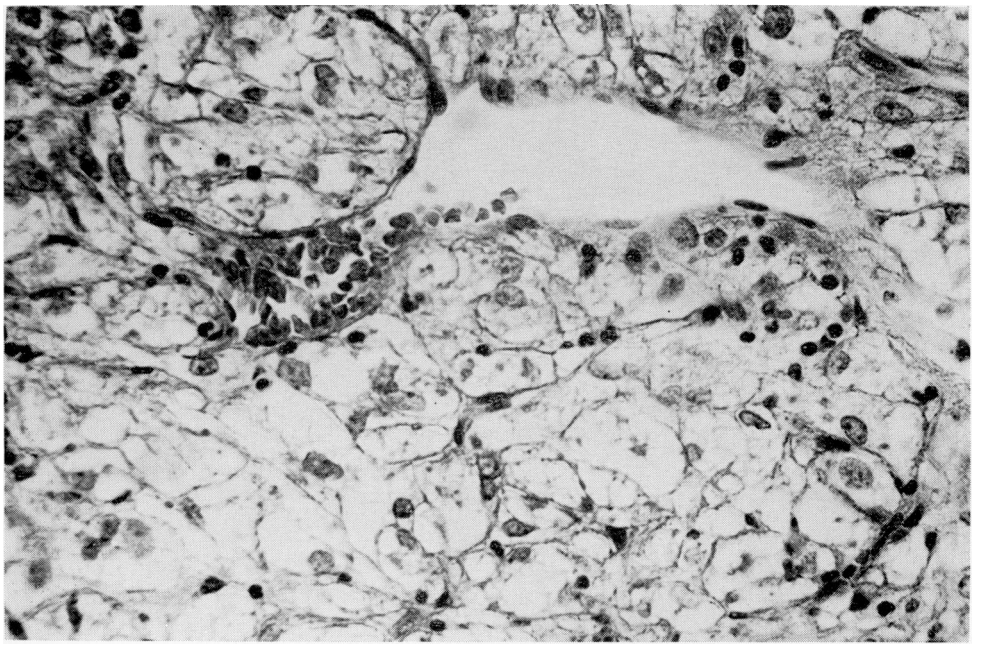

FIG. 6. Masses of rounded or polygonal "clear cells" with well-defined boundaries surround a large sinusoid which is devoid of muscle. This vessel is lined by endothelial cells that continue into narrow capillaries. A few lymphocytes are scattered among the tumor cells. Case 1, × 390.

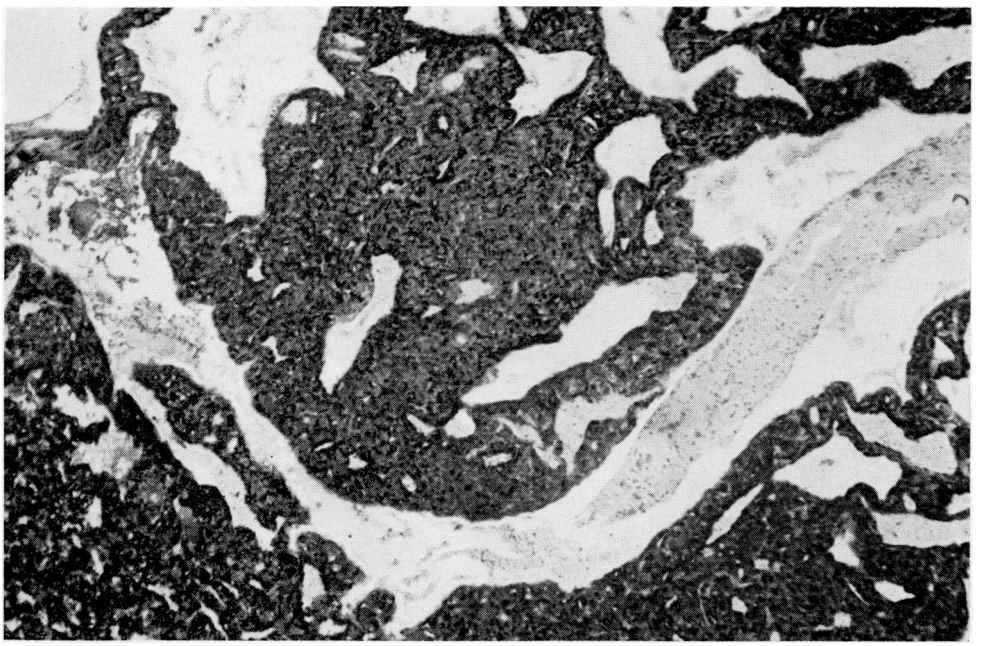

FIG. 7. The tremendous vascularity of the tumor is demonstrated. Large and small vessels of sinusoidal type ramify through the masses of tumor cells. No thick-walled arterioles are present. Tumor cells stain intensely by the PAS method. Case 3, × 55.

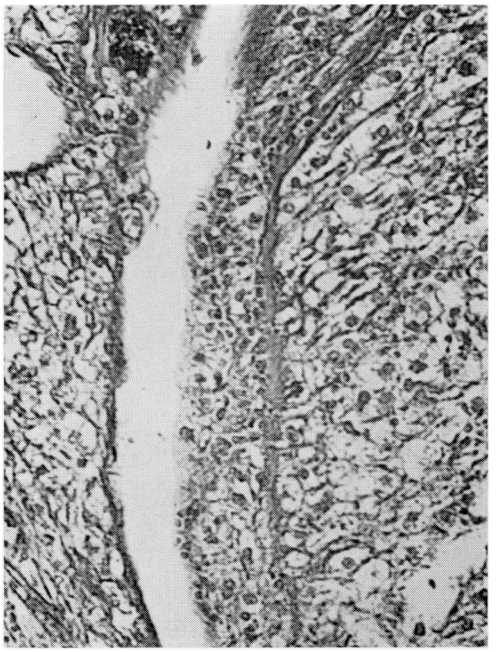

FIG. 8. Penetration of the partly hyalinized wall of a sinusoid by tumor cells. Case 5, × 190.

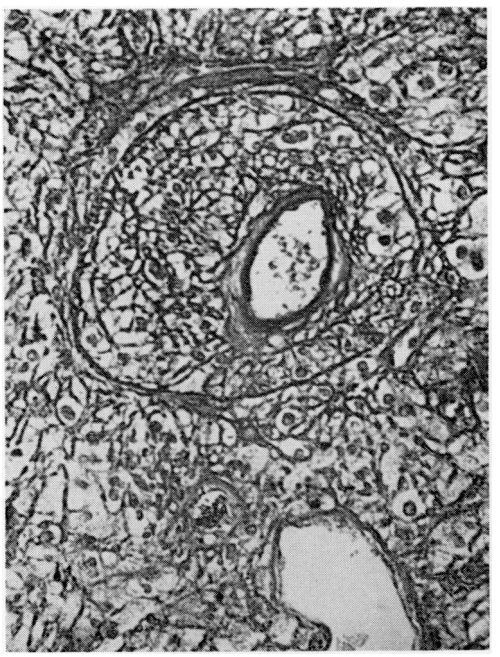

FIG. 9. Reticulum stain showing penetration of tumor cells into sinusoids. The cells, however, are separated from the lumen by a thin layer of hyalinized tissue. Case 5, × 190.

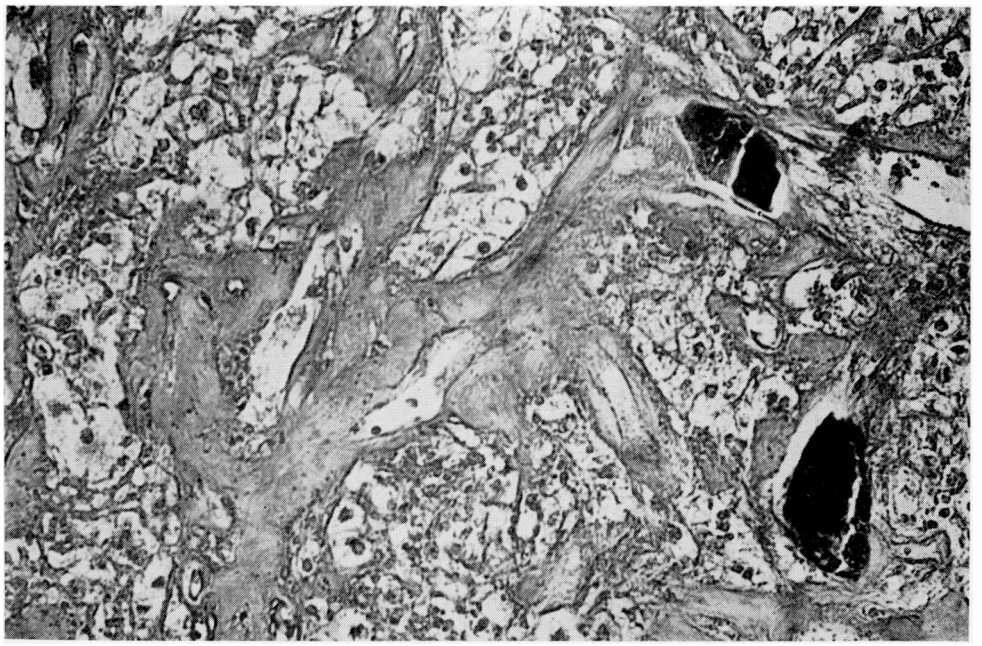

FIG. 10. Deposition of hyalinized connective tissue in walls of sinusoids with reduction of the lumen. There are focal deposits of calcium visible as black masses within the hyalinized tissue. Case 5, × 190.

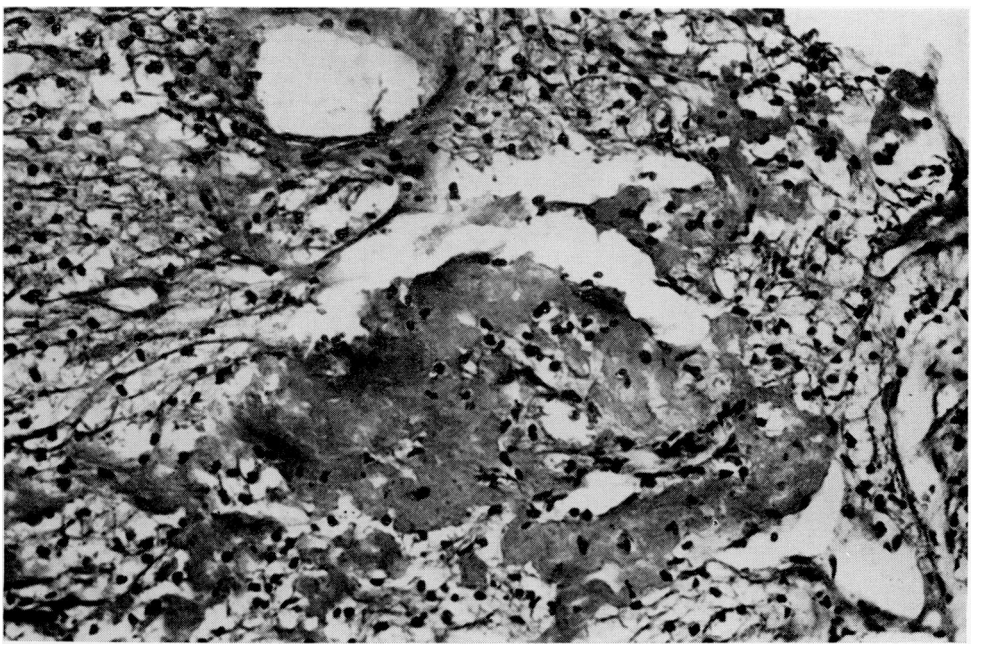

FIG. 11. Amorphous floccular interstitial proteinaceous deposit. Case 9, × 190.

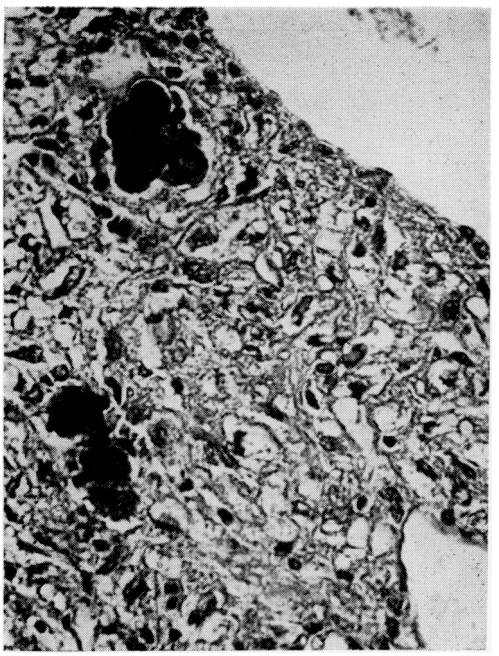

FIG. 12. Calcification of amorphous interstitial deposit. Case 1, × 190.

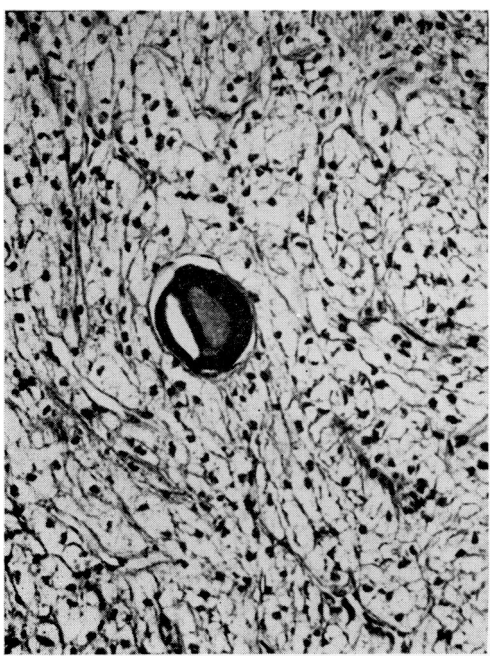

FIG. 13. Psammoma body among masses of "clear cells." Case 9, × 190.

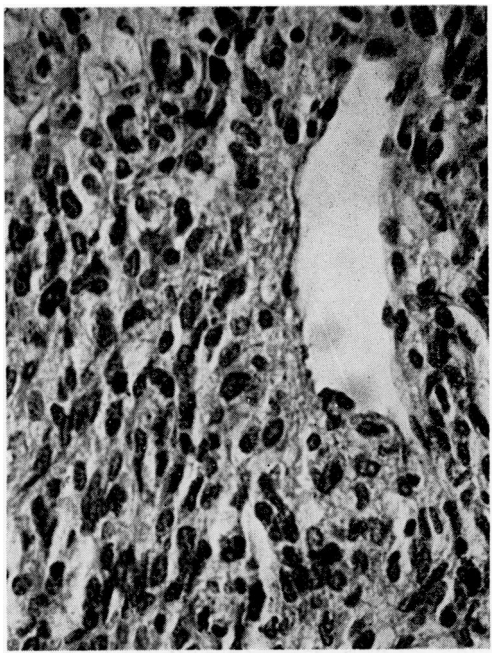

FIG. 14. Relatively small cells, many of spindle shape, in the vicinity of a large sinusoidal vessel. Case 4, × 380.

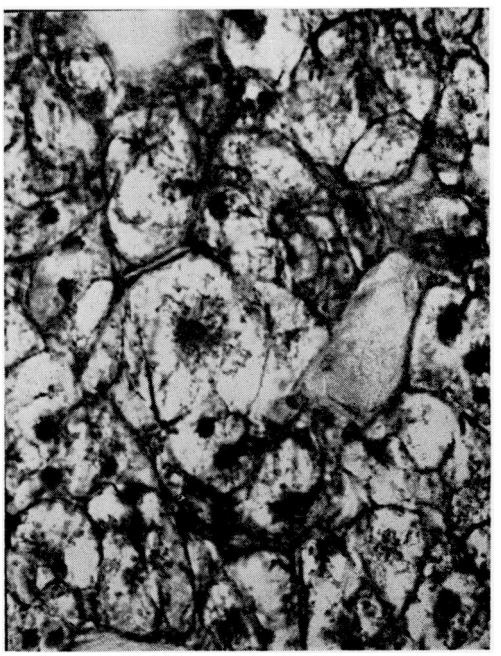

FIG. 15. Several "spider cells" are seen. These are characterized by linear arrays of granules radiating from the nucleus. Case 5, × 650.

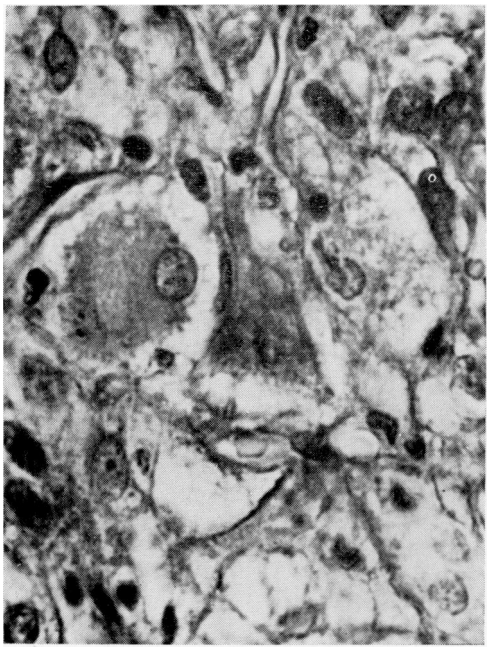

FIG. 16. Two "neuroid" cells with relatively homogeneous eosinophilic cytoplasm. One has a somewhat triangular shape in the section. The other, just to the left, has an eccentric nucleus and two brown pigment granules at the level of section. Case 1, × 650.

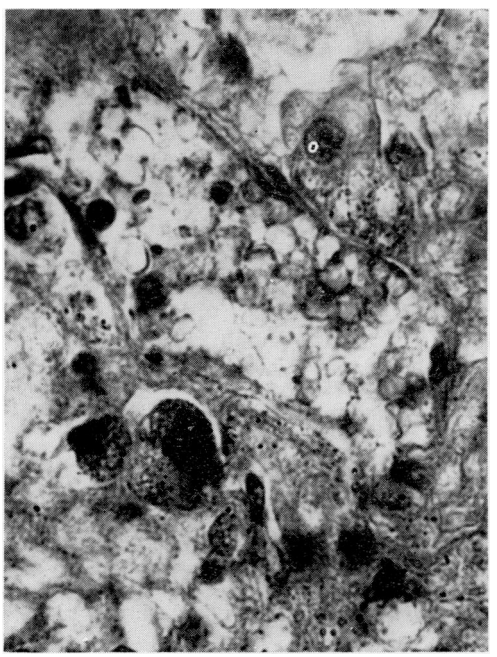

FIG. 17. Several tumor cells in the near vicinity of a blood vessel contain scattered granules of brown pigment that does not stain for iron. Case 2, × 650.

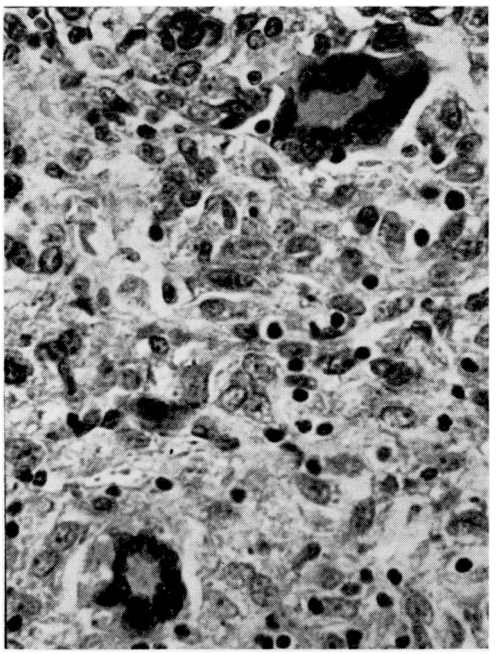

FIG. 18. Multinucleated giant cell resembling a Touton cell. Lymphocytes in considerable numbers also are scattered among the tumor cells. Case 1, × 380.

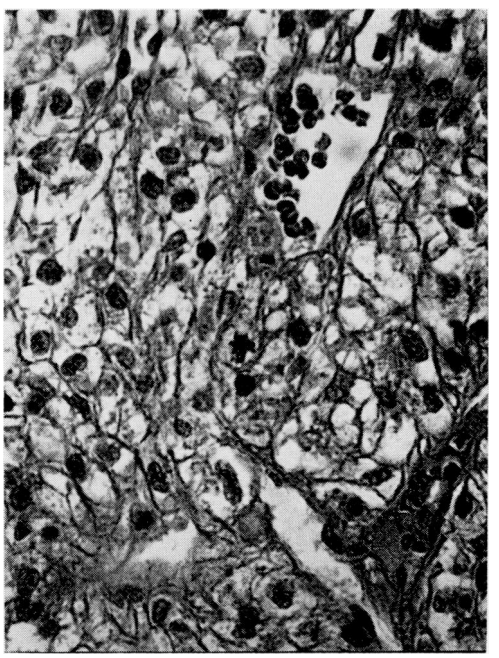

FIG. 19. A tumor cell in mitosis—the only one found in many hundreds of fields examined from all twelve tumors. Case 8, × 380.

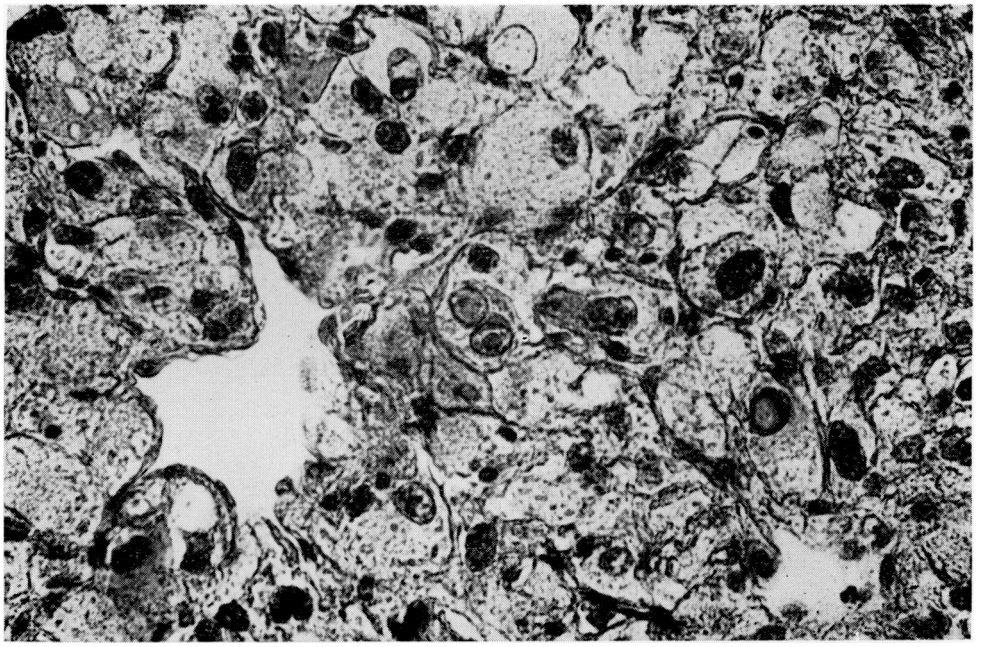

FIG. 20. Acidophilic granular intranuclear "inclusions." Some of these stain even more intensely with PAS than the cytoplasm and are interpreted as intranuclear glycogen deposits. Case 3, × 650.

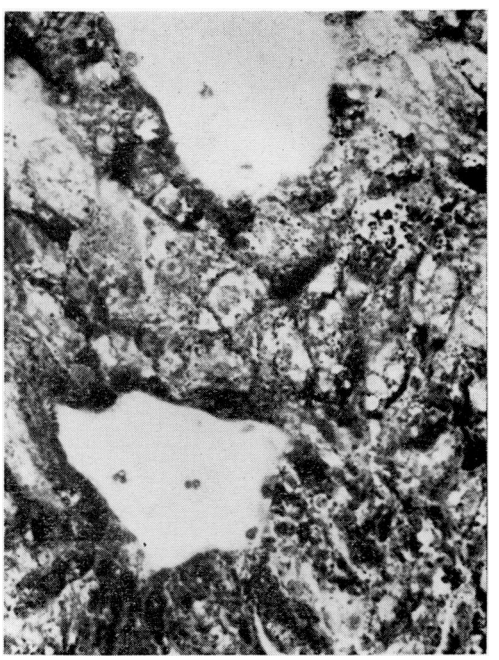

FIG. 21. PAS stain demonstrating intensely staining granules and floccular masses within the cytoplasm. Case 1, × 380.

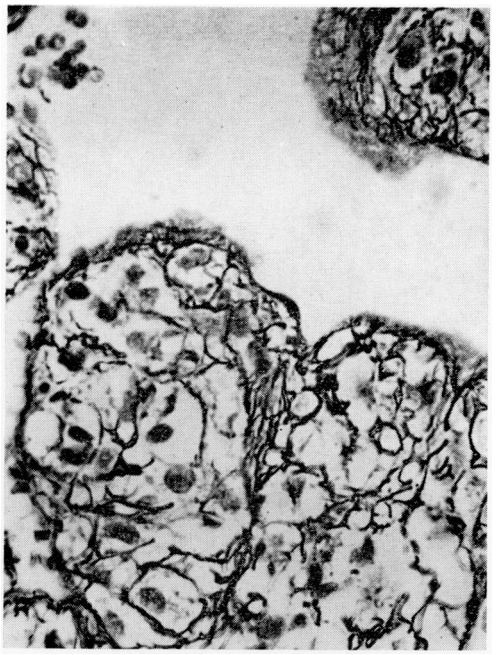

FIG. 22. Reticulum stain showing fibers embracing individual cells. Case 1, × 380.

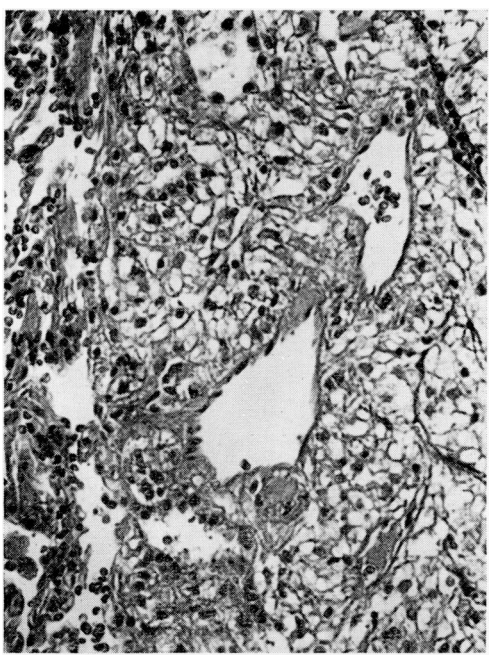

FIG. 23. Junctional zone between tumor and surrounding pulmonary parenchyma. A capsule is not in evidence, but the tumor is demarcated along a sharp line. There is no evidence of invasion of the lung. Case 8, × 190.

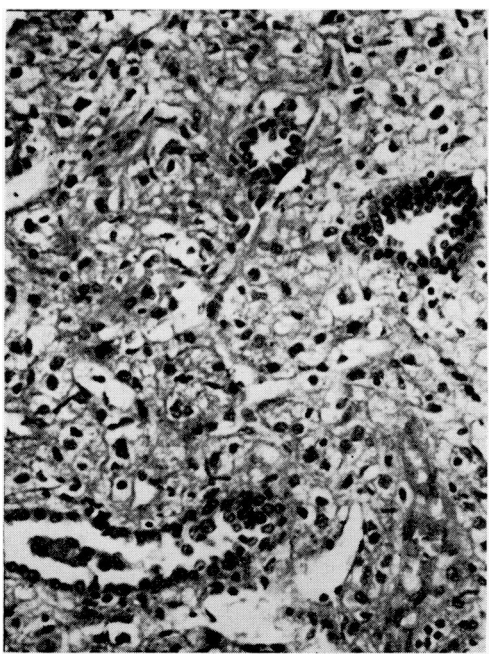

FIG. 24. Epithelial lined spaces included within the tumor. This is interpreted to be the result of entrapment of alveoli, a process common in slow growing intrapulmonary tumors. Case 10, × 190.

paraffin. They were then cut and stained by the periodic acid-Schiff method and with Best's carmine. Some of the large free cells in the alveoli, probably representing both granular pneumocytes and phagocytic pneumocytes, contained closely crowded uniform PAS positive granules that were interpreted as cytosomes or residual bodies. No cells resembling those of the clear cell tumor were discovered. The "alveolar brush cells" identified in electron micrographs by Meyrick and Reid[4] have been shown to contain glycogen but, as judged from the published micrographs, the amount is not large. Tumors derived from cells lining alveoli or bronchioles might be expected to have, in part at least, an acinar structure, but this was not the case in any of the neoplasms of the present series. None of these has as yet been examined with the electron microscope, a procedure that would indeed be of interest.

A myoid origin for the benign clear cell tumor was considered, especially because of the existence of descriptions of clear cell leiomyomas of the uterus[5] and of the stomach.[6] In these leiomyomas the cells are rounded or spindle-shaped, with strikingly clear cytoplasm and sharply defined cell boundaries. These resemblances, however, are superficial, since Rywlin and coworkers[5] have reported that stains for glycogen, as well as for mucopolysaccharides, were negative in the clear cell tumors of the uterus. Moreover, it may be expected that smooth muscle tumors would arise in relation to bronchioles or the large pulmonary vessels, rather than in the very periphery of the lung, as appears to be the case with the benign clear cell tumors.

There has been considerable confusion between the diagnosis of benign clear cell tumor and the "Grawitz," hypernephroid or clear cell tumor of the kidney metastatic in the lung. One would expect that such metastatic tumors would be multiple, and it is also well known that many involve bronchi. While such tumors stain with PAS, they do not contain the immense quantities of glycogen typical of these benign primary tumors of the lung, and they are further distinguished by their content of lipid and sometimes of iron. Necrosis occurs often in renal carcinomas, and the process may be accompanied by hemorrhage. Mitoses also are commonly present, while these are exceedingly rare in the benign clear cell tumors. Of importance in differential diagnosis is that the blood supply is at least in part by means of thick walled arterioles, although sinusoidal vessels may also be present.

Reports of "clear cell carcinomas" of the lung have appeared.[7-9] These are bronchogenic tumors that have histological and biological characteristics of malignancy. They contain only small droplets of PAS-positive material. Characteristically large masses of cells are isolated or bundled by the connective tissue stroma and reticulum fibers do not extend among the indi-

vidual cells. All of these features, as well as the proximal position and lack of sinusoidal blood supply, clearly distinguish these neoplasms from the benign proliferations.

TABLE 3. CHARACTERISTICS OF BENIGN CLEAR CELL TUMOR AND OF OTHER LESIONS

Lesion | Feature	*PAS*	*Fe*	*Fat*	*Retic.*	*Vessels*	*Necrosis*
Benign clear cell	4+	0	0	i	S	0
Metastatic renal ca.	+-2+	0-3+	+-3+	g	A	+-4+
Chemodectoma	0	0	0	g	S	0
Carcinoid tumor	0	0		g	S	0
Sclerosing hemangioma	0-+	+-3+	2+-4+	g	S,A	0
Alveolar soft parts tumor	0-+	0	0	g	A	0
Hemangiopericytoma	0	0	0	i	S	0-+

Key: Retic.: i = Individual cells surrounded.
g = Cell groups surrounded.
Vessels: S = Large, thin-walled or sinusoidal vessels.
A = Thick-walled arterioles.

Features that are helpful in distinguishing the benign clear cell tumors from other pulmonary lesions are recorded in Table 3. Chemodectomas[10] in the lung are usually quite minute, although some quite large peripheral tumors have been described. In their peripheral position and sinusoidal and capillary type of blood supply they are quite reminiscent of the clear cell tumor, but they lack glycogen. The same is true of bronchial carcinoid tumors, which additionally are related to bronchi or bronchioles, to the lumina of which the tumor cells usually present without intervention of a connective tissue barrier at some point. In both instances reticulum surrounds groups of cells. This relationship also exists in the "alveolar soft parts sarcoma." This tumor is of controversial histogenesis, since some consider it to represent chemodectoma, whereas others interpret it as malignant granular cell myoblastoma. In several such tumors Ross and coworkers[11] reported occasional fine carminophilic granules after staining by the Best carmine method—but not a massive content of glycogen. Likewise, in benign granular cell myoblastoma Pearse[12] demonstrated both PAS-positive granules and, contrary to the findings of others, lipid as well. Granular cell myoblastomas do occur in the lung but in bronchi[7] rather than in the periphery, and their blood supply also bears no resemblance to that of the benign clear cell tumor. Hemangiopericytomas[13,14] also do not contain significant quantities of glycogen.

In sclerosing hemangioma large vacuolated or clear cells can be related in part to sinusoidal channels. This is exemplified both in lung[15] and in the central nervous system, especially the cerebellum.[16] The cells in sclerosing hemangioma, however, include large numbers of histiocytes laden with fat and usually replete with hemosiderin. Thus, the differential diagnosis is not difficult, especially since the hemangiomatous characteristics of the lesion are usually quite evident in the less cellular parts.

Thus the clear cell tumor of the lung appears to be distinctive and possibly unique.

SUMMARY AND CONCLUSIONS

Benign peripheral tumors composed of "clear cells" present silently in the lung, chiefly in middle-aged persons, as "coin lesions." The most distinctive feature is their immense content of glycogen demonstrable after appropriate histological preparation or by analysis. This feature, the absence of fat and hemosiderin within tumor cells, the great scarcity of mitoses, the fact that necrosis does not occur, and the sinusoidal rather than arteriolar blood supply, make possible an unequivocal differentiation from metastases in the lung from renal tumors, with which these benign neoplasms have commonly been confused. The cell of origin is as yet unknown.

There is evidence that the benign clear cell tumors of the lung are usually slow growing and that they do not recur or metastasize even after simple enucleation, which is facilitated by the absence of invasion or of a relationship to larger vessels or bronchi.

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