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Bronchial adenomas

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A series comprising 26 patients with bronchial adenoma, consisting of 23 carcinoid tumours, 2 mucoepidermoid tumours, and 1 cylindroma, treated during the period 1956–71 is presented.

Eighteen of the carcinoid adenomas showed invasive growth, and six had metastases, five with lymph node metastases and one with hepatic metastases without node involvement (Case 17) at the time of operation. Both of the mucoepidermoid tumours and the cylindroma showed invasive growth, and one of the former had metastases. The average history of the patients was three to six months. The diagnosis was established preoperatively in 13 cases. It should be stressed that a cytological examination in 21 patients revealed pathological cells in seven.

The patients have been treated according to the same principles followed in the case of malignant lung tumours.

Four patients died owing to progression of the tumour, two from complicating diseases, and four from postoperative complications. Sixteen patients are alive and have been followed up. Three of these patients have been submitted to a non-curative operation. One year later they show no clinical signs of tumour progression. Twelve patients were submitted to a curative operation six months to 15 years before the follow-up. None shows any signs of recurrence. One patient refused operation. The five-year survival rate for lung carcinoids was 56%, or 68% after exclusion of four immediate postoperative deaths.

It is concluded that bronchial adenomas are potentially malignant tumours and should be treated like other malignant lung tumours; because of their slow growth rate and the later development of metastases, extensive operations in cases of invasive tumours and reoperations in cases of recurrence may be carried out with good results. It is further concluded that cytological examinations have greater value than was hitherto assumed.

The designation, bronchial adenoma, which should actually describe a benign, glandlike mucosal tumour, has for the last 30 years been used to designate a group of endobronchial tumours which, by their localization, growth rate, and malignancy, differ from bronchogenic carcinoma. The group comprises carcinoids, cylindromas, and mucoepidermoid tumours (Liebow, 1952). These tumours have for years been considered to be benign and have, until some years ago, been treated accordingly, most commonly by local resection. However, in recent years some publications have described invasive growth as well as metastases in connexion with these tumours (Goodner, Berg, and Watson, 1961; Weiss and Ingram, 1961; Zellos, 1962; Logan, Sehdeva, Hatcher, and Abbott, 1970). The tumours may now be considered malignant tumours with a slower rate of growth and a slower development of metastases than that of bronchogenic carcinoma. On the background of a change in attitude to the tumours the treatment has now been changed to a more radical operation.

TABLE I

AGE AND SEX DISTRIBUTION

Age	Female	Male
10–19	2	
20–29	2	2
30–39	1	
40–49		4
50–59	3	5
60–69	3	3
>70	1	
Total	12	14

TABLE II

HISTOLOGICAL DIAGNOSIS OF 26 BRONCHIAL ADENOMAS

			Metastases
Carcinoid 23	Invasive	18	6
	Non-invasive	5	0
Cylindroma 1	Invasive	1	0
Mucoepidermoid 2	Invasive	2	1

TABLE III

No.	Sex/Age	Tumour Type	Histological Evidence of Invasion	Metastases	Treatment	Type of Operation	Post-operative Follow-up	Necropsy
1	M 27	Carcinoid	No	No	Bronchial resection and lobectomy	Curative	Alive 15 yr	
2	F 13	Carcinoid	No	No	Lobectomy	Curative	Alive 9 yr	
3	F 52	Carcinoid	No	No	Wedge resection	Curative	Alive 9 yr	
4	F 24	Carcinoid	Yes	No	Bronchial resection and lobectomy	Curative	Alive 7 yr	
5	M 48	Carcinoid	Yes	No	Pneumonectomy	Curative	Died postoperatively	No metastases
6	M 68	Carcinoid	No	No	Pneumonectomy	Curative	Died postoperatively	No metastases
7	F 37	Carcinoid	Yes	No	Bi-lobectomy	Curative	Alive 6 yr	
8	M 50	Carcinoid	Yes	Lymph nodes	Tracheal and carinal resection and pneumonectomy	Non-curative	Died postoperatively	
9	M 45	Carcinoid	1. Yes 2. Yes	No Lymph nodes	Lobectomy Pneumonectomy	Curative Non-curative	Alive 5 yr Alive 2 yr	
10	M 57	Carcinoid	Yes	Lymph nodes	Exploratory thoracotomy	Irresectable	Died after 1½ yr	Cerebral haemorrhage
11	M 65	Carcinoid	Yes	No	Lobectomy	Curative	Died after 2½ yr	Metastases to lymph nodes, peritoneum, liver, and suprarenals
12	F 15	Carcinoid	Yes	No	Lobectomy	Curative	Alive 3 yr	
13	M 26	Carcinoid	Yes	No	Lobectomy	Curative	Alive 3 yr	
14	F 28	Carcinoid	Yes	Lymph nodes	Tracheal resection and pneumonectomy	Curative	Alive 2½ yr	
15	M 43	Carcinoid	No	No	Lobectomy	Curative	Alive 2½ yr	
16	F 58	Cylindroma	Yes	No	Tracheal resection	Curative	Died postoperatively	No metastases
17	M 57	Carcinoid	Yes	No	Lobectomy	Non-curative	Died postoperatively	Bleeding stomach-ulcer, metastases to liver
18	M 62	Mucoepidermoid	Yes	No	Pneumonectomy	Curative	Alive 2 yr	
19	M 46	Carcinoid	Yes	Lymph nodes	Pneumonectomy	Non-curative	Died after 6 mth	Metastases to lymph nodes, liver and vertebral column
20	M 55	Carcinoid	Yes	Lymph nodes	Exploratory thoracotomy	Irresectable	Died after 6 mth	Metastases to lymph nodes and liver
21	F 63	Carcinoid	Yes		No treatment	Inoperable	Died after 2 mth	No necropsy
22	M 56	Mucoepidermoid	Yes	Lymph nodes	Bronchial resection and lobectomy	Non-curative	Alive 1 yr	
23	F 65	Carcinoid	Yes	No	Local excision and coagulation	Non-curative	Alive 6 mth	
24	F 73	Carcinoid	Yes	No	No treatment	Refused op.	Alive 6 mth	
25	F 64	Carcinoid	Yes	No	Lobectomy	Curative	Alive 6 mth	
26	F 52	Carcinoid	Yes	No	Pneumonectomy	Curative	Alive 6 mth	

A series of 26 bronchial adenomas treated according to these more recent principles is presented.

MATERIAL

Twenty-six patients have been treated during the period 1956–71 (23 of these during 1964–71). During the same period 2,217 bronchogenic carcinomas were found corresponding to a ratio between bronchial adenoma and bronchogenic carcinoma of 1:85 or approximately 1·2%. Twelve of the 26 patients were women, 14 men; the average age was 48·0 years (Table I). The diagnosis was based on histological examination of tissue from a biopsy and on the tissue removed during the operation. In connexion with the present work the histological specimens were re-examined and the diagnosis confirmed. According to the criteria of the World Health Organization (Kreyberg, 1967), the 26 bronchial adenomas may be classified as 23 carcinoid tumours, 2 mucoepidermoid tumours, and 1 cylindroma (Table II). Eighteen of the carcinoid tumours showed invasive growth histologically (78%), five had local metastases (22%) at first operation, and one had a metastasis to the liver without any local metastases being found, a total of six tumours with metastases (26%). Both of the mucoepidermoid tumours showed invasive growth and one had local metastases. The cylindroma also showed invasive growth but no metastases (Table II). Taken as a whole, 21 out of 26 (81%) of the bronchial adenomas showed invasive growth and 7 had metastases (27%) (Table III).

CLINICAL FEATURES

The most important clinical symptoms and their duration are shown in Table IV. The symptoms were bronchial, pulmonary, and general. It will be noticed that cough, rise in temperature, expectoration, and recurring pneumonia were among the most important and most frequent symptoms, usually caused by endobronchial obstruction by the tumour. The symptoms had, on average, lasted from three to six months. However, a few of the patients had had symptoms for a much longer period. Thus, in six of the patients radiological changes corresponding to those seen preoperatively had been registered earlier, namely 2, 4, 5, 9, 13, and 25 years, respectively. Three of these patients had had recurring symptoms for 2, 13, and 25 years, respectively; the other three were without symptoms. All six patients were referred to hospital for operation because of increasing clinical or radiological symptoms. It was not possible clinically to distinguish between carcinoid tumours, mucoepidermoid tumours, and cylindroma. None of the 26 patients showed any signs indicating the carcinoid syndrome.

TABLE IV

SYMPTOMS AND DURATION OF SYMPTOMS BEFORE DIAGNOSIS

Symptom	No.	Duration (mth)
Cough	18	3–6
Expectoration	11	3–30
Haemoptysis	7	3–6
Recurrent pneumonia	9	0–6
Dyspnoea	6	3–5
Thoracic pains	4	1–6
Fever	12	3–12
Weight loss	5	0–3
Fatigue	4	2–3
None	3	

DIAGNOSIS

All 26 patients presented because of their clinical symptoms or the radiological changes found in chest radiographs. Spherical infiltrations indicating a tumour were found in six cases, less specific infiltrations were found in 13 cases, and in five cases atelectasis occurred, this being the only sign in two of these patients. In three patients with non-specific infiltrations additional tomographic exposures showed changes indicating tumours. Bronchography carried out in five patients with non-specific changes showed obstruction of one bronchial branch. In one of the two patients with a tracheal adenoma radiological examination of the trachea showed deformity indicative of a tumour.

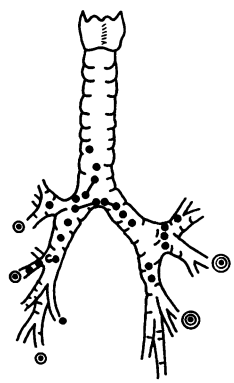

FIG. 1. *The distribution of 26 bronchial adenomas.*

Bronchoscopy was carried out in 24 patients (Fig. 1). In one patient bronchoscopy could not be carried out owing to the position of the patient's

teeth, and in one patient the chest film showed a small, tumorous infiltration placed so peripherally in the sixth segment that bronchoscopy was not performed. As in other studies, bronchoscopy afforded a high rate of diagnostic certainty. In this series 21 tumours were visible at bronchoscopy.

The localization of the tumours is seen in Figure 1. As in other series (Carlens, Wiklund, and Bergstrand, 1954; Haupt and Weiske, 1967; Spencer, 1968) they are most frequently found in the main bronchi and the bronchial branches. The localization of three tumours was so peripheral as to render them not visible at bronchoscopy. One tumour was found to be localized subpleurally. Two tumours were confined to the trachea alone. Out of three tumours localized centrally in the main bronchi, one invaded the trachea and two the carina. The cylindroma was found in the trachea, and the mucoepidermoid tumours in the left main bronchus and in the bronchus of the right upper lobe.

Cytological examination of the sputum and/or bronchial secretion obtained at bronchoscopy was carried out in 21 patients. Examination of sputum was carried out in 13 patients and examination of the bronchial secretion in 17 patients (Table V) In nine patients both sputum and bronchial secretion were examined. Abnormal cells were found in seven patients, in the sputum in two cases and in the bronchial secretion in six. In five of these cases the cells had the character of adenoma cells. In two cases the cells were classified as anaplastic tumour cells. The four bronchial secretions containing adenoma cells were examined at the same time as the biopsies from the tumours. In three of these biopsies carcinoid tumour cells were found, while the fourth contained no tumour tissue.

TABLE V

CYTOLOGICAL EXAMINATION FOR TUMOUR CELLS IN 21 PATIENTS

	No. of Patients	Negative Cytology	
Sputum	13	9	Atypical cells 1 Adenoma cells 1
Bronchial secretion	17	11	Anaplastic cells 2 Adenoma cells 4

TABLE VI

BRONCHIAL BIOPSY

Biopsy negative	4
Carcinoma	2
Anaplastic 1	
Solid 1	
Bronchial adenoma	10
Carcinoid 10	
Total	16

As shown in Table VI, biopsies of the tumours were taken at bronchoscopy in 16 cases. In 10 of the 12 cases in which the findings were positive an exact diagnosis could be established. In two patients the results of the biopsies showed carcinoma (one anaplastic (case 8) and one solid carcinoma (case 18)). The correct diagnosis was later established when fresh histological material was examined. In the patient with 'solid carcinoma' the operative finding revealed a mucoepidermoid tumour. In the patient with 'anaplastic carcinoma' a mediastinoscopy was carried out, revealing glandular metastases around the bifurcation from a carcinoid tumour. Radiotherapy led to a reduction of the tumour and a pneumonectomy was then carried out, but it was not curative. The diagnosis of carcinoid was confirmed by the operative finding.

In eight patients no biopsies were taken during bronchoscopy. In three the appearances were normal; in two cases a bronchial constriction was observed apparently lined by normal mucous membrane. In three cases with a visible tumour no biopsy was taken, the two tumours being situated so far peripherally in the segment bronchus that it was not possible to take a biopsy; the third tumour was a tracheal tumour and the risk of causing haemorrhages was thus too great.

In 13 of 26 patients the correct histological diagnosis was established preoperatively, while in the remaining 13 patients the exact diagnosis was established only when the operative specimens were examined.

TREATMENT

The operations carried out are shown in Table III and in Figure 2. In one patient (case 21) the bronchoscopic findings showed the condition to be inoperable as the tumour had invaded both main bronchi as well as the trachea and tracheal carina. The patient died two months later. In two patients (cases 1 and 20) an exploratory thoracotomy was carried out and each tumour was found to be irresectable. One patient (case 24) refused thoracotomy.

Figure 2a shows the treatment of two patients with tracheal adenoma. One of the patients (case 23) had a tumour, 3 cm in circumference, in the lower third of the trachea causing an almost complete obstruction, and the greater part of the

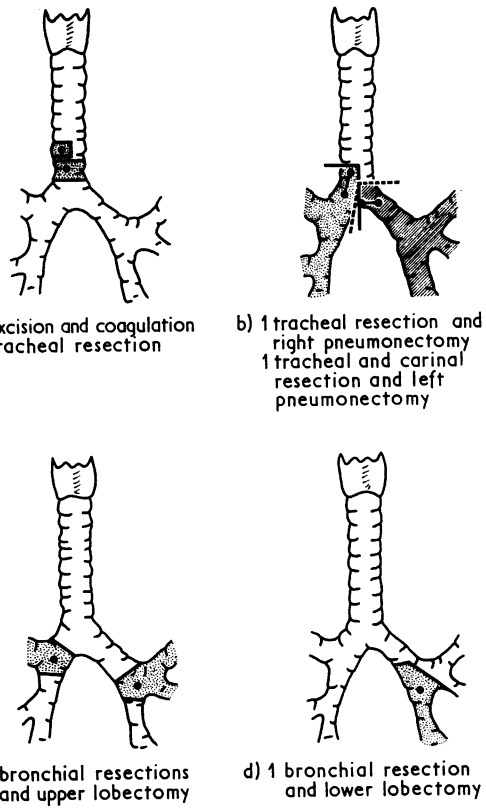

FIG. 2. *Schematic representation of tracheal and bronchial resections.*

tumour was therefore removed from within the trachea by excision and coagulation. A few days later the patient was submitted to vagotomy and pyloroplasty because of a bleeding peptic ulcer. Postoperative recovery was very slow and was characterized by sepsis and uraemia, and further treatment had to be limited to endotracheal electrocoagulation of the remaining part of the tumour. The other patient (case 16) had an adenoma, 2 cm in circumference, in the middle of the trachea (cylindroma). A partial resection of the trachea as well as a tracheal graft by the Gebauer method was carried out. The operation was curative, but the patient died 12 days later due to difficulties connected with secretion and tracheal haemorrhage.

In one patient (case 3) a small adenoma situated just subpleurally was removed by wedge resection. Eleven patients had a lobectomy performed which in three cases was combined with a bronchial resection due to localization of the tumour in the lobe and stem bronchus (Fig. 2c and d). In two patients bilobectomy was carried out, and seven patients were submitted to pneumonectomy which, in one case (case 14), was combined with a tracheal resection due to tumour infiltration, and in another case (case 8) was combined with resection of the trachea as well as of the tracheal carina also due to infiltration by the tumour (Fig. 2b).

One patient (case 9) with a carcinoid tumour was primarily submitted to an apparently curative middle lobectomy. Three and a half years later recurrence was demonstrated radiologically as well as bronchoscopically, and a pneumonectomy and pericardial resection with resection of the left atrium, parietal pleura, and phrenic and vagal nerves was performed. Complete removal of all tumour was not possible, however.

One patient (case 26) had a carcinoid tumour in the right main bronchus. The patient had had radiological signs and clinical symptoms for 13 years. Besides recurrent pneumonias she had severe asthma. She showed no other signs of carcinoid syndrome. The quantitative content of 5-hydroxyindole-acetic acid in the urine was normal. The tumour was 10·0 cm in circumference, invading parietal pleura, pericardium, left atrium, and mediastinum. Pneumonectomy, pericardial resection, resection of the left atrium, parietal pleura, and mediastinal tissue, and gland dissection were performed. Histological examination showed that the tumour had been removed from surrounding healthy tissue. Postoperatively the patient has been well without any asthmatic symptoms.

RESULTS

In 17 patients the treatment was considered curative, neither metastases—or at the most a solitary, positive lymph node in the vicinity of the tumour (two cases)—nor any infiltration at the bronchial cuff of the resection being found. Palliative procedures were performed in six patients. Two patients were submitted to an exploratory thoracotomy only, while one patient was considered inoperable and one patient refused thoracotomy (Table III).

Five patients died postoperatively, one from a bleeding gastric ulcer (case 17) and four from pulmonary complications. Four of these patients had been submitted to a curative resection, but in one case (case 17) metastases to the liver were found at necropsy (which also revealed a bilateral hypernephroma).

All the patients have been followed up. The

TABLE VII
FOLLOW-UP

	No. Died	No. Alive
0–1 year	8	5
5 dead in postoperative period 3 dead later		
1–3 years	2	4
4–6 years		2
7–10 years		4
More than 10 years		1
Total	26	

period of observation was from six months to 15 years (Table VII). Five patients died between two months and two and a half years after operation. One patient (case 11) had been submitted to what must be considered a curative operation, but died two and a half years later from a recurrence. One patient (case 10), in whom an exploratory thoracotomy had been carried out, died one and a half years later from cerebral haemorrhage.

Sixteen patients are still alive six months to 15 years after operation. Three patients had been submitted to a non-curative operation one year previously. They showed no progression of the tumour. Twelve patients who had been submitted to curative operations were completely well, showing no signs of recurrence six months to 15 years postoperatively (Tables III and VII). In patients with large tumours and/or metastases and in patients in whom the operation was not curative, the quantitative content of 5-hydroxyindole-acetic acid in 24-hour samples of urine was determined. No increased values were found. None of the patients showed signs of a carcinoid syndrome.

The five-year survival rate for carcinoid tumours, estimated according to the life table method (Berkson and Gage, 1950), was 56%. Exclusion of the four immediate postoperative deaths yielded a rate of 68%.

DISCUSSION

Most authors (Vogt-Moykopf, 1967; Spencer, 1968; Simpson, 1969) find an incidence of bronchial adenomas of from 2 to 5% of all primary lung tumours. Our incidence was 1·2% (26 out of 2,243 primary lung tumours). The incidence appears to have been increasing over the years, probably due to a greater diagnostic accuracy.

As in other series, no definite difference in the incidence between men and women was found. The average age of the patients was 48 years, also in accordance with other authors who found an average age from 40 to 50 years (Carlens, Wiklund, and Bergstrand, 1954; Goodner *et al.*, 1961; Markel, Abell, Haight and French, 1964). There are several quite young patients in our series, and this has also been found by others (Borrie, 1963; Verska and Connolly, 1968; Logan *et al.*, 1970). The average age of patients with cylindroma and mucoepidermoid tumours appears to be slightly higher than that of patients with carcinoid adenoma (Liebow, 1952; Weiss and Ingram, 1961; Wilkins, Darling, Soutter, and Sniffen, 1963). The ages of the two patients with mucoepidermoid tumours were 56 and 62 years, while the patient with cylindroma was 58 years old.

In the majority of other series the carcinoid adenomas constitute 90%, the cylindroma 10%, and the mucoepidermoid tumours 1–2% of the bronchial adenomas (Liebow, 1952; Payne, Ellis, Woolner, and Moersch, 1959; Spencer, 1968). The distribution of the various types in our series corresponds with these figures, with the exception of the two mucoepidermoid tumours. Some authors have described tumours of a mixed type, most frequently the occurrence of carcinoid and cylindroma within the same tumour (Engelbreth-Holm, 1944; Carlens *et al.*, 1954; Zellos, 1962). This was not found in any of our tumours. In recent publications (Weiss and Ingram, 1961; Markel *et al.*, 1964) doubts have been raised as to the existence of such mixed tumours.

The incidence of metastases arising from bronchial adenomas varies considerably in different reports. In carcinoid adenomas the incidence of regional metastases varies from 5% to as much as 45% (Goodner *et al.*, 1961; Markel *et al.*, 1964; Stephenson, Sawyers, and Adkins, 1967); in the majority of studies the incidence is given as 20–30% (Zellos, 1962; Valdoni, 1966; Logan *et al.*, 1970). Metastases to other regions occur in about 5–10% of the cases, localized mainly in the liver, bones, and suprarenals (Spencer, 1968). In our series regional metastases were found in 22%, and in one case hepatic metastases were encountered without any simultaneous occurrence of regional metastases. This represents an incidence of metastases of 26% for carcinoid adenomas.

Cylindroma is said to grow more rapidly and more invasively with an earlier appearance of metastases than carcinoid adenoma (Weiss and Ingram, 1961; Tauxe, McDonald, and Devine, 1962; Spencer, 1968). The cylindroma in this series showed invasive growth but no metastases.

The mucoepidermoid tumours are usually described as relatively benign with infrequent occurrence of invasive growth or metastases (Payne *et al.*, 1959; Ozlu, Christopherson, and Allen, 1961). Both of the mucoepidermoid tumours

in this series showed invasive growth, and one had metastasized locally.

The symptoms do not differ from the symptoms found in other forms of lung tumour, although haemoptysis occurs quite frequently in cases of bronchial adenoma, probably owing to their profuse vascularization. The duration of symptoms is longer in the case of bronchial adenoma than in bronchogenic carcinoma owing to the slow growth rate of the former. The duration of the symptoms is often given as more than two years. In this series the symptoms had lasted from three to six months, although there were exceptions; thus in six patients the tumour had existed radiologically and in three cases also clinically for 2, 4, 5, 9, 13, and 25 years respectively before operation. Some authors have described patients in whom the tumour had existed for 15 to 45 years without showing any real progression (Carlens *et al.*, 1954; Borrie, 1963; Wilkins *et al.*, 1963).

Bronchial adenomas are usually described as localized in the main bronchi and in the larger bronchial branches. In three of the patients in this series the localization of the tumour was peripheral, so that they could not be diagnosed by means of conventional bronchoscopy.

Bronchial adenomas are usually covered by an intact mucous membrane, and the results of cytological examination of sputum and bronchial secretion are often described as negative (Wilkins *et al.*, 1963; Koss, 1968). Most authors do not report the results of examinations of secretion, therefore it is interesting to note that in 8 of 30 cytological examinations in this series the results were positive (Table V).

Biopsies (Table VI) afford a suitable diagnostic method with positive results in 12 out of 16 cases. Both in cytological and histological examinations an attempt must be made to secure the most suitable material owing to the morphological similarity to anaplastic or solid carcinoma. We would here refer to our two cases previously described.

Examination with electron microscopy (Bensch, Corrin, Pariente, and Spencer, 1968; Hattori *et al.*, 1968) has shown oat-cell tumours and carcinoid tumours to be closely related. These authors described the two types of tumour as the malignant tumour and the 'locally malignant' tumour arising from the Kultschitzky-type cells in normal bronchial mucosa.

The histological picture of the bronchial adenoma will not be described here. In accordance with Goodner *et al.* (1961) we do not think it is possible to distinguish between benign and malignant carcinoid tumours on the basis of the histological findings. Accordingly, all carcinoid tumours must be regarded as potentially malignant tumours and treated according to the principles described.

The follow-up showed that in 2 out of the 13 patients treated apparently curatively, recurrences were found. One of these patients (case 11) died two and a half years after operation. The other patient (case 9) was re-operated three and a half years after the primary lobectomy for a carcinoid adenoma by pneumonectomy and resection of pericardium, left atrium, parietal pleura, and the phrenic and vagal nerves. The operation revealed invasive growth to the mediastinum and the thoracic wall as well as metastases to the regional lymph nodes. The patient is still alive one and a half years after operation without any signs of progression of the tumour.

Three of the 23 patients in the series with a carcinoid adenoma had a peptic ulcer (two gastric and one pyloric). The presence of the latter ulcer was known before operation, and it healed when the patient was submitted to a vagotomy at the time of thoracotomy for bronchial adenoma (case 9). The patients with gastric ulcers had severe gastrointestinal bleeding in the postoperative period necessitating an operation. This led to a fatality in one case (case 17). A connexion may possibly exist, as already suggested by others (Williams and Celestin, 1962), between bronchial adenoma of the carcinoid type and gastrointestinal ulcer. McGuigan (1968) has advanced the theory that argentaffin cells in the stomach produce gastrin. Similar cells are found in bronchial carcinoid adenomas and may possibly explain the occurrence of peptic ulcer in patients with bronchial adenoma.

CONCLUSION

Until recently bronchial adenoma has by many been considered a relatively benign tumour and has for that reason frequently been treated by either local excision or limited resection.

On the basis of the series presented it is stressed that bronchial adenomas often grow invasively (81%) and frequently metastasize (27%). Bronchial adenomas should therefore be regarded as tumours in the same sense as other malignant lung tumours from which the bronchial adenoma differs only by its slow growth and late onset of metastases. Classification of bronchial adenomas as potentially malignant tumours should lead to treatment based on the same principles as those

followed in the case of malignant lung tumours with radical resection determined by frozen section.

This series also shows that a bronchial adenoma may often be diagnosed preoperatively. Because of its slow growth rate and the slower development of metastases extensive surgery is recommended in cases of extensive, infiltrating tumours, and reoperation in the event of recurrence.

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