Pulmonary carcinoid tumours: a comparative regional study

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SUMMARY   Twenty-two pulmonary carcinoid tumours (18 central, 4 peripheral) were seen in this department over an 11-year period. The majority of the tumours displayed a mixed pattern on microscopic examination, and cell-nest formation was a prominent feature in sixteen. The findings are at variance with the results of a similar series reported from Japan and suggest that there is regional variation in the tumour pattern of pulmonary carcinoids. Various aspects of the histopathology are discussed, and a causal relationship between ossification of bronchial cartilage in these tumours and locally produced calcitonin is postulated.

There have been numerous reports of series of pulmonary carcinoid tumours over the past 17 years. A review of the literature reveals the characteristic mode of presentation, features of prognostic significance, and the range of histological appearances of tumours. Most reports, however, have emanated from centres in the western hemisphere (Table 1), particularly the United States, and it is possible that

Table 1   *Series of bronchial carcinoid tumours according to geographic location*

Location	Author	Year
USA	Goodner *et al.*	1961
USA	Weiss and Ingram	1961
USA	Markel *et al.*	1964
USA	Donahue *et al.*	1968
England	Smith	1969
USA	Meffert and Lindskog	1970
USA	O'Grady *et al.*	1970
Japan	Soga and Tazawa	1971
USA	Arrigoni *et al.*	1972
USA	Tolis *et al.*	1972
USA	Turnbull *et al.*	1972
Denmark	Burcharth and Axelsson	1973
Denmark	Hage	1973
France	Renault and Verley	1973
Finland	Koikkalainen *et al.*	1974
USA	Godwin	1975
USA	Salyer *et al.*	1975
USA	Bonikos *et al.*	1976
England	Lawson *et al.*	1976
USA	Okike *et al.*	1976
USA	Marks and Lamberty	1977
England	Jones and Dawson	1977
USA	Fisher *et al.*	1978

the data derived from these studies might not be representative of pulmonary carcinoid tumours in other populations. Accepting the premise that there are racial differences in the occurrence and distribution of argyrophil cells in adult human lungs (Tateishi, 1973), it is possible that tumours derived from these cells (Bensch *et al.*, 1965, 1968; Gmelich *et al.*, 1967) might also display racial variation in their incidence, distribution, or composition. Some support for this suggestion has been provided by Godwin (1975), who showed a significant difference in the incidence of pulmonary carcinoid tumours in white and black populations of the United States. We have reviewed a series of 22 pulmonary carcinoids occurring in adults in Ireland and have compared our findings, particularly in relation to tumour composition, with those of similar studies performed elsewhere.

Material and methods

Formalin-fixed tissue obtained at thoracotomy was examined in each case. The tissue was routinely processed and embedded in paraffin. Sections were stained with haematoxylin and eosin, Alcian blue, and Congo red and by the Weigert-van Gieson method for connective tissue and elastic. The Masson-Fontana technique was utilised for demonstration of argentaffin cells and the Grimelius and modified Bodian techniques for demonstration of argyrophilia. Solcia's lead haematoxylin method was also used for the demonstration of endocrine cell granules. In 10 cases sections were incubated with

rabbit antiserum to human calcitonin[1] and stained by a peroxidase technique (Burns, 1975). Sections of a medullary carcinoma of the thyroid were used as a positive control. Small portions of tumour from the more recent cases were washed in cacodylate buffer, transferred to 0·3% glutaraldehyde, and postfixed in 0·1% osmium tetroxide. Blocks were embedded in epon and sections were stained with uranyl acetate/lead citrate. The sections were examined using a Jeol 100 CX TEM. Tumours arising from subsegmental bronchi and distal bronchioles were designated 'peripheral' carcinoids.

Observations and results

The clinical presentation and radiological findings,

[1]Antihuman calcitonin antiserum kindly supplied by Dr F. T. Bosman, Leiden, Holland.

together with tumour site and size, presence or absence of metatases, and results of treatment are given in Table 2. These data do not show significant divergence from those documented in other series. None of the patients had evidence of carcinoid syndrome.

MICROSCOPIC FEATURES
The majority of tumours were composed of uniform cells with round to oval nuclei containing coarse chromatin strands and one or two small nucleoli. The cells possessed moderate amounts of granular eosinophilic cytoplasm and distinct cell borders. Significant mitotic activity was present in five tumours, four of which (cases 7, 16, 19, and 22) showed the additional features of focal necrosis and nuclear pleomorphism associated with the atypical variant of pulmonary carcinoid (Arrigoni

Table 2 *Clinical data on 22 patients with pulmonary carcinoid tumour*

Case	Age/Sex	Clinical presentation	Radiological features	Tumour location	Size (cm)	Operation	Metastases		Date of operation	Results
							Nodal	Distant		
1	19 M	Haemoptysis and recurrent pneumonia	LLL consolidation	LLL central	1·5	LL lobectomy	−	−	1967	Well at 5 yr
2	47 M	R scapular pain	R hilar opacity	RLL peripheral	2·0	Peripheral RLL resection	NE	−	1969	Lost to follow-up
3	29 F	Cough	R basal opacity	RML central	1·5	RM and RL lobectomy	−	−	1969	Well at 9 yr
4	60 M	Haemoptysis	RUL opacity	RUL central	0·5	RU lobectomy	−	−	1970	Well at 4 yr
5	56 F	Haemoptysis	R midzone opacity	RUL central	1·5	RU lobectomy	NE	−	1971	Well at 6 yr
6	52 F	Pneumonia	R hilar opacity	RUL central	2·0	RM lobectomy	NE	−	1972	Well at 5 yr
7	55 F	Cough. R chest 'soreness'	R apical opacity	RUL central	?	RU lobectomy	NE	−	1974	Well at 3 yr
8	59 M	Cough	RUL opacity	RUL peripheral	2·0	RU lobectomy	−	−	1977	Well at 4 mth
9	51 M	Haemoptysis and pneumonia	RLL collapse	RLL central	6·0	RM and RL lobectomy	−	−	1977	Well at 6 mth
10	55 F	L chest pain. Haemoptysis	L lung collapse	L main bronchus, central	5·0	L pneumonectomy	−	−	1975	Well at 3 yr
11	59 M	Asymptomatic	Coin lesion L midzone	LUL peripheral	< 1·0	Peripheral LUL resection	−	−	1976	Well at 1 yr
12	57 F	Cough	L lung collapse	L main bronchus, central	2·5	L pneumonectomy	−	−	1974	Well at 4 yr
13	58 F	Cough. L chest pain	LUL consolidation	L lingular bronchus, central	3·0	LU lobectomy	−	−	1975	Well at 2 yr
14	53 F	Cough	LLL consolidation	LLL central	5·0	LL lobectomy	−	+ Liver	1975	Metastases at 2 yr
15	38 M	Recurrent pneumonia	LU hilar opacity	LUL central	1·5	LU lobectomy	−	−	1974	Well at 3 yr
16	40 M	L chest pain	LUL opacity	LUL central	5·0	LU lobectomy	+	+ Lung spleen	1977	Postoperative death
17	39 F	R chest pain. Recurrent pneumonia	RLL opacity	RLL central	5·0	RM and RL lobectomy	−	−	1978	Well at 6 mth
18	36 M	No details	RML opacity	RML central	1·5	RM lobectomy	NE	−	1972	Lost to follow-up
19	32 F	No details	L hilar opacity	LUL central	4·0	L pneumonectomy	NE	+ Brain	1973	Died at 2 yr
20	57 F	L chest pain. Haemoptysis	L hilar opacity	LLL central	2·0	LL lobectomy	−	−	1971	Lost to follow-up
21	70 M	R chest pain	Coin lesion R lung	R lung peripheral	< 1·0	Peripheral RLL resection	NE	−	1971	Well at 2 yr
22	65 F	Haemoptysis	RLL collapse	RLL central	9·0	RM and RL lobectomy	+	−	1978	Well at 2 mth

NE = not examined, + present, − not present

et al., 1972). Anisonucleosis without pleomorphism was present in five tumours, two of which were peripheral. One centrally located tumour was composed predominantly of spindle-shaped cells (Fig. 1). No oncocytic variants were seen in this series.

A striking feature in seven cases was the presence of bone formation in bronchial cartilage which was contiguous with or had been engulfed by tumour. In most cases the bone formation appeared to have taken place in close relation to the perichondrium
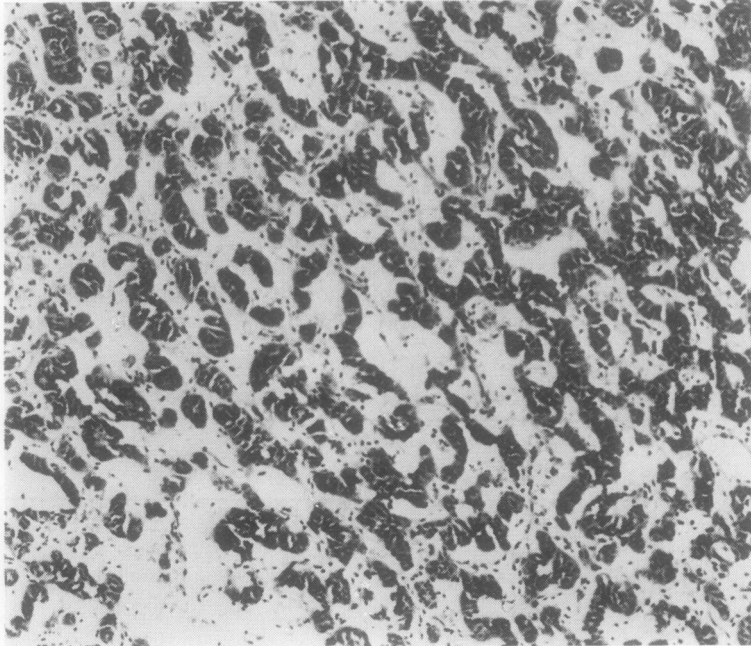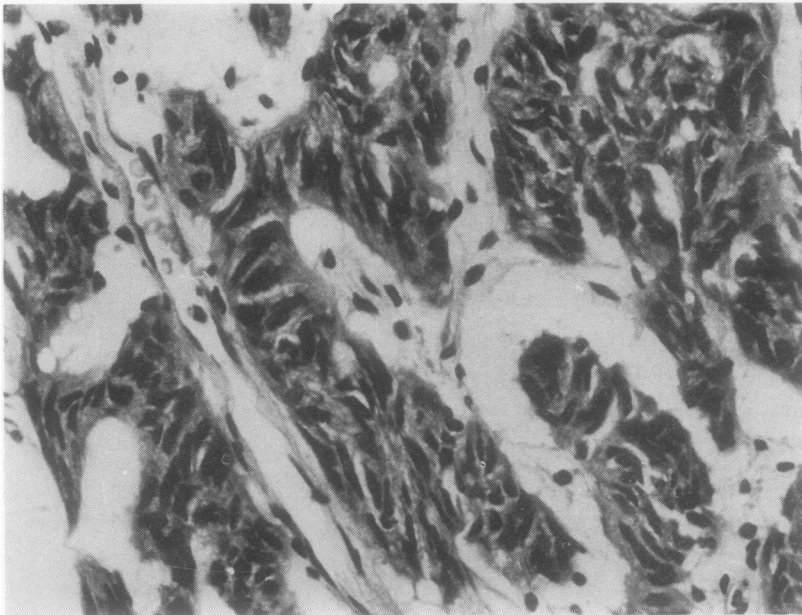

Fig. 1a

Fig. 1b

Fig. 1   *Spindle-cell tumour showing (a) trabecular pattern and (b) cell morphology. (a) H and E × 50; (b) H and E × 500.*
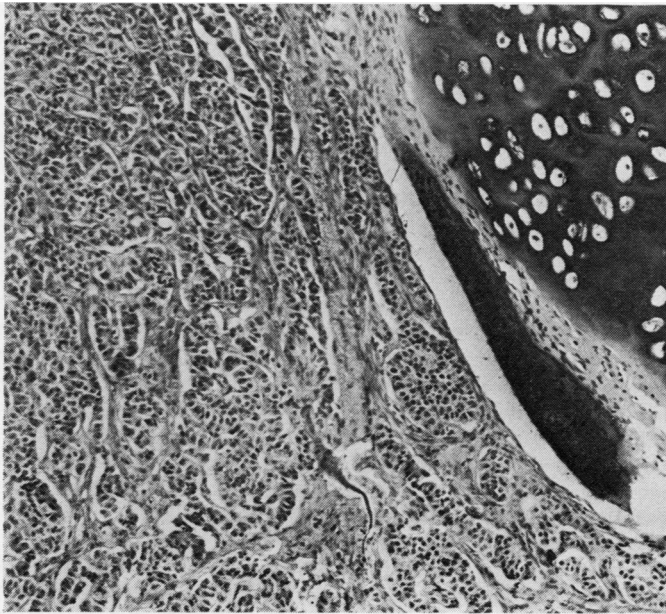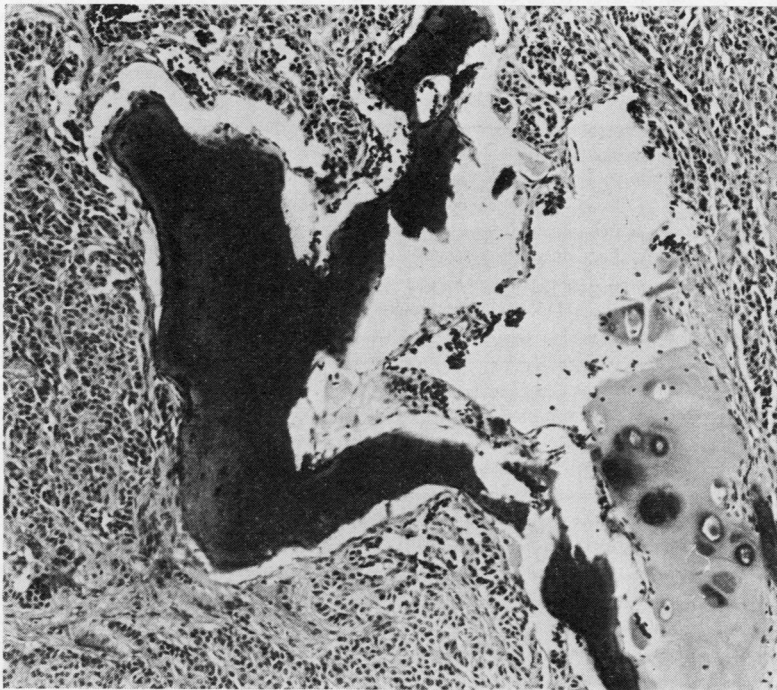
Fig. 2a

Fig. 2b

Fig. 2 *Bone formation in relation to bronchial cartilage The earliest change visualised. (a) Consists of bone developing in close relation to the tumour but separated from cartilage by perichondrium. (b) Demonstrates more extensive bone formation around cartilage engulfed by tumour. (a) H and E ×50; (b) H and E × 50.*

(Fig. 2) and in some instances marrow development within the bone was evident. The histological pattern of the tumours was very varied. Cell nest formation (Fig. 3) was evident in 16 cases and trabeculation (Fig. 4) in 16 (not always coincident). A tubular, acinar, or rosette pattern was noted in eight tumours (Fig. 5). The spindle-cell tumour displayed a predominantly trabecular pattern with elongated and condensed nuclei of variable size. The tumour stroma in most cases consisted of a delicate fibrovascular network, although case 7 showed a markedly expanded and hyalinised fibrous stroma with heavy perivascular elastosis. Four patients (18%) had metastatic disease. These included three of the patients with atypical carcinoid and case 14. The latter tumour appeared innocuous at surgery and despite minimal mitotic activity was classified as a typical carcinoid. In common with occasional cases of typical pulmonary carcinoid documented by other authors (Arrigoni et al., 1972), the patient developed distant metastases two years postoperatively. Perineural invasion was evident in two cases (7 and 9), neither of which metastasised, although one (case 7) had a high mitotic rate.

The tumours in this series were classified according to the system devised by Soga and Tazawa (1971) to facilitate comparison, and the results are given in Table 3. In this system, types A, B, and C denote tumours composed basically of cell nests, trabeculae, or tubules respectively. Type D includes tumours 'with structures of lower or atypical differentiations', and mixed type is the term used for tumours with any combination of the preceding types. In 15 of our cases (68%), a mixed pattern was evident, the remaining seven cases (32%) being of an unmixed or 'pure' type. Of the four atypical tumours (18%), one consisted of cell nests only whereas the remainder showed a mixed pattern and were classified as such. Three of the four peripheral tumours were of a 'pure' type, a very high proportion relative to the overall series composition.

STAINING PROPERTIES
The results of special staining procedures are listed in Table 4. Argentaffin reaction and staining for amyloid were uniformly negative. Twelve tumours (54%) were argyrophilic and five (23%) contained alcianophilic material, both within the cytoplasm of cells and within distinct tubular lumina. The lead haematoxylin stain proved fickle, definite positivity being found in only five of the 12 argyrophil tumours. It is of interest that while ossification did not appear to be significantly related to any particular histological pattern in this series it was more common in argyrophilic tumours. Of the 10 tumours stained by an immunoperoxidase technique for calcitonin, there was a positive correlation between the presence or absence of bone and the presence or absence of calcitonin containing cells in eight (Fig. 6). In the remaining two cases, calcitonin was present but bone
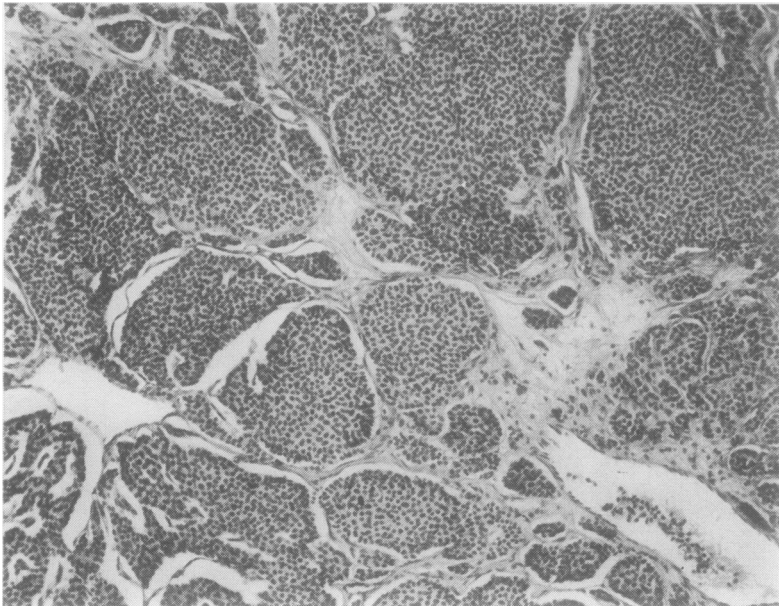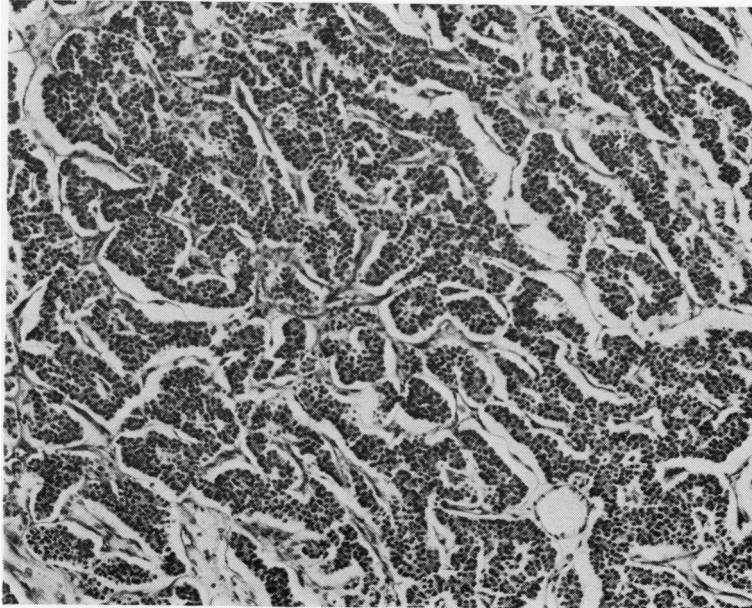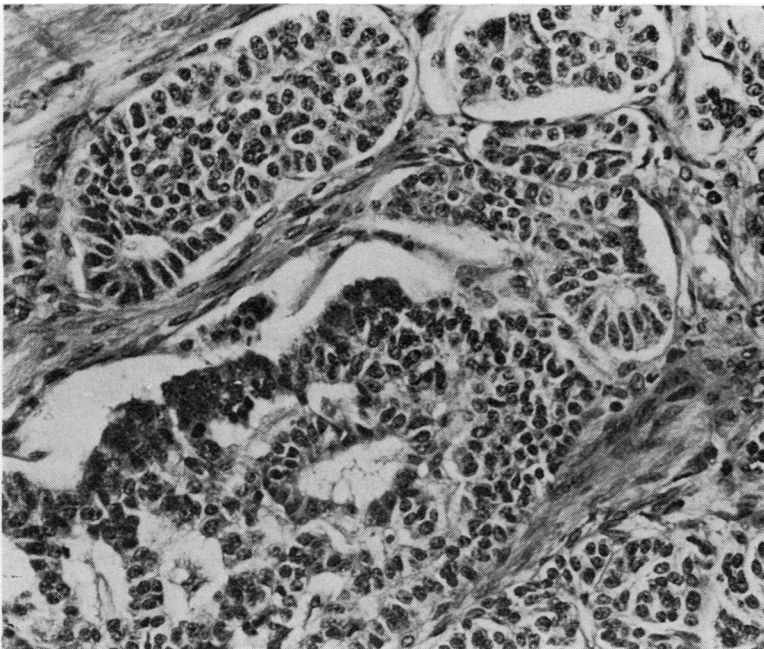

Fig. 3 Cell-nest formation. Groups of uniform cells separated by delicate fibrovascular stroma. H and E ×50.

Fig. 4 *Trabecular pattern. Uniform cells arranged in anastomosing cords separated by loose connective tissue. H and E × 50.*

Fig. 5. *Tubular arrangement of cells evident in areas of eight tumours. H and E × 310.*

was not identified in the sections examined. The number of calcitonin containing cells in each tumour was very small and bore no relationship to the degree of argyrophilia.

ELECTRON MICROSCOPY
In the cases studied by this method (8, 16, 17, and 22) characteristic neurosecretory granules were easily identified in the cells. Lumina lined by

Table 3 *Histological types and distribution of 22 pulmonary carcinoids*

Location in lung	Nests	Trabeculae	Tubules or rosettes	Mixed					Total
	A	B	C	A + B	B + C	A + C	A + B + C		
Central	2*	2	0	7*	3	2†	2		18
Peripheral	2	1	0	0	0	0	1		4
Total	4	3	0	7	3	2	3		22

*One tumour of each of these groups
†Both tumours of this group showed atypical features
(D type: Soga and Tazawa (1971))

Table 4 *Histological features and staining properties of 22 pulmonary carcinoids*

No.	Pattern (Soga and Tazawa, 1971)	Mitoses per 10 HPF	Necrosis	Bone	Perineural invasion	Nuclear variability	Mucin	Argyrophilia	Lead haematoxylin	Calcitonin
1	A + B	−	−	+	−	−	−	−	−	ND
2	A	−	−	−	−	+	−	−	−	ND
3	A	−	−	−	−	−	−	+	+	ND
4	A + B	−	−	+	−	−	−	−	−	ND
5	B	−	−	−	−	+	−	−	−	ND
6	A + B + C	−	−	−	−	+	+	+	+	ND
7	B + C	5	+	−	+	−	−	−	−	−
8	A + B + C	−	−	−	−	−	−	−	−	ND
9	A + B + C	−	−	+	+	+	−	+	−	+
10	B	−	−	−	−	−	−	+	+	−
11	B	−	−	−	−	−	+	−	−	−
12	A + B	−	−	−	−	−	−	+	−	+
13	B + C	−	−	−	−	−	−	+	−	ND
14	A + B	2	−	+	−	−	−	+	−	+
15	B + C	−	−	+	−	−	+	+	+	+
16	A + C	35	+ + +	−	−	−	+ + +	−	−	ND
17	A + B	−	−	−	−	−	−	+	−	+
18	A + B	−	−	−	−	−	−	−	−	ND
19	A	10	+ +	+	−	−	−	+	+	ND
20	A + B	−	−	+	−	−	−	+	−	+
21	A	−	−	−	−	−	−	−	−	−
22	A + C	40	+ + +	−	−	+	+ + +	+	−	ND

ND = not done

microvilli were identified in case 16, the ultrastructure of which has been documented elsewhere (Sweeney and Cooney, 1978). The other mucin-producing atypical tumour in this series (case 22) contained intracytoplasmic mucin (Fig. 7) but, in keeping with its lesser degree of structural differentiation when compared with case 16, lumina or canaliculi were not readily identified electron microscopically.

Discussion

The predominant pattern in our series was that of a mixed tumour type similar to that documented in England by Jones and Dawson (1977) and in the United States by Salyer *et al.* (1975). In contrast, 50% of the bronchial carcinoids and the majority of foregut carcinoids described by Soga and Tazawa (1971) in Japan were of the pure trabecular type. The significance of this regional variation is difficult to assess because other workers in both England and the United States (Williams and Sandler, 1963;

Markel *et al.*, 1964; Fisher *et al.*, 1978) also recognise the trabecular arrangement as the commonest growth pattern in bronchial and other foregut carcinoids although precise comparison between their series and that of Soga and Tazawa (1971) is not possible.

In 16 (72%) of our cases the tumour demonstrated cell-nest formation, a feature of two-thirds of the cases recorded by Jones and Dawson (1977) and most of the cases of Salyer *et al.* (1975). In the Japanese series, however, cell-nest formation was present in only a minority of foregut carcinoids (Soga and Tazawa, 1971). The apparent differences between the structure of pulmonary carcinoid tumours in Japan and in this and other countries requires further study. It would be of interest if comparable variations were shown in other racially distinct populations, bearing in mind the documented variation in incidence of these tumours in white and black Americans (Godwin, 1975).
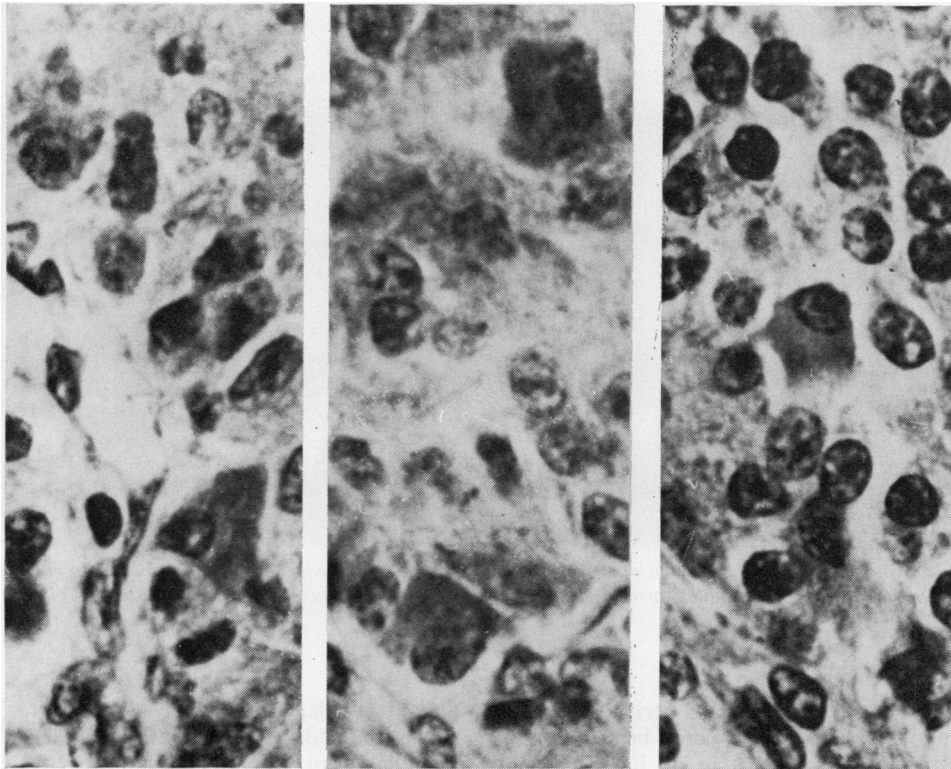
Tateishi (1973) noted that the density of argyrophil

Fig. 6 *Dense granular staining of the cytoplasm in occasional cells of six tumours incubated with anti-human calcitonin antiserum at a dilution of 1:160 (PAP counterstained with haematoxylin × 1250).*

cell population in the bronchial mucosa increased with increasing distance from the hilum of the lung, being maximal in the bronchioles. In contrast, the majority of tumours derived from these cells (Bensch *et al.*, 1965, 1968; Gmelich *et al.*, 1967) occur in the larger and more central bronchi. In our series, only 18% of the tumours were peripheral, intermediate in the range of 13-25% documented by other authors (Burcharth and Axelsson, 1973; Salyer *et al.*, 1975). Derivation of central tumours from occult, non-argyrophil endocrine cells has been suggested as a means of resolving this paradox (Tateishi, 1973), but whatever the functional stage of their progenitor, no distinctive cell or pattern type was identified among our peripheral pulmonary carcinoids. It is of interest that the clearly defined subgroup of peripheral tumours documented by Salyer *et al.* (1975) was characterised by spindle cell composition, anisocytosis, anisonucleosis, and overall disorganisation of structure. Our finding of peripheral tumours which generally resembled their central counterparts is consonant with the work of

other authors (Felton *et al.*, 1953; Bonikos *et al.*, 1976). It is possible that the unmixed pattern seen in three of the peripheral lesions may have been related to size as two of the tumours were less than 1 cm diameter.

The atypical variant of pulmonary carcinoid tumour has a well recognised propensity for metastatic spread (Goodner *et al.*, 1961; Arrigoni *et al.*, 1972; Lawson *et al.*, 1976; Okike *et al.*, 1976). It is significant that these tumours were among the largest in our series (Table 2), which accords well with the experience of Arrigoni *et al.* (1972). Case 14, which metastasised, was also a large tumour but the mitotic rate was low. Perineural invasion (cases 7 and 9) was not related to the development of metastases, as noted previously (Markel *et al.*, 1964; Marks and Lamberty, 1977).

In this series, as in others (Markel *et al.*, 1964; Okike *et al.*, 1976), bone formation was seen in approximately 30% of cases This phenomenon, which has been elegantly described by Price-Thomas and Morgan (1958), differs from age-associated
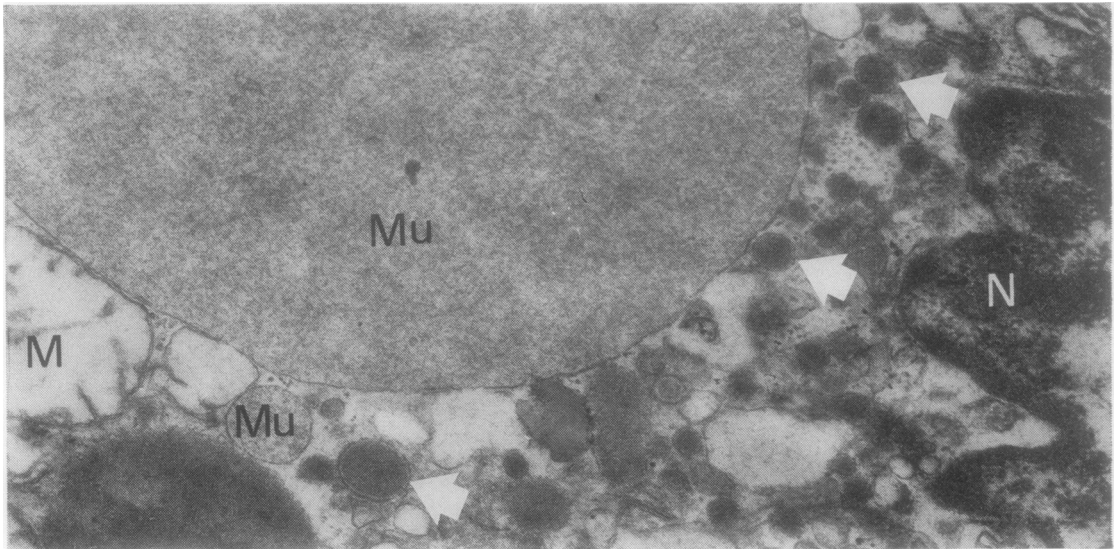
Fig. 7   *Electron micrograph of a portion of a tumour cell from case 22 showing large and small mucin vacuoles (Mu) and numerous neurosecretory granules (arrows). M = mitochondria, N = nucleus. Uranyl acetate/lead citrate × 30 000.*

ossification (Spencer, 1977) in its perichondrial distribution and from tracheo- and broncho-pathia osteoplastica (Ashley, 1970) in its limited extent. The amount of bone formed in these tumours is rarely sufficient to be visible on chest x-ray (Lawson et al., 1976) and was not seen in any of our cases. The cause of this ossification is not known and there has been little speculation on its genesis. The intimate relationship of tumour and bronchial cartilage in these cases and the known propensity of carcinoids for producing polypeptide hormones suggests that high local concentrations of an osteogenic factor might be responsible. While ossification did not appear to be significantly related to any particular histological pattern in this series it was more common in argyrophilic tumours. The majority of bone metastases of medullary carcinoma of the thyroid exhibit new bone formation (Williams, 1975) related to a high local concentration of calcitonin. Secretion of calcitonin by carcinoid tumours has been recorded (Rosen and Weintraub, 1974; De Lellis and Wolfe, 1976; Welbourne and Joffe, 1977) and interestingly the majority of bony metastases from pulmonary carcinoid tumours also show new bone formation (Okike et al., 1976). Accordingly, we felt that locally produced calcitonin might be the factor responsible for ossification of cartilage in our pulmonary carcinoids. The presence of calcitonin containing cells in four tumours showing ossification and the absence of such cells in tumours without

altered cartilage is possibly significant. The two cases (12 and 17) apparently devoid of osseous metaplasia but which did contain reactive cells may have been inadequately sampled. It is clear that this observation requires further study, and radio-immunoassay of tumour extracts would possibly yield more satisfactory results because the quantity of calcitonin detected by the immunoperoxidase technique appeared minute when compared with that visible in the control sections of a medullary carcinoma of thyroid.

Mucin production was found in five (23%) of the tumours. All these showed a clearly tubular pattern in areas. We have commented elsewhere (Sweeney and Cooney, 1978) on the histogenetic problems raised by mucin production in pulmonary carcinoid. We feel it important to stress the possibility of incorrectly diagnosing as adenocarcinoma a poorly differentiated mucin-producing carcinoid (eg, case 22) as the prognosis in the latter is considerably better.

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