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Bronchial Mucous Gland Tumours*

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Summary. Tumours arising in the bronchial mucous glands closely resemble tumours arising in the mixed salivary glands. Bronchial mucous gland tumours account for less than 0.5 per cent of all lung tumours. Twenty six tumours are reviewed and they have been divided into five types, (a) adenoid-cystic carcinomas, (b) muco-epidermoid tumours, (c) mixed (pleomorphic) tumours, (d) cystadenomas and (f) oxyphilic adenoma. The clinical features, and postoperative course of the patients are reviewed. Adenocystic carcinomas arising in the bronchus frequently involve the neighbouring trachea and spread mainly by direct infiltration. Most muco-epidermoid bronchial tumours were confined to young persons, and the only malignant muco-epidermoid tumour occurred in an elderly person. The prognosis in young persons is good provided the tumours are completely excised. The two mixed bronchial tumours resembled their salivary counterparts and one subsequently behaved as a carcinoma and metastasised. Bronchial cystadenomas all proved to be benign tumours but in two cases were associated with surface papillary proliferation. The only example of an oxyphil cell adenoma was discovered at post mortem examination. The histogenesis of the tumours is considered.

Key words: Adenoid cystic carcinoma – Muco-epidermoid tumours – Pleomorphic adenomas – Cystadenomas – Oxyphilic adenoma.

Introduction

Bronchial and tracheal mucous glands possess a similar structure to the mixed type of salivary glands except that they incorporate APUD system cells. The tumours to which they give rise closely resemble salivary gland tumours apart from the common forms of bronchial carcinoma which arise simultaneously from bronchial surface, ductular and gland acinar epithelium and also those tumours which arise from the APUD cells.

* Dedicated to Professor E. Uehlinger on the occasion of his 80th birthday

This account does not include the common histological forms of bronchial cancer or the bronchial carcinoid tumours but only those tumours that arise from the exocrine cells of the bronchial and tracheal mucous glands and their ducts. Such tumours form less than 0.5 per cent of all bronchial tumours and they are divided for convenience of description into five varieties: (a) the adenoid cystic carcinomas, (b) muco-epidermoid tumours, (c) mixed (pleomorphic) bronchial tumours (adenoma and carcinoma), (d) cystadenomas and (e) the oxyphilic bronchial gland adenoma. Of all these rare tumours the first two varieties are those most commonly encountered. The true mixed bronchial tumours should not be confused with bronchial carcinoid tumours, the stroma of which may not infrequently undergo osseous, cartilaginous or amyloid changes but such carcinoid tumours are not regarded as true mixed bronchial tumours.

Methods and Materials

In the ensuing account the clinical data have been collected and analysed when obtainable, and in some instances it has been possible to follow the subsequent course of the patients. In other cases, however, only the microscopic slides of the tumours have still been available. Each group of bronchial tumours will be considered in turn, firstly the pertinent clinical data are analysed followed by the microscopical features of the tumours.

Since many of the cases included in this survey have been collected over a period of forty years and were often referred cases from many sources and countries, only haematoxylin and eosin stained slides were still available. When possible other staining methods have been applied including the PAS method with and without diastase digestion, Southgate's mucicarmine stain, Best's glycogen stain, alcian blue stain and Masson's trichrome stain.

Adenoid Cystic Carcinomas

Of the 10 cases of adenoid cystic carcinoma clinical details were obtained for eight and in the case of the remaining two only the microscopic slides were available. All the patients were white and 5 were female and 3 male. Their ages ranged from 31 to 62 years with an average age of 47 years. In four the tumours involved the trachea to a greater or lesser extent and in one almost the entire length of the trachea was invaded by growth which had arisen in the adjacent main bronchus. All the tumours arose either in a main bronchus or in an upper lobe lobar bronchus. In 6 cases the right lung was the site of origin and in 2 the left. In two cases there was microscopical evidence of direct invasion of hilar lymph glands but in the remaining cases details were not available concerning hilar lymph gland involvement.

Most patients complained of a chronic cough and sputum production, the latter having become increasingly mucopurulent in character. They also complained of the gradual onset of increasing dyspnoea. In one case these symptoms had existed for 9 years but on average the symptoms had only been noticed for 2 years. Other common symptoms and signs included chest pain and intermittent slight blood tingeing of the sputum. Most of these clinical changes resulted from an obstructive pneumonitis caused by the tumour. The lung opacities noted on radiological examination were also compatible with chronic pneumonia in the obstructed portion of lung. Bronchoscopic examination revealed the obstructing tumour in all cases where this investigation was recorded, the tumour being variously described as polypoidal, sessile or diffusely infiltrative. The treatment

of most of the cases consisted of either a lobectomy or pneumonectomy and unfortunately follow-up information was only available in one case, the patient being alive and well 5 years later. Spread of the tumour to the trachea increased the operative risk and in one case the patient later developed a tracheal fistula. In the case in which almost the entire length of the trachea was involved by growth, surgical treatment was impossible and radiation therapy was employed and led to some subsequent contraction of the growth and partial relief of the airway obstruction. In 3 cases the tumour extended directly into the adjacent lung and if this was extensive such tumours were readily confused with a growth which had arisen in the periphery of the lung. One tumour was discovered as a chance finding during a post mortem examination on a patient who had died from an unrelated disease. Unfortunately the smoking histories of the patients were not recorded.

Microscopically, all the tumours presented the same general appearance as similar tumours encountered in the salivary glands. The tumour cells were arranged either in clumps with a cribriform pattern enclosing pseudocystic spaces (Fig. 1), in trabeculae and in the less differentiated tumours in solid masses of small round cells without any glandular pattern. Some tumours showed areas containing small ducts and tubule formation. The nuclei of the individual tumour cells were mostly vesicular with scattered chromatin dots and few mitoses. In those tumours showing a cribriform pattern the centres of the cell masses contained PAS-positive mucin and their outer margins were outlined by a palisade layer of cuboidal or columnar cells. In those tumours in which the cells were arranged in solid masses the small often oat-shaped cells might be confused with a true oat-celled (small round celled) type of lung cancer (Fig. 2), but mitotic activity was minimal and the tumour cell nuclei lacked the dense chromatin content found in a true oat-celled carcinoma.

The stroma of the tumours varied. In some a well formed hyaline basement membrane expanded into dense sclerotic fibrous tissue separating one mass of tumour cells from another (Fig. 2) but in others a loose oedematous alcian positive connective tissue stroma was present. Invasion of the bronchial walls resulted in cartilage destruction and spread into the peribronchial tissues including especially the perineural lymphatics (Fig. 3). The capsule and substance of adjacent hilar lymph glands were not infrequently infiltrated by tumour cells (Fig. 4), and direct invasion of lung alveolar tissue was observed.

Because of its distinctive cellular appearance adenoid cystic carcinoma seldom leads to confusion with other forms of lung cancer and it rarely metastasises. If metastasis does occur to distant sites which include liver, kidney and bone marrow, the metastases retain the characteristic histological features of the primary tumour.

Muco-Epidermoid Bronchial Tumours

Eight examples of bronchial muco-epidermoid tumours have been reviewed one of which was undoubtedly malignant and behaved as a lung carcinoma. Six of the patients were white and two were black, and 4 were male and 4 female. With the exception of the one undoubted case of adenocarcinoma, which was thought to have arisen in a muco-epidermoid tumour and who was aged 68 years, all the other patients' ages ranged from $4^1/_2$ years to 20 years with an average age of $10^1/_2$ years. Five tumours were located in the

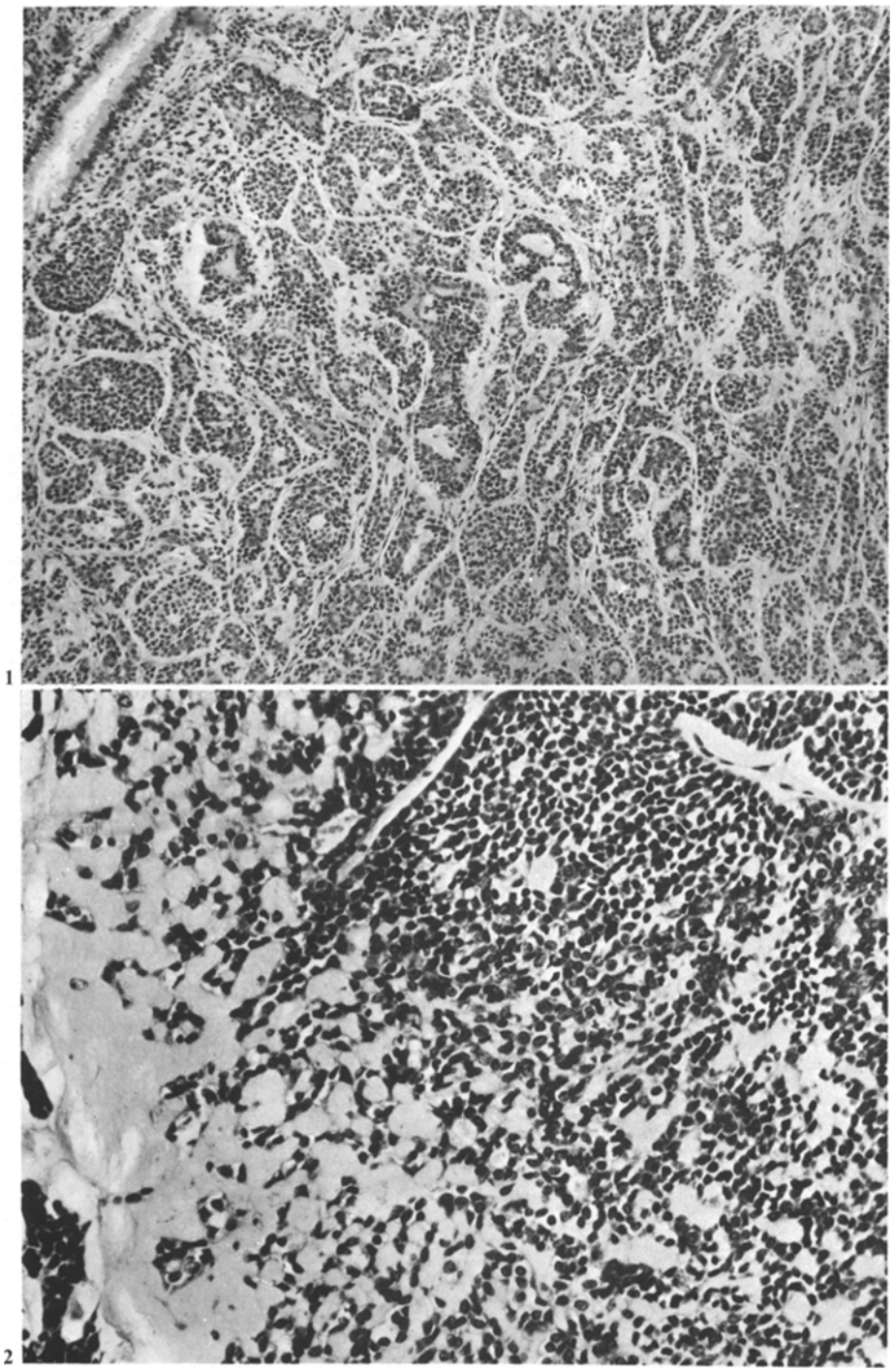


Fig. 1. Adenoid cystic carcinoma arising in bronchial glands showing typical pseudocysts within the masses of tumour cells. × 100 H and E

Fig. 2. Adenoid cystic carcinoma of bronchus showing sclerotic reaction and diffuse tumour cell infiltration. × 250 H and E

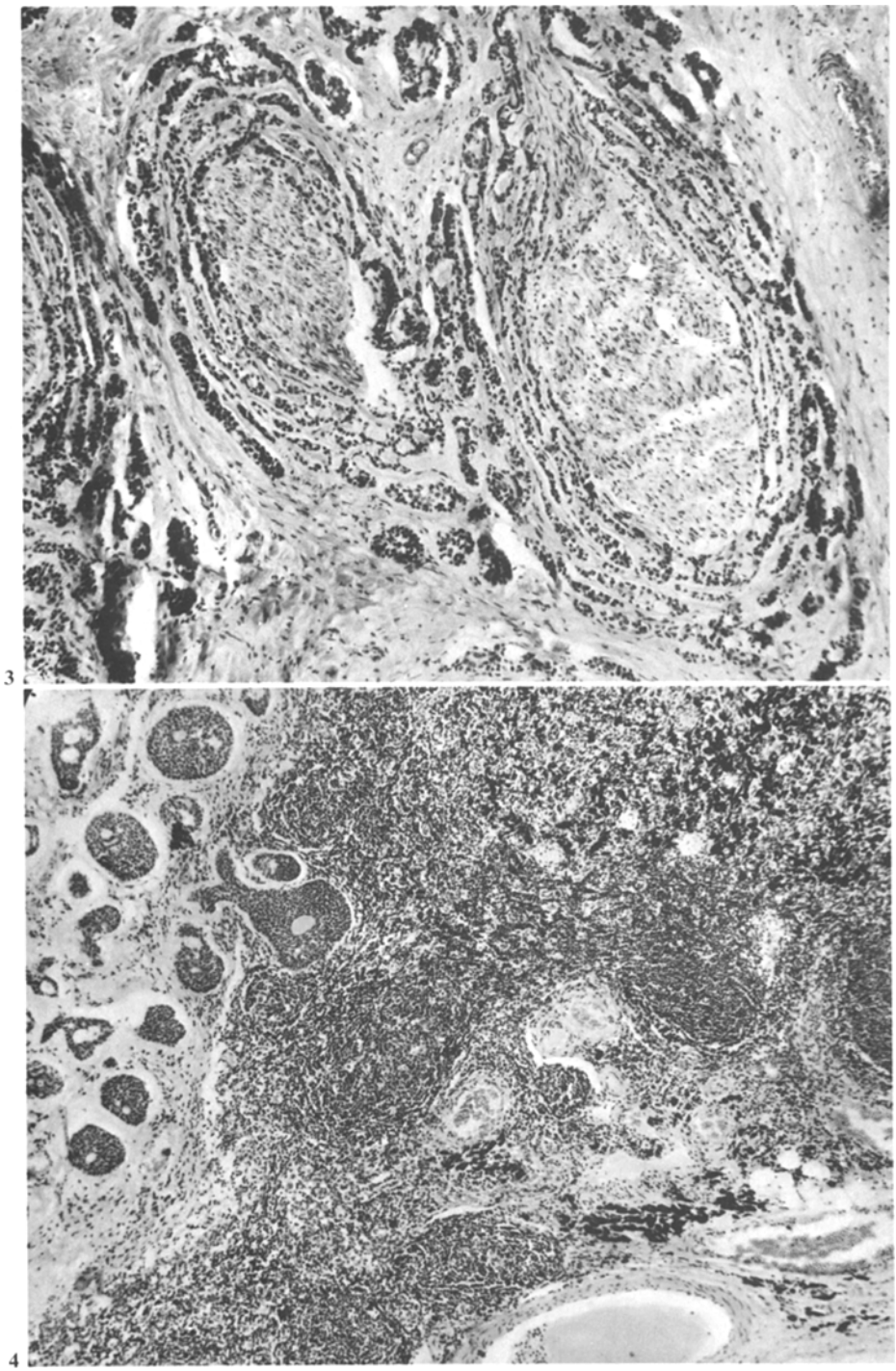


Fig. 3. Adenoid cystic carcinoma of bronchus spreading in the perineural lymphatics outside the bronchial wall. ×100 H and E

Fig. 4. Adenoid cystic carcinoma of bronchus spreading through peribronchial tissues and invading by direct infiltration a hilar lymph gland. ×63 H and E

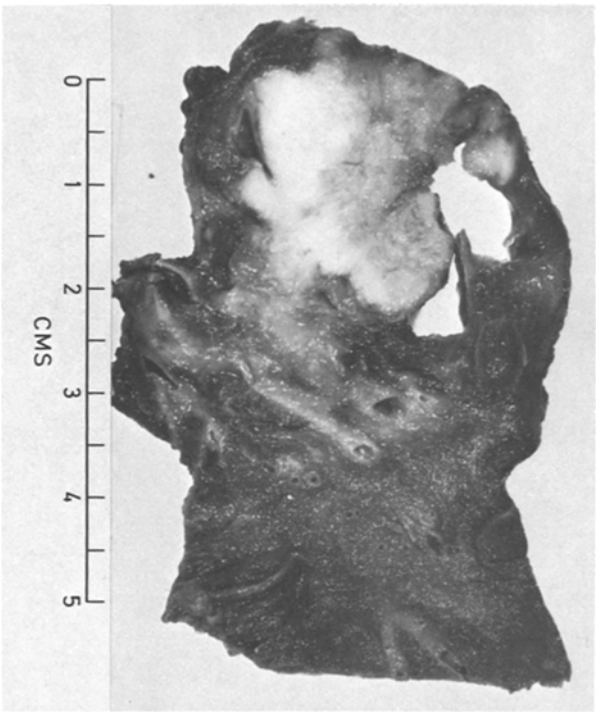
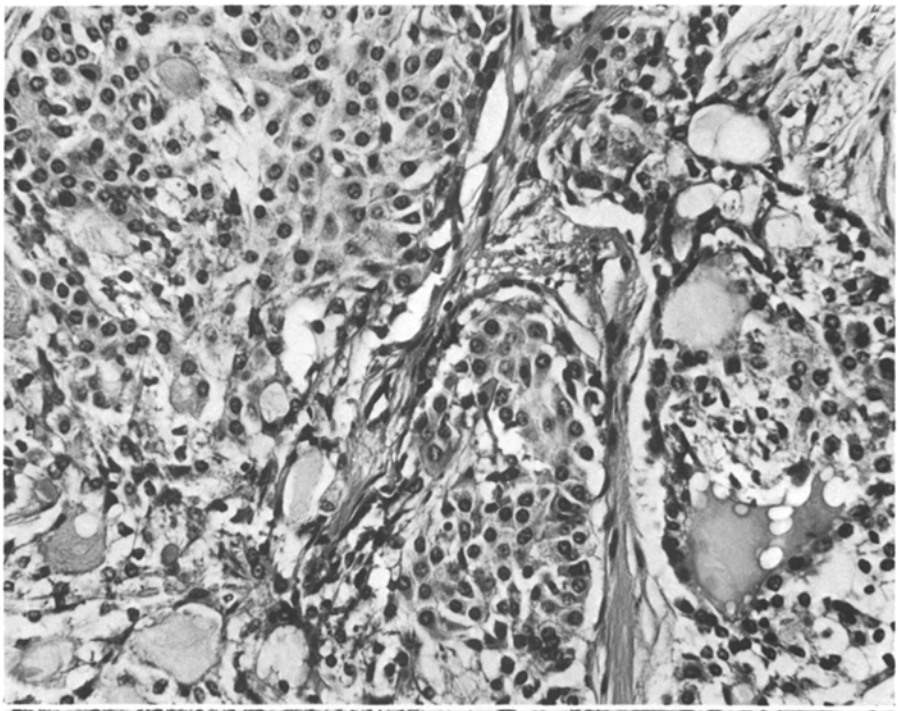


Fig. 5. A muco-epidermoid tumour arising in a bronchial wall and spreading directly into the peribronchial tissues

left lung and 3 in the right and with the exception of 1 tumour located in a main bronchus the remainder were found either in a lower or upper lobe lobar bronchus and in 2 instances in an apical segmental bronchus within a lower lobe (Fig. 5).

The symptoms and signs caused by this group of tumours closely resembled those that occurred in patients with adenoid cystic carcinoma. The duration of symptoms before the patients sought treatment varied from 8 years to a month. In every case in which the patient had been bronchoscoped the tumour was seen and was described as a reddish-grey smooth, glistening polypoidal tumour which projected into or completely obstructed the bronchus. In no instance except in the one case of the undoubted carcinoma were the hilar lymph glands involved. In 3 cases of muco-epidermoid tumours treated by extirpative surgery and that were followed, the patients were alive and well 20, 7 and 14 years later. The patient with the malignant tumour died within 18 months of its discovery despite a total pneumonectomy.

The microscopical appearances of all the tumours with the exception of the one malignant tumour all presented a similar appearance to the tumours of the same type arising in salivary glands. The tumours consisted of solid clumps of pale staining and often vacuolated, polymorphic or columnar cells some of which secreted mucin together with glandular spaces filled with pale staining mucus (Fig. 6). Many of the glandular spaces formed an integral part of the tumour cell clumps and formed large mucus-filled spaces. The bronchial



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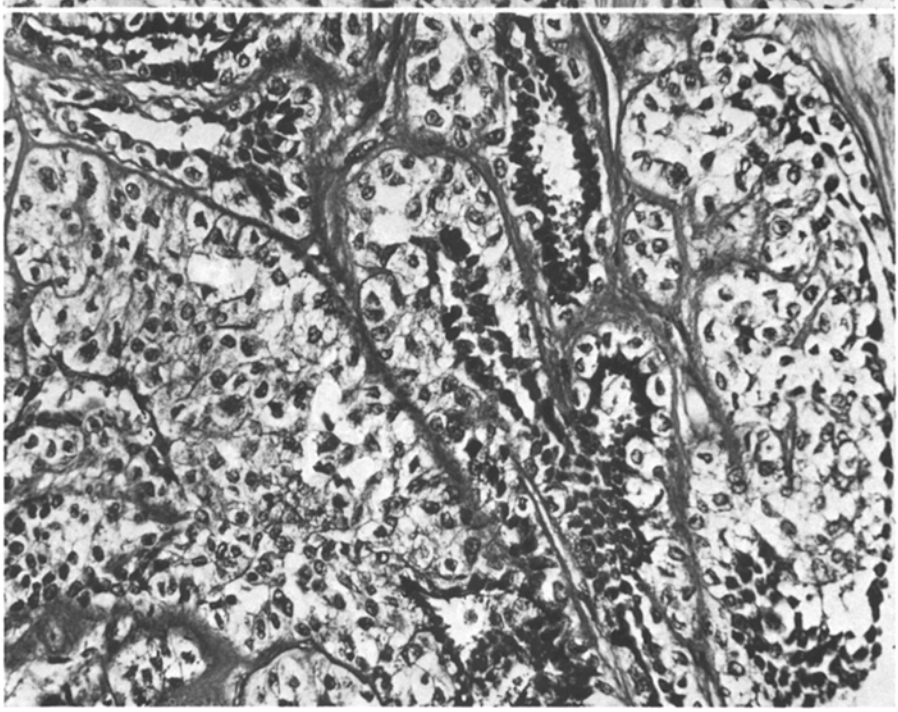

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Fig. 6. Muco-epidermoid tumour of bronchus showing mucus filled spaces forming part of the solid cell masses. ×250 H and E

Fig. 7. A pleomorphic adenoma of bronchus showing the ductular structures with surrounding periductular cells. ×250 H and E

surface of the tumours was covered with metaplastic squamous epithelium, and the surface epithelium and ducts of the mucous glands could be traced and seen to be continuous with the underlying tumour cells.

Although the term muco-epidermoid is used to describe these tumours, none of the features traditionally diagnostic of squamous epithelium, i.e. keratin formation or the presence of intercellular prickles (desmosomes), were seen. The tumour cell clumps were intersected with a minimal amount of fibrous tissue but the tumours were not encapsuled. Mitotic activity varied, some tumours showing none while others contained up to one or two in each high power field. Corpora amylaceae were found in two cases and calcification in one. In one case a very large number of mature plasma cells were observed scattered throughout the tumour, and in another tumour there were cystadenomatous areas. As the tumours expanded and grew they compressed but did not destroy the bronchial cartilages and in no case except the one that was carcinomatous were lymph glands invaded.

The one undoubted malignant tumour occurred in a much older person. Most of the tumour was composed of a small round celled adenocarcinoma but in some places the tumour formed solid clumps of cells with glandular spaces resembling in appearance the muco-epidermoid tumours. The individual tumour cells however, unlike those in the benign muco-epidermoid tumours had prominent nucleoli and were much more hyperchromatic and spread to the hilar lymph glands had occurred.

Mixed (Pleomorphic) Bronchial Tumours

Two examples of these very rare bronchial tumours have been seen. Both occurred in men aged 58 and 68 years. The first was located in the right lower lobe lobar bronchus and the second was a tumour occupying much of the lower lobe of the right lung and because of its size it had extended almost to the pleural surface. The patient with the clearly identifiable bronchial tumour suffered from symptoms and signs caused by the resulting obstructive pneumonitis and the tumour was observed by bronchoscopy. The second patient also complained of cough and increased sputum but bronchoscopic examination was unhelpful. A large opacity was however, seen on X-ray occupying much of the lower lobe of the right lung and was deemed pre-operatively to be due to a carcinoma. The tumours in both cases were removed by lobectomy. The second patient remained well for 4 years but then developed collapse of the 4th lumbar vertebra due to metastic growth for which he received radiotherapy.

Microscopical appearances of the first tumour showed numerous branching ducts lined by dark staining cuboidal cells. Many of the smaller ducts were flattened and collapsed. The luminal surface of the duct cells were either flattened or rounded but their opposite poles were spiked and interdigitated with pale, vesicular polymorphic cells (Fig. 7). The latter extended in an irregular fashion outwards and were mostly bounded by connective tissue but in a few places were lost in oedematous and myxomatous ground substance which stained

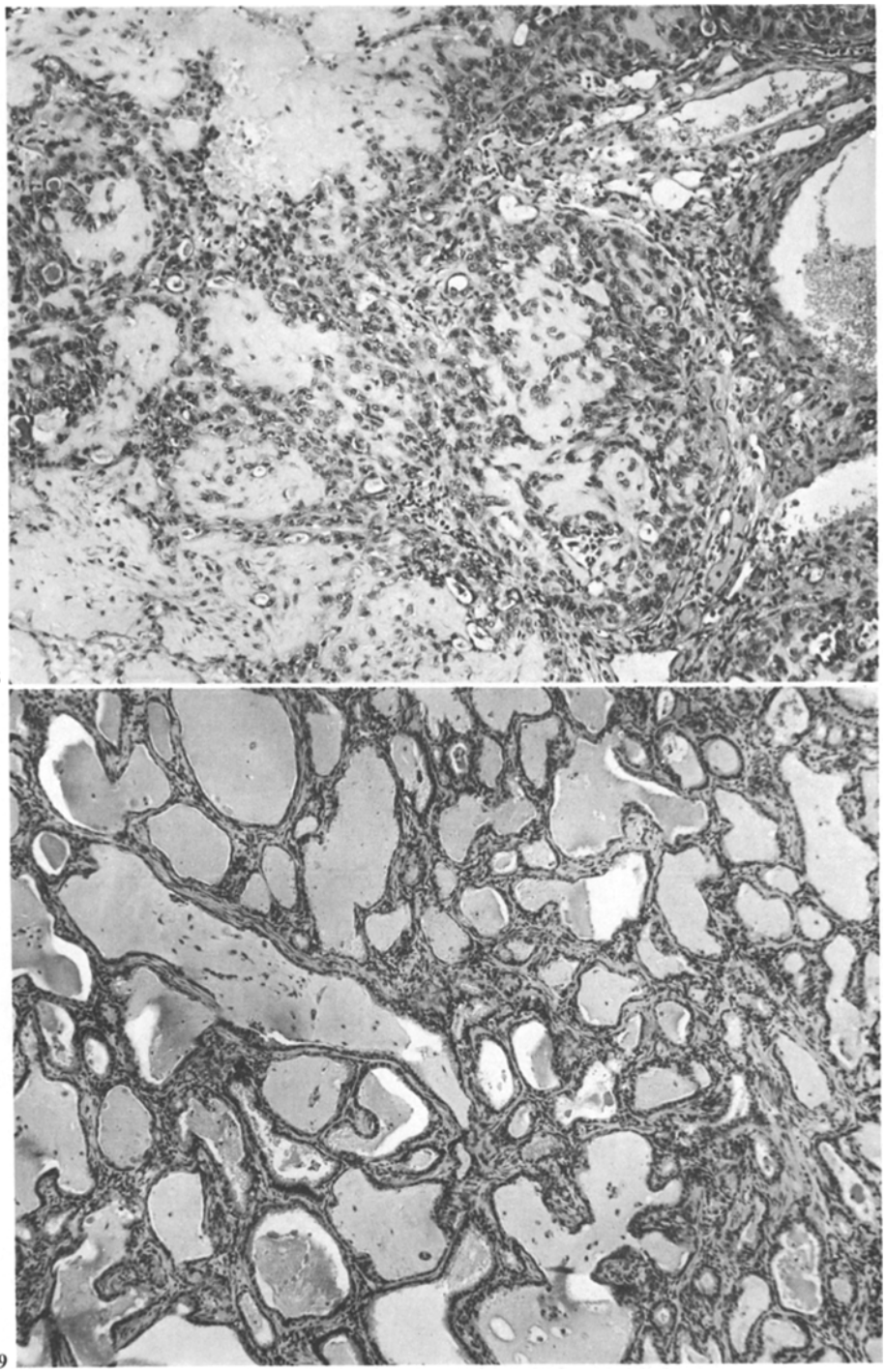

Fig. 8. A pleomorphic (mixed) tumour of bronchus showing ductular structures and periductular cells spreading outwards and becoming surrounded by cartilage-like ground substance. × 100 H and E

Fig. 9. A bronchial cystadenoma showing dilated adenomatous spaces filled with mucus and lined by cuboidal cells. × 63 H and E

strongly with alcian blue. A few strands of fibrous tissue intersected the tumour mass dividing it into lobular masses. No mitotic activity was seen in the tumour cells but the edges of the tumour though well demarcated were not encapsuled. It was regarded as a mixed (pleomorphic) bronchial adenoma.

The second tumour in this group extended almost to the pleural surface and was similar in appearance to the first. Some of the ducts were totally collapsed and appeared to be solid buds of cells. The periductal cells were less vesicular and more stellate and spindle-shaped. The outermost periductal cells were diffusely scattered and were surrounded by alcian positive chondroid and myxomatous ground substance (Fig. 8). A few small areas of necrosis containing amorphous material and cholesterol clefts were present. Scattered mitoses were observed and a guarded prognosis was given which was subsequently supported by the further behaviour of the tumour. The tumour was intersected by a few strands of fibrous tissue which divided it into lobules but like the first tumour in this group there was no capsule. Initially it was regarded as a mixed bronchial adenoma but which nevertheless displayed suspicious malignant features.

Bronchial Cystadenomas

Five examples of bronchial cystadenomas have been examined. In two of the cases the cystadenomas were associated with overlying intrabronchial surface papillary tumours. Four patients were males and their ages ranged from 43 to 67 years with an average age of 53 years. All of the tumours were found in either the main or lobar bronchi. The symptoms and signs caused by these tumours included cough, excess sputum production, dyspnoea and slight haemoptyses which on average had been present for about 3 years before the patients sought treatment. The diagnosis was established by bronchoscopy when the tumours appeared as polypoidal, glistening pinkish-grey masses. Treatment consisted either of a lobectomy or pneumonectomy.

Microscopically, all 5 tumours showed a similar appearance. In 3 the cystically dilated, mucus-filled bronchial gland mass was covered on its surface by metaplastic squamous bronchial epithelium. The adenomatous glands were lined by a single layer of cuboidal or columnar cells and were filled with mucus (Fig. 9). The tumour was situated entirely in the submucous coat and was superficial to the bronchial cartilages. Ducts could be seen connecting the adenomatous tissue with the bronchial lumen. No malignant changes were observed. In 2 cases the cystadenomas were accompanied by a papillomatous proliferation on the luminal surface of the tumour, the papillary epithelium being partly columnar-celled and partly squamous.

Bronchial Oxyphilic Adenoma

Only one example of this very rare bronchial tumour has been seen. It was discovered as an incidental finding during a post mortem examination on a

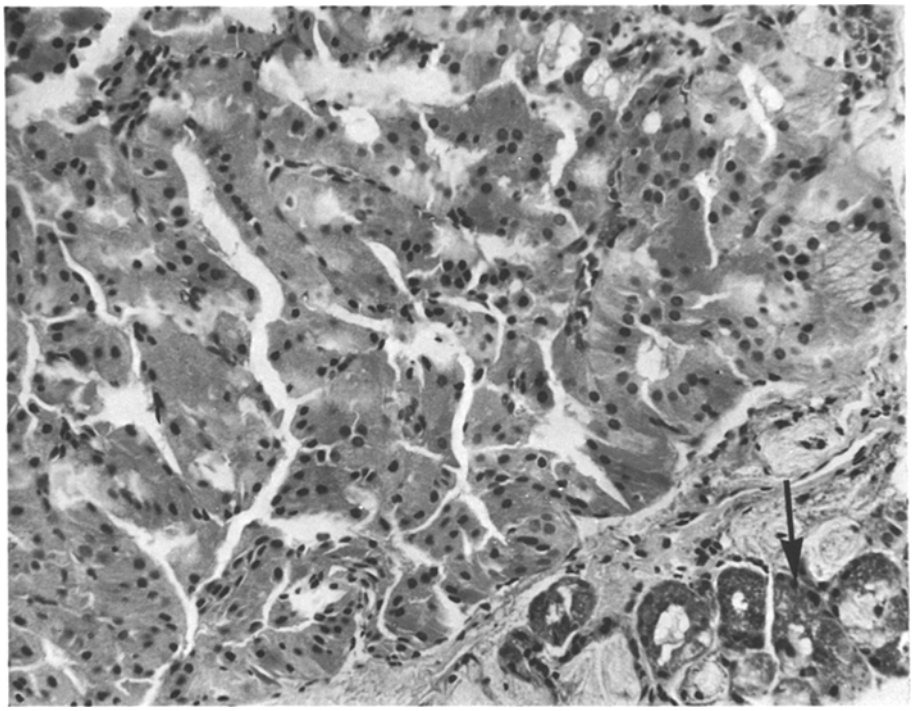

Fig. 10. An oxyphil cell bronchial adenoma showing adjacent normal bronchial mucous gland tissue (*arrow*). ×250 H & E

man aged 57 who had died from a cerebrovascular accident and congestive heart failure. The tumour measured 2–3 mm in diameter and was present in a lobar bronchus.

Microscopically, the tumour consisted of acinar tissue the epithelium of which was columnar and strongly eosinophilic (Fig. 10). There was minimal stromal tissue and the tumour cells showed no mitoses or malignant features. The adenomatous tissue was continuous with a mucous gland duct which was also partly lined by oxyphilic cells.

Discussion

The first description of a bronchial adenoid cystic carcinoma was that given by Heschl (1877) who described a "Cylindrom der Lunge". The term "cylindroma" had previously been coined by Billroth (1859) and persisted in general use to describe these tumours until recent years. Further confusion also arose because adenoid cystic bronchial tumours were included under the omnibus term of bronchial adenoma which continued until Hamperl (1937) divided "bronchial adenomas" into bronchial carcinoids and the true bronchial mucous gland tumours. The latter consisted almost entirely of what are now known

as adenoid cystic carcinoma of the bronchus. Adenoid cystic tumours comprised about 10 per cent of the group of "bronchial adenomas".

Adenoid cystic carcinoma are mainly locally malignant tumours which may arise from both the tracheal and bronchial mucous glands and often spread to involve both structures. Occasionally they metastasise to distant sites such as liver, kidney and bone marrow and their metastases reproduce the same histological features as the primary tumour (Bryson and Spencer, 1951). Bronchial adenoid cystic carcinomas have been described by Foster-Carter (1941, case 16), McDonald et al. (1945), Holley (1946), Reid (1952), Payne et al. (1959), Weiss and Ingram (1961), Wilkins et al. (1963) and Heilbrunn and Crosby (1972). Cann (1938) described 2 early examples in the trachea.

Although the clinical data of the present series of cases was incomplete, the average duration of symptoms before treatment was sought was similar to that found by Payne et al., namely about 2 years. The signs and symptoms resulted mainly from bronchial obstruction and its sequelae. Complete surgical excision is often followed by long survival though Wilkins et al. (1963) found that postoperative recurrence could occur up to 17 years later.

Although it is generally agreed that the tumours arise from the bronchial mucous glands the exact histogenesis of the tumour cells is still a matter of debate. Azzopardi and Smith (1959) showed that the mucin occupying the pseudocystic spaces within the tumour cell masses differed in character from that filling the small ducts, and Goldman and Conner (1950) regarded the palisade layer of cells surrounding the clumps of tumour cells as probably of myoepithelial origin.

Spread of adenoid cystic bronchial carcinomas is mainly by direct infiltration and incomplete removal results in local recurrence of the tumour. Radiation therapy as shown both in one case of the present series and in earlier reports of 2 cases by Cann does have some inhibitory effect on tumour cell growth and may lead to improvement of the symptoms though probably not to permanent cure.

Muco-epidermoid tumours were first described in salivary glands and the term was introduced by Stewart et al. (1945). They divided the salivary gland tumours into benign and malignant forms. Muco-epidermoid tumours in the respiratory passages are confined to the trachea and larger bronchi in the walls of which mucous glands are present. The first example to be reported in the bronchi was by Smetana et al. (1952). A similar but unrecognised case was included in a review of the origins of lung cancer by Spencer (1954) and since then further examples have been described by Hellweg and Ricken (1957), Leschke (1957), Payne et al. (1959), Meckstroth et al. (1961), Dowling et al. (1962), Wilkins et al. (1963), and Reichle and Rosemond (1966) and an example of a muco-epidermoid tumour arising in the trachea was described by Larson et al. (1965).

The present series of tumours were unusual inasmuch as the average age of the patients has been $10^1/_2$ years whereas most of the reported cases have occurred between 30 and 40 years of age. The symptoms and signs caused by the tumours are almost entirely attributable to bronchial obstruction and have often been present for many years before treatment was sought. Some

cases reported in the literature as bronchial muco-epidermoid tumours would not now be acceptable as such but would be regarded as bronchial adenocarcinomas (Ozlu et al., 1961). Little difficulty, however, is usually experienced in differentiating the malignant tumours from the benign forms. Patients with malignant tumours are older and the histology of the growth resembles a carcinoma though showing here and there features suggesting its origin from a benign muco-epidermoid tumour. Dowling et al. also reported malignant change in one of their series of cases.

Treatment consists in the radical excision of the tumour and conservative measures often end in a fatal outcome. Complete cure of a muco-epidermoid adenoma may be anticipated if the tumour is removed completely.

The two very rare mixed (pleomorphic) bronchial tumours were examples of bronchial gland counterparts of mixed (pleomorphic) salivary gland tumours. The histogenesis of such tumours has been a subject of long debate. Azzopardi and Smith concluded the salivary mixed tumours were derived from both duct epithelium and myoepithelial cells, the latter being responsible for inducing the islands of chondroid and myxomatous tissue so characteristic of these tumours. Doyle et al. (1968) concluded, however, that neoplastic myoepithelial cells underwent metaplasia to chondroid cells. The problem is still unresolved.

Because of the extreme rarity of these bronchial tumours little is known about their behaviour. One of the present 2 cases behaved as a carcinoma and too short a time has elapsed to judge the ultimate behaviour of the other. These tumours may grow and in so doing occupy much of a lobe of a lung and their bronchial origin may then not be appreciated. The presence of mitoses in the tumour cells should excite suspicion of its possible malignant nature.

Bronchial cystadenomas are very rare tumours examples of which have been described by Mallory (1949), Ramsey and Reimann (1953), Weinberger et al. (1955), Gilman et al. (1956), Allen et al. (1974) and Spencer (1977). With the exception of the case described by Weinberger et al. all the tumours occurred in the large central bronchi. Most are simple cystadenomas removal of which cured the patient. Two of the present series were associated with overlying bronchial papillomas similar to that seen in the case described by Allen et al.

No reference in the literature can be found to any previous example of an oxyphilic bronchial mucous gland adenoma. The case described appeared to be a completely benign tumour and was quite distinct from the better recognised oncocytic form of bronchial carcinoid tumour.

Seifert and Donath (1976) described a condition of unknown aetiology in salivary glands which they named oncocytosis and in which both the acinar and duct epithelial cells were of oncocytic type and foci of lymphocytes were present. The lobular structure of the glands was also retained. Thackray and Lucas (1974) included a similar lesion in their classification of salivary tumours and called it an oxyphilic (oncocytoma) adenoma. The absence of lymphocytes and the proliferation of acinar structures in this bronchial tumour favours the concept of it being a neoplasm.

The author wishes to thank all those pathologists who referred many of these cases over a period of years and without whose help the survey of these rare tumours would not have been possible.

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