

Mucin-producing atypical bronchial carcinoid

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SUMMARY In a case of atypical mucin-producing bronchial carcinoid in a 40-year-old man covert metastases were present at the time of lobectomy and were revealed at necropsy—a feature highlighting the malignant potential of the atypical carcinoid.

Mucin-producing bronchial carcinoid tumours have been recorded sporadically over the past 40 years (Hamperl, 1937; Leschke, 1957; Goodner *et al.*, 1961; Weiss and Ingram, 1961; Markel *et al.*, 1964; Fu *et al.*, 1974; Salyer *et al.*, 1975). On light microscopy the tumours resemble those found in the appendix (Dische, 1968; Hernandez and Reid, 1969), stomach, colon, and rectum (Gibbs, 1963; Hernandez and Reid, 1969) but differ significantly from the goblet-cell carcinoids of the appendix (Klein, 1974; Subbuswamy *et al.*, 1974; Abt and Carter, 1976; Haqqani and Williams, 1977; McDonald and Hourihane, 1977). The presence of a glandular or tubular pattern in the tumours is well recognised (Weiss and Ingram, 1961; Fu *et al.*, 1974), and in a number of cases simple and complex gland lumina with bordering microvilli have been demonstrated on electron microscopy (Fu *et al.*, 1974; Bell *et al.*, 1975; Sönksen *et al.*, 1976). More frequently, ultrastructural study of bronchial carcinoid tumours has revealed the presence of intercellular canaliculi with projecting microvilli (Elliott and Hardy, 1971; Renault and Verley, 1973; Patchefsky *et al.*, 1974; Bell *et al.*, 1975; Bonikos *et al.*, 1976).

The demonstration of mucin production has caused considerable speculation on the histogenesis of carcinoid tumours. The question whether this phenomenon weakens the hypothesis of neuroectodermal derivation of carcinoids (Pearse, 1969; Pearse *et al.*, 1974) or lends weight to their putative entodermal origin (Andrew, 1963; Ellison and Neville, 1973) remains unresolved at the present time. Whatever their embryological derivation, the progenitor of bronchial carcinoid tumours is believed to be the Kultchitsky cell of the bronchial epithelium (Bensch *et al.*, 1965, 1968; Gmelich *et al.*, 1967). Because bronchial carcinoid tumour and oat-cell

carcinoma of the bronchus display certain common characteristics it is suggested that oat-cell carcinoma is also derived from the bronchial Kultchitsky cell (Bensch, *et al.*, 1968; Hattori *et al.*, 1972). Some support for this concept is given by the documented cases of carcinoid syndrome developing in patients with oat-cell carcinoma (Kinloch *et al.*, 1965; Hattori *et al.*, 1972; Salyer and Eggleston, 1975) but conflicting evidence has been provided by an epidemiological study of the two tumours (Godwin and Brown, 1977).

The atypical variant of bronchial carcinoid tumour, characterised by histological features such as increased cellularity, cellular and nuclear pleomorphism, increased mitoses, and focal necrosis (Arrigoni *et al.*, 1972; Okike *et al.*, 1976), often strongly resembles oat-cell carcinoma (Goodner *et al.*, 1961; Markel *et al.*, 1964; Smith, 1969; Arrigoni *et al.*, 1972). It is possible that the atypical variant holds an intermediate position in the spectrum of endocrine cell tumours of the bronchus, which ranges from the benign and biosynthetically active carcinoid to the malignant and often biosynthetically inert oat-cell carcinoma.

In a retrospective study of 22 cases of pulmonary carcinoid tumour a mucin-producing variant, which had many atypical features, was identified. The intraoperative frozen sections in this case bore a marked similarity to oat-cell carcinoma. We present here the results of a light and electron microscopic study of this tumour.

Case report

A 40-year-old man presented with lassitude, dyspnoea on exertion, and left subscapular pain of four weeks' duration. Physical examination was normal but a chest radiograph showed an opacity in the left upper lobe and soft shadowing in the right

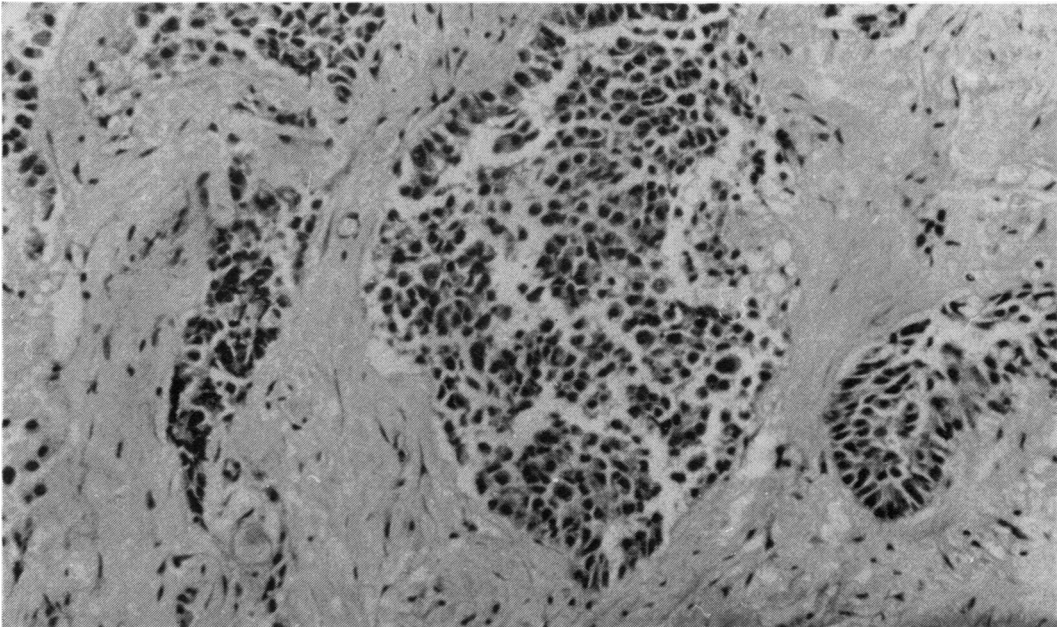


Fig. 1 *Frozen section of tumour biopsy showing cellular aggregates set in a dense fibrous stroma. Elsewhere the cell clumps showed prominent central necrosis. (H and E $\times 90$).*

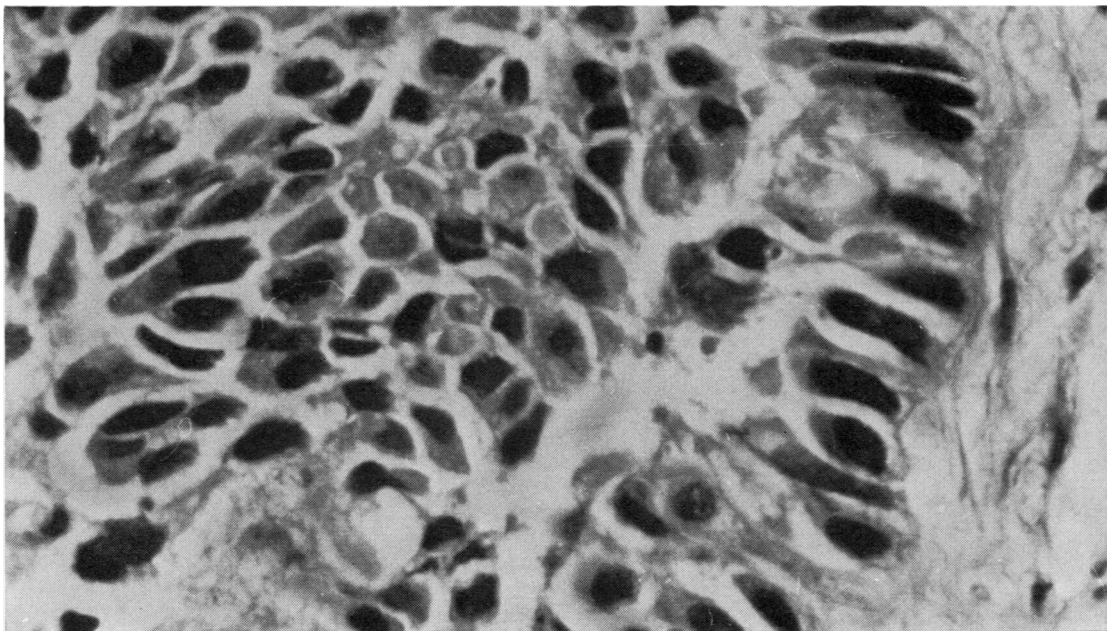


Fig. 2 *Higher magnification of frozen-section biopsy showing strong resemblance to oat-cell carcinoma. Peripheral palisading is seen on the right. (H and E $\times 345$).*

midzone. Bronchoscopy was normal. At mediastinoscopy enlarged subcarinal nodes were seen. A biopsy of these nodes showed reactive changes only. After a one-month therapeutic trial of antituberculosis drugs the patient's symptoms remained unchanged. Tomography showed that the lesion in the left upper lobe had increased in size and now measured 4 cm diameter. The patient deferred further investigation for four months. A thoracotomy was then performed, which revealed a tumour in the left upper lobe. There was apparent extension of the tumour to the hilar nodes and the apex of the left lower lobe. A frozen section of the tumour was interpreted as showing oat-cell carcinoma. A left upper lobectomy and excision of the lower lobe apex were performed. The patient subsequently suffered intractable pulmonary infection and died after cardiac arrest on the sixth postoperative day.

Necropsy revealed confluent bilateral bronchopneumonia with microabscess formation and a small embolus in one of the vessels to the left lower lobe. Small metastatic tumour deposits were present in the left hilar nodes, the peribronchial lymphatics of both lungs, and the spleen. The remainder of the necropsy was unremarkable.

Material and methods

The tissue removed at thoracotomy consisted of the upper lobe of the left lung with the apical portion of the lower lobe attached by fibrous adhesions across the fissure. On bisection of the lobe a 5 cm diameter, firm, circumscribed tumour was seen apparently arising from the wall of the main bronchus 1 cm from the resected end. The tumour projected into the lumen on a broad front and was covered by intact bronchial epithelium. The cut surface of the mass was greyish-white in colour with a whorled appearance but there was no evidence of haemorrhage or necrosis. Similar tumour was seen to replace a 1.7 cm diameter hilar lymph node.

Tissue for light microscopic examination (including the cryostat material) was fixed in 10% formalin, routinely processed, and embedded in paraffin. Sections were stained with haematoxylin and eosin, Alcian blue, and Congo red. Masson-Fontana argentaffin and Grimelius and modified Bodian argyrophil stains were also performed.

Blocks of formalin-fixed tissue were used for electron microscopic examination. The blocks were washed in veronal acetate buffer, postfixed in 0.1%

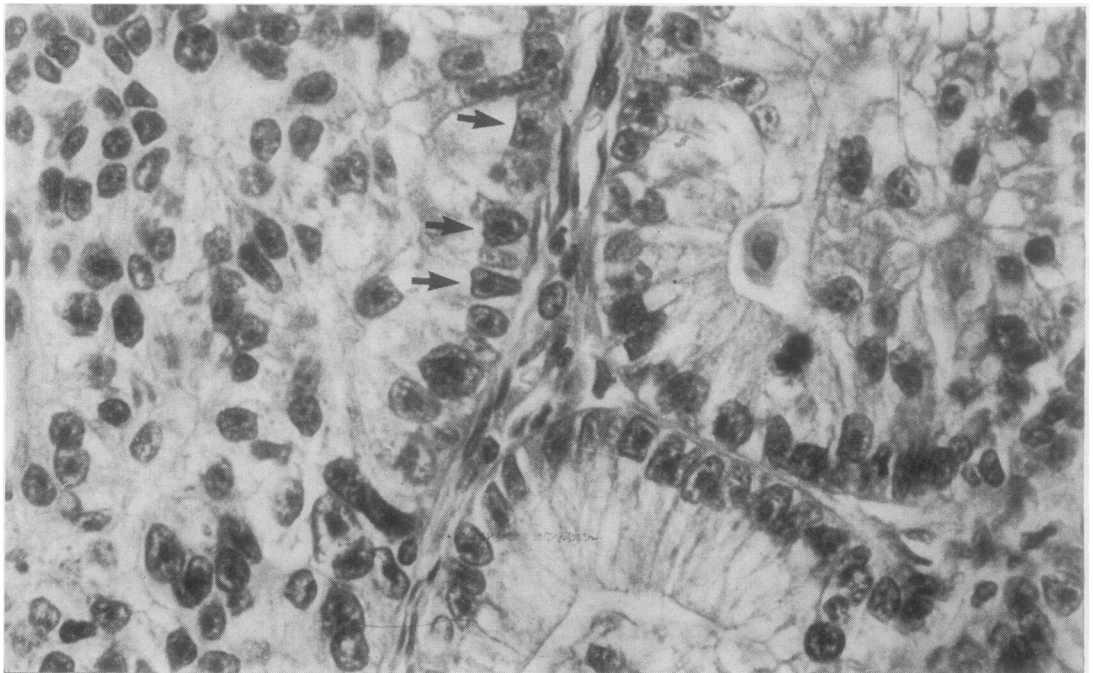


Fig. 3 Lobectomy specimen showing organoid tumour pattern with distinct tubule formation. Note the rounded basal outline of some nuclei with indentation of the apical aspect (arrows). (H and E $\times 300$).

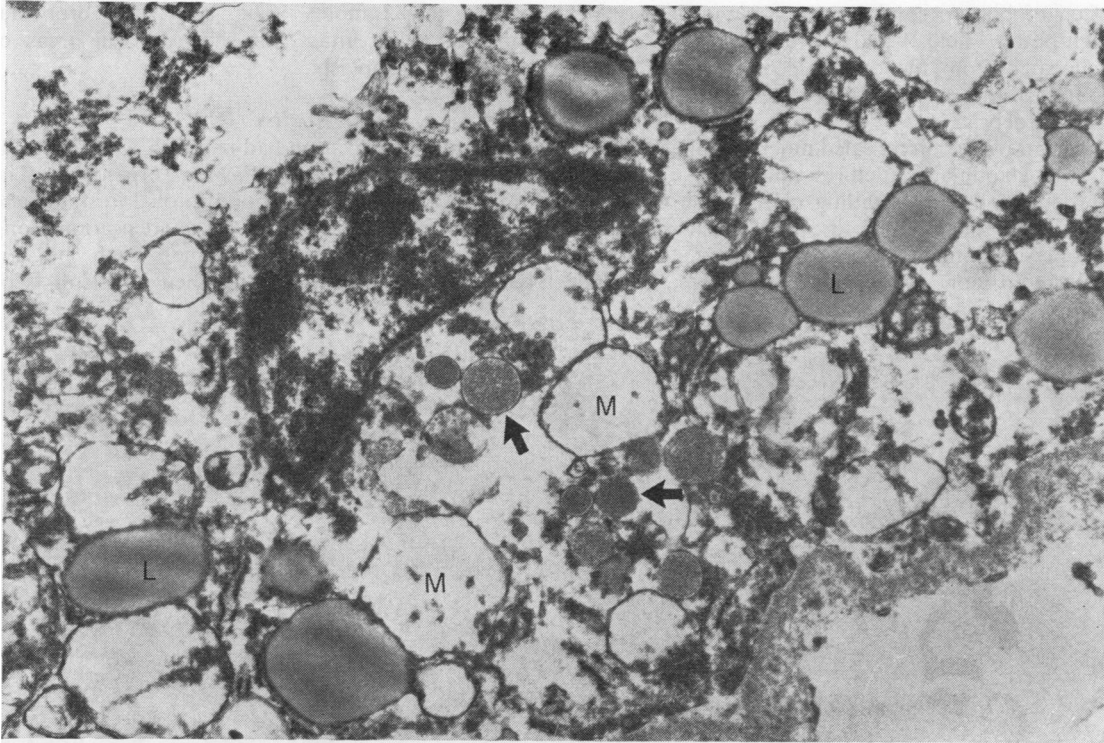


Fig. 4 Electron micrograph showing the typical appearance of the cells in the lobectomy specimen. Mucin vacuoles (M), lipid droplets (L), and membrane-bound neurosecretory granules (arrows) are evident within the cytoplasm. (Uranyl acetate/lead citrate $\times 16\ 100$).

osmium tetroxide, dehydrated through graded ethanol, and embedded in epon. Sections were cut on an LKB ultramicrotome, stained with uranyl acetate/lead citrate, and examined with a Jeol 100CX electron microscope.

Results

LIGHT MICROSCOPY

The original frozen section of the lung lesion and sections of the paraffin-embedded cryostat material showed tumour composed of aggregates of cells with central necrotic zones set in a dense fibrous stroma (Fig. 1). The cells appeared small with scanty cytoplasm and moderately pleomorphic hyperchromatic nuclei (Fig. 2). Many mitoses were present. There was no evidence of a glandular or tubular pattern in the sections although there was a suggestion of peripheral palisading of the cells in the tumour aggregates. It is likely that freeze artefact was responsible to a large extent for the spurious resemblance to oat-cell carcinoma.

Sections of the lobectomy specimen revealed a distinctive organoid pattern in the tumour (Fig. 3).

Cellular aggregates were again evident, ranging from small tubular structures lined by a single layer of cells to large, rounded or serpiginous islands of cells with prominent peripheral palisading and often with central areas of necrosis. The cell groups composing the tumour were separated by a delicate fibrovascular stroma. The cells lining the tubules and the peripheral cells in the larger aggregates were similar and columnar in shape. The basally situated nuclei contained one or two large eosinophilic nucleoli, from which coarse strands of chromatin radiated to the thick nuclear membrane. The shape of the nuclei was distinctive: a significant proportion showed a rounded outline basally with flattening or indentation of the apical aspect due to compression by vacuolated eosinophilic cytoplasm in the centrally orientated pole of the cell. In the larger cell groups the layer between the peripheral palisade and the central necrotic zone was composed of more rounded cells with equal distribution of vacuolated cytoplasm around the nucleus. In many areas the haphazard scattering of the cells in this layer was replaced by a regular glandular or tubular arrangement. Occasional tumour giant cells were present in all areas. Mitoses,

often of bizarre configuration, averaged three per high-power field. Viable tumour was sharply delineated from the central necrotic areas, which contained the ghost outlines of cells and fragmented nuclear debris.

Alcian blue stain revealed mucin within the lumen of the glandular structures and along the apical borders of the surrounding cells. Some cells contained fine alcianophilic droplets within the apical cytoplasm. Congo red stain was negative, and neither argentaffin nor argyrophilic cells were identified

within the tumour. The overlying bronchial epithelium was intact but showed focal areas of squamous metaplasia.

ELECTRON MICROSCOPY

Initial formalin fixation had resulted in considerable disruption of the cytoplasmic organelles. The tumour cell nuclei were round to oval in shape and exhibited peripheral chromatin condensation along the smooth nuclear membrane. Each nucleus contained one or two prominent nucleoli. The

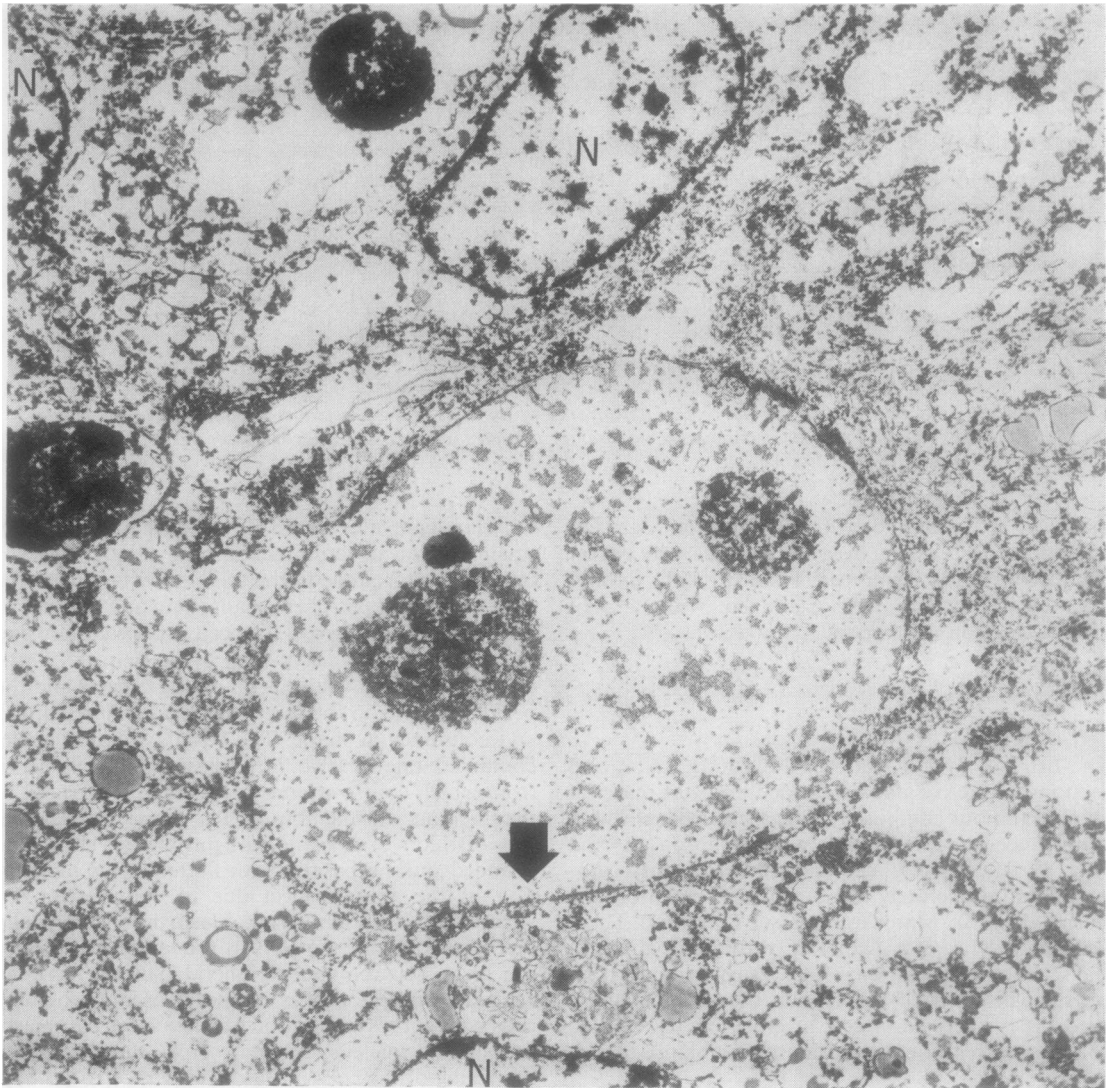


Fig. 5 Electron micrograph showing distinct gland lumen with bordering microvilli (arrow). Portions of three related nuclei (N) are seen. (Uranyl acetate/lead citrate $\times 4600$).

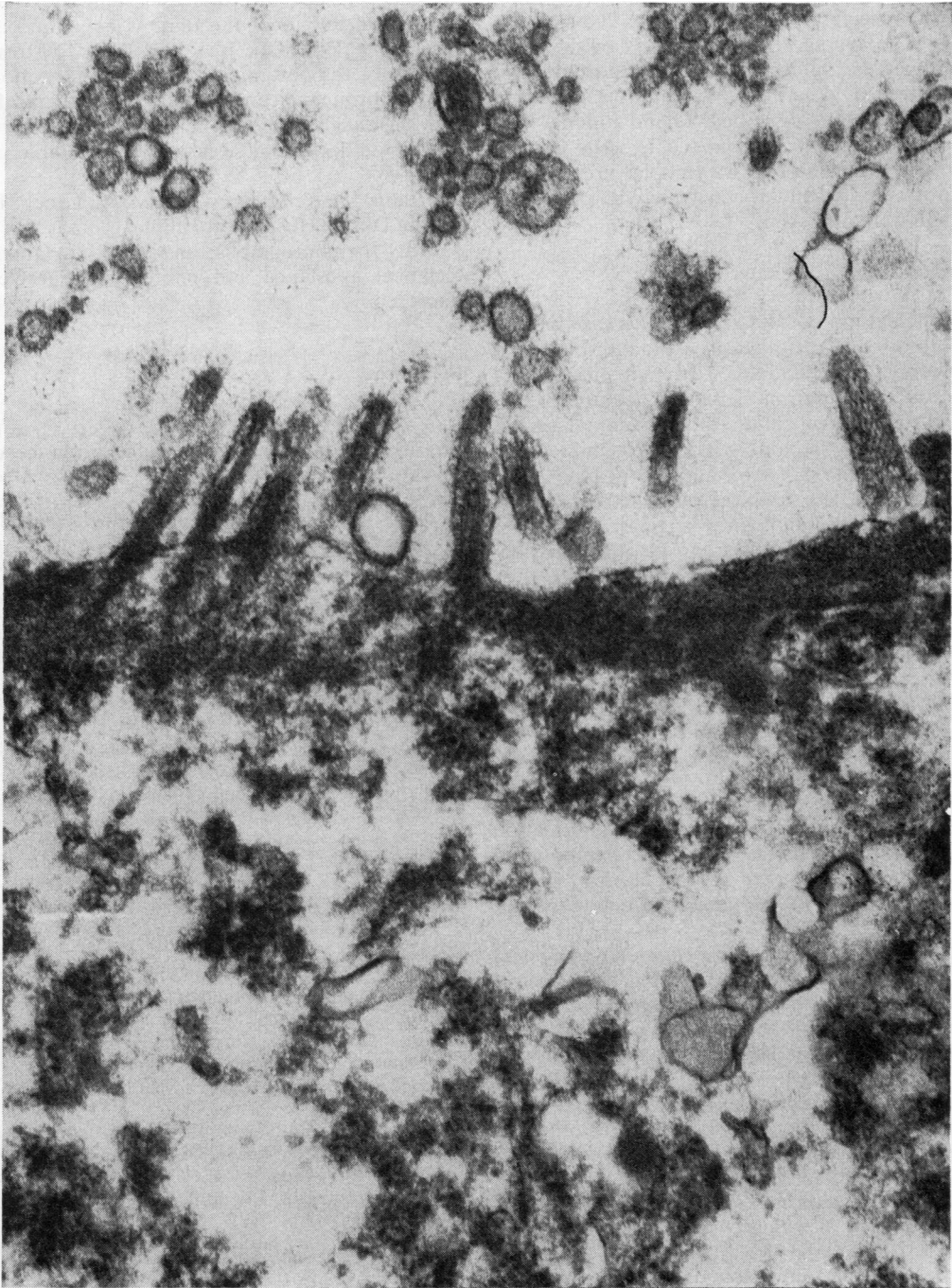


Fig. 6 *High-power electron micrograph showing microvilli projecting into a gland lumen. (Uranyl acetate/lead citrate $\times 52500$).*

cytoplasm of these cells contained numerous mucin vacuoles, lipid droplets, and membrane-bound neurosecretory granules (range 200-500 nm) (Fig. 4). The average electron density of the cytoplasm appeared uniform in all cells, and dark and light varieties as described by some workers (Fu *et al.*, 1974) were not discerned. Gland lumina were easily identified (Fig. 5) bounded by cells bearing numerous microvilli (Fig. 6). In solid areas of the tumour small intercellular canaliculi with projecting microvilli were also seen.

Discussion

The bronchial tumour described in this case has the architectural and cytological characteristics of a mucin-producing carcinoid. The high mitotic rate and areas of tumour necrosis are features which allow further classification of the tumour as an atypical variant (Arrigoni *et al.*, 1972; Okike *et al.*, 1976). In the opinion of some authors (Markel *et al.*, 1964; Smith, 1969), atypical bronchial carcinoids display no greater biological aggressiveness than their typical counterparts. We consider that the widespread dissemination of the tumour in this case gives credence to the more widely held belief (Goodner *et al.*, 1961; Arrigoni *et al.*, 1972; Okike *et al.*, 1976) that atypical features denote a significant malignant potential.

The lack of reactivity to argentaffin and argyrophil stains in the tumour is not surprising. Soga and Tazawa (1971) found that 50% or more of the carcinoids in their series that resembled our case histologically (their type C or mixed types) failed to show argentaffin or argyrophil cells. Confirmation that the tumour in this case was in fact composed of endocrine cells depended on the electron microscopic demonstration of membrane-bound neurosecretory granules.

The mucin production in our tumour was evident by both light and electron microscopy. The principal difference between the goblet-cell carcinoid of the appendix and mucin-secreting carcinoids at other sites appears to be the larger amount of mucin that accumulates intracytoplasmically in the former tumour. The crescentic basal nuclei, which are characteristic of the goblet-cell carcinoid, are probably the result of nuclear indentation, as described in our tumour, but of an exaggerated degree. Ultrastructurally the tumours are similar (Bensch *et al.*, 1965; Bensch *et al.*, 1968; Abt and Carter, 1976).

The fact that the tumour in our case was diagnosed as oat-cell carcinoma on frozen section is of interest. Freeze artefact resulted in a false impression of condensed hyperchromatic nuclei, and there was loss

of the distinctive tubular pattern of the tumour. The presence of focal necrosis and numerous mitoses weighed in favour of the tumour being an oat-cell carcinoma. We think it is important to stress the possibility that examination of frozen sections of atypical bronchial carcinoid tumours may result in a spurious diagnosis of oat-cell carcinoma leading the surgeon to designate the case as unresectable.

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