Morphology and the natural history of cribriform adenocarcinoma (adenoid cystic carcinoma)

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SUMMARY   Forty-three examples of cribriform adenocarcinoma (adenoid cystic carcinoma) of mixed glandular origin are reported. Structural studies emphasise the classical cribriform pattern which indicates the capacity of this neoplasm to behave as both an epithelial and a connective tissue type tumour. In terms of survival, it does not appear to be as malignant as other forms of carcinoma arising in similar anatomical locations. The five-year crude survival rate (56%) compares favourably with that of other carcinomas of the palate and paranasal sinuses. A recurrence rate of the order of 20% may persist up to 10 years after primary treatment, and while this is not inimical to longer survival there is clearly a high morbidity.

This well-recognised tumour of exocrine glands was first described by Billroth in 1856 under the name 'Zylindrome'. Subsequently, many alternative names have been proposed and, although the term 'cylindroma' is still in common use, Friedmann and Osborn (1966) introduced the expression 'cribriform adenocarcinoma' as being more appropriate to its origin, morphology, and behaviour. More recently, however, the WHO Subcommittee on classification of tumours recommended adoption of the term 'adenoid cystic carcinoma' which was first used by Reid (1952). The widespread distribution in the upper alimentary and respiratory tracts underlines its origin more particularly in mucosal as compared with major salivary glands. Morphological similarity to tumours in other locations has led inevitably to some blurring of the general picture and, although the malignant character of most of these tumours is no longer in doubt, the behavioural pattern still requires elucidation and definition.

Material and methods

Between 1948 and 1973 the pathological records of the Institute of Laryngology and Otology acquired 129 tumours arising in mucosal glands and, of these, 34 (26%) were cribriform adenocarcinomas. During the same period, five examples of similar structure were seen in neoplasms of major salivary glands (5%) while a further four (23%) were found in a

group of tumours of the external auditory meatus designated ceruminomas.

Light microscopy was carried out on all cases and material was available for electron microscopy in one parotid, one ceruminous, and five mucosal gland tumours. Paraffin sections were stained with haematoxylin and eosin, Alcian Blue, PAS/diastase, toluidine blue/hyaluronidase, Van Gieson, and PTAH. Material fixed in buffered glutaraldehyde (Sabatini *et al.*, 1963) and postfixed in osmium tetroxide was embedded in Araldite. Sections were cut on an LKB microtome (pale gold to silver), stained with aqueous uranyl acetate and lead citrate, and examined under an AEI Corinth 275 electron microscope.

Results

The anatomical distribution in the mucosal gland group is shown in Table 1 in which it can be seen that the major sites were the palate and maxillary sinus. The five major gland tumours were all of parotid origin. Twenty-five of the cases were females, and Table 2 shows that the age distribution was broadly based, an appreciable number of cases presenting at a relatively early age. Furthermore, when the age-specific incidence was calculated it was found to be maximal in the fourth decade.

The cases of palatal origin presented with local swelling of variable duration ranging from one month to two years but, in the majority, not exceeding six months. In the antral group, facial pain and

Table 1 *Cribriform adenocarcinomas of mucosal gland origin: anatomical distribution*

Site	No.
Palate	11
Maxillary sinus	10
Ethmoid sinus	1
Nasal cavity	1
Nasopharynx	4
Trachea	2
Tongue	2
Oropharynx	1
Lachrymal gland	2
	Total 34

Table 2 *Cribriform adenocarcinomas: age distribution and incidence*

Decade	1	2	3	4	5	6	7	8
Age distribution	0	0	5	9	9	8	8	4
Age specific incidence[1]			0·83	1·81	1·68	1·50	1·63	0·95

[1]Based on the estimated population in the South Metropolitan Cancer Registry area (Registrar General's Statistical Review, 1970)

swelling were common forms of presentation, and the duration ranged from two months to four years, over 50% giving a history of one year or more. In the nasopharyngeal cases, nasal obstruction, deafness and diplopia were common symptoms which had been present for six weeks to two years. In cases involving the major salivary glands, swelling had been present for periods ranging from three to 12 years, only one patient (the youngest) having a history of less than six years. The aural cases presented with pain or swelling in the external auditory meatus of one to three years' duration.

GROSS APPEARANCES
The demarcation of these tumours varied greatly. Palatal tumours were often lobulated, sometimes sufficiently discrete to be described as having 'shelled out' but in others the boundaries were obscured by infiltration of the surrounding tissues. In antral cases the sinus was filled with solid tumour tissue showing varying degrees of mural involvement. The cut surface revealed unremarkable, solid white growth which was usually readily distinguishable from the other common glandular tumour, the pleomorphic or 'mixed' type, by virtue of the absence of semitranslucent areas indicative of the chondromyxoid component in the latter.

MICROSCOPY
The structural features of these tumours can be divided into four main patterns as follows:

1 Common to all is the typical cribriform appearance due to the presence of numerous microcystic spaces (Fig. 1). The latter often contain mucoid

Fig. 1 *Case 19. Cribriform adenocarcinoma of maxillary sinus. Pseudolumina constituting the classical cribriform pattern. Haematoxylin and eosin × 100.*

material exhibiting the histochemical reactions of connective tissue type mucin and, in so far as such spaces lack a definitive epithelial lining, they have been conveniently designated pseudolumina (Azzopardi and Smith, 1959), a term which receives additional support from ultrastructural studies. Under the electron microscope there is a notable lack of microvilli which often characterise an epithelial lumen, but the pseudolumen frequently contains a well-defined layer of amorphous material resembling a basal lamina (Fig. 2), and sometimes the bordering cells contain bundles of filaments resembling either tonofilaments or myofilaments while desmosomal attachments are frequently seen. Collagen and even cells resembling fibroblasts may sometimes be found in the pseudolumina.

2 Contrasting with the pseudolumina are the not infrequent tubular structures lined by clearly defined cubical epithelium and often containing material showing the staining reactions of epithelial type mucin. Sometimes seen within cellular masses, they often appear more isolated when the darkly stained surrounding cells are reduced to a single layer (Fig. 3). These are true lumina, characteristically
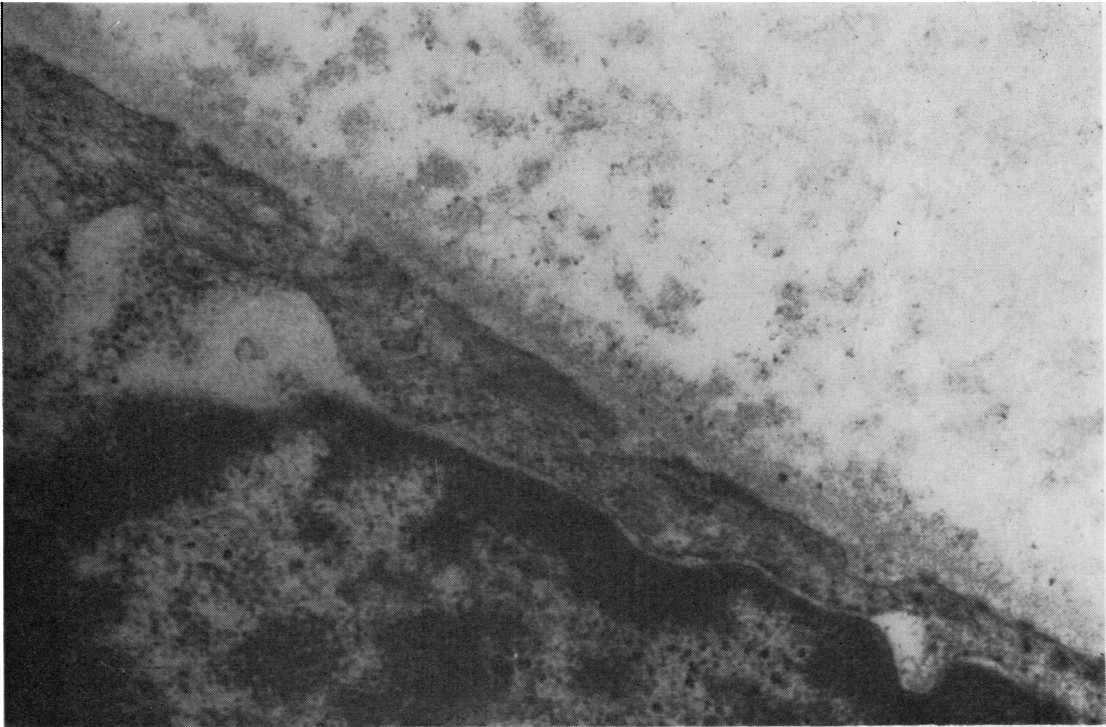
Fig. 2   Case 45. Cribriform adenocarcinoma of hard palate. Cell bordering pseudolumen. Microvilli are absent and a concentration of amorphous material resembles a basal lamina. The cytoplasm contains numerous loosely arranged filaments of the order of 75 A in diameter. Occasional denser zones of the basal plasma membrane suggest the formation of hemidesmosomes. Many fine particles are consistent with glycogen. × 48 750.
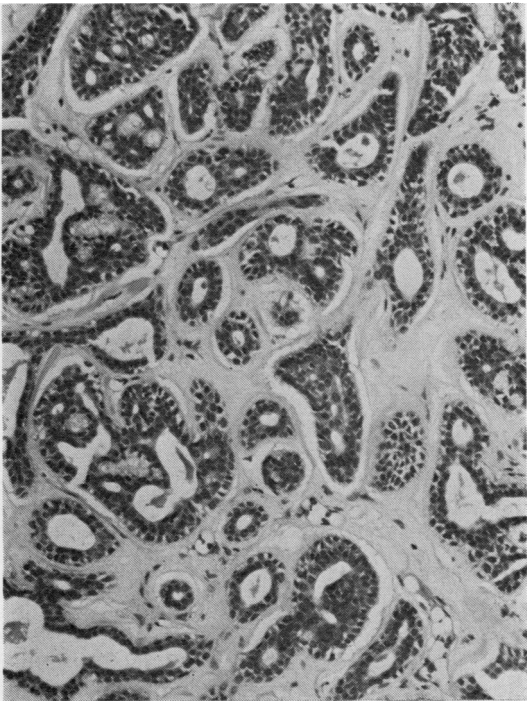

Fig. 3   Case 249. Cribriform adenocarcinoma of naso-pharynx. Predominance of true lumina containing eosinophilic material. H and E × 160.
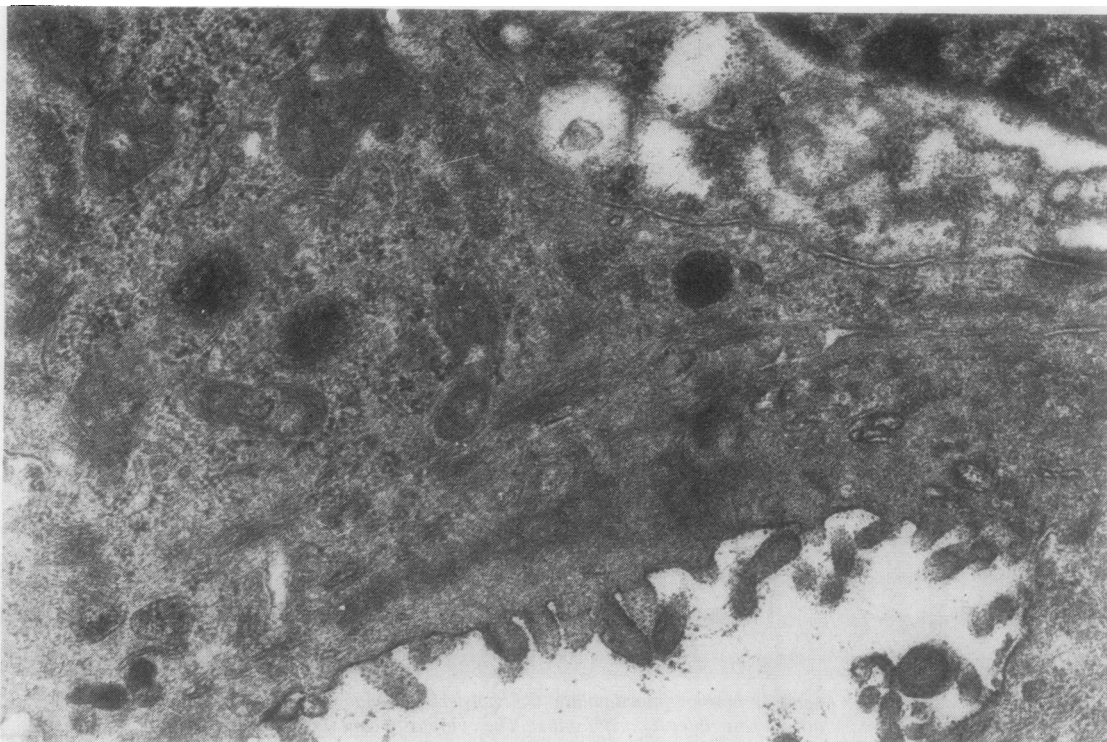
Fig. 4   *Case 254. Cribriform adenocarcinoma of hard palate. Cell bordering true lumen showing well developed microvilli and many loose bundles of fine filaments, 40 to 50 A in diameter.* × *37 500.*

lined by microvilli (Fig. 4). Again, the bordering cells may show filamentous bundles not necessarily related to desmosomes. Cells on the periphery of true lumina may show typical features of myoepithelial cells with numerous bundles of fine filaments.

3 Tumour masses, which always tend to be sharply circumscribed, occasionally present a solid appearance composed of the same small, darkly staining cells found between pseudolumina in cribriform areas (Fig. 5). Sometimes larger, more palely staining cells of squamoid appearance may be seen in such masses, and marginal cells may present a clear form though this is partly illusory due to shrinkage. The fine structure of the constituent cells is variable. Many have no particular characteristics but some display the heavy, fused, filamentous bundles resembling the tonofibrils of squamous cells and occasionally the paraphernalia of secretory cells (profiles of rough endoplasmic reticulum and secretory granules). Particulate material resembling glycogen granules and unspecifiable filaments are often present.

4 The stroma varies greatly in amount and consistency, ranging from scanty loose connective tissue to a densely fibrous background. Although occasionally myxomatous, it never shows the myxochondroid appearance so characteristic of the pleomorphic tumour. A frequent, though not invariable, feature is the presence of hyaline material surrounding or surrounded by the epithelial component (Fig. 6). Such material often stains poorly but may show the staining reactions of collagen and sometimes exhibits a positive PAS reaction. When it is surrounding groups of tumour cells, this material constitutes the 'glashelle Zylinder' of Billroth from which the well-known term 'cylindroma' was derived. Under the electron microscope the walls of the cylinder present a partly amorphous, partly laminated appearance, giving a superficial impression of fibrillar structure (Fig. 7). However, these 'fibrils' show no evidence of the periodic banding characteristic of collagen although such material may be identifiable on the periphery.

BEHAVIOURAL PATTERN
All cases were treated by varying combinations of surgery and irradiation, the former usually preceding the latter though not necessarily of a radical nature
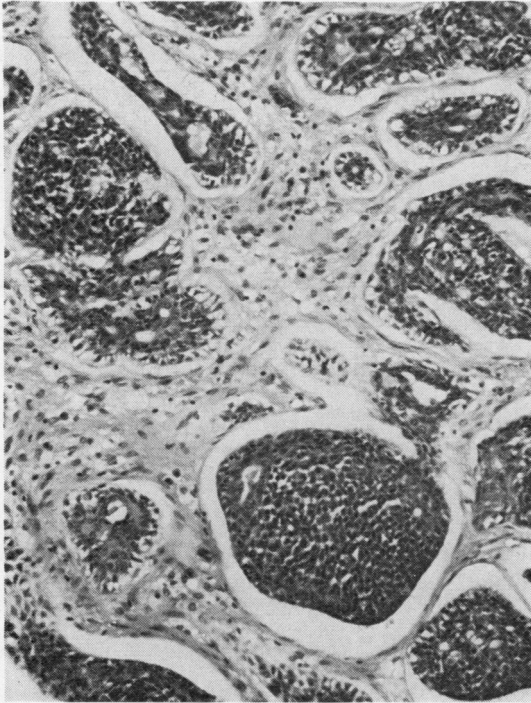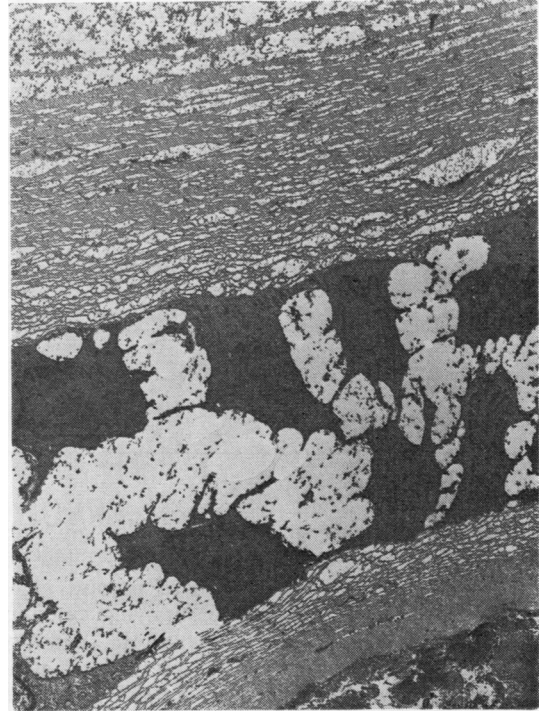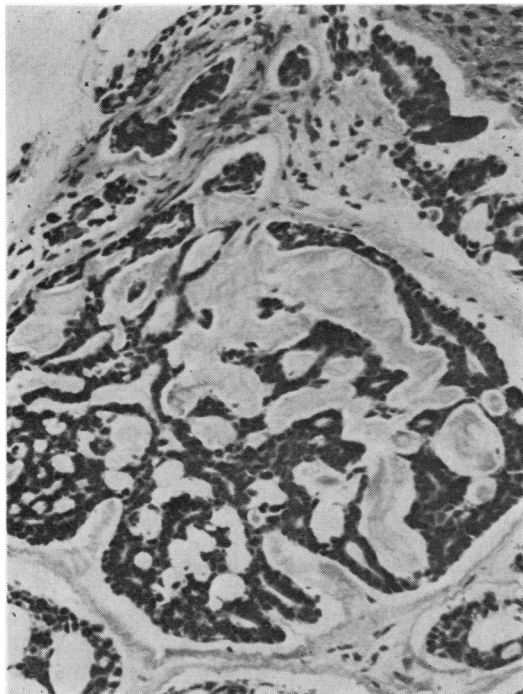
Fig. 5

Fig. 7

Fig. 6

Fig. 5 *Case 115. Cribriform adenocarcinoma of maxillary sinus. Area of solid cellular growth sharply demarcated from the stroma by shrinkage spaces and showing peripheral 'clear' cells. H and E × 145.*

Fig. 6 *Case 19. Cribriform adenocarcinoma of maxillary sinus. Hyaline stroma intimately related to the epithelial component and forming 'cylinders' and enclavements. Van Gieson × 250.*

Fig. 7 *Case 254. Cribriform adenocarcinoma of hard palate. Longitudinal section through a 'cylinder'. Tumour cells surrounded by partly amorphous, partly fibrillar material. × 3000.*

Table 3 *Cribriform adenocarcinoma: follow-up*

Time (years)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Surviving																											
without recurrence		1			1	2		3											1								1
with recurrence		1				1	1							1									1				
Death from tumour	2		2		4	2	1		1		2		1	1										1			
Unrelated death	1	2	1			1								1													
Lost trace	4		2																								

Table 4 *Recurrence in cribriform adenocarcinomas*

Interval (yr)	Totals at yearly intervals after primary treatment																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Total cases alive at each interval	40	38	35	35	31	28	27	27	26	26	24	24	22	21	21	21	21	21	20	20	20	20	19
Recurrences																							
Number	9	6	6	6	3	2	0	2	3	6	0	1	1	0	0	0	0	0	1	0	0	0	1
%	22	16	17	17	10	7	0	7	11	23	0	4	4	0	0	0	0	0	5	0	0	0	5

in the first instance. The follow-up data are summarised in Table 3. Of the six cases lost to follow-up, four were mucosal and two were parotid gland tumours while the 14 currently surviving cases included 10 mucosal gland, two parotid, and two aural tumours. Six cases, all in the mucosal gland group, have died from unrelated causes. Recurrence is known to have taken place in 16 mucosal, two parotid, and two aural tumours; they were often multiple and the frequency did not diminish significantly until 10 years after primary treatment (Table 4).

In the 11 palatal neoplasms, the hard palate was involved in 10 (in most cases primarily) and the soft palate in three. Extension to the alveolar margin occurred in two cases, to the nasal cavity in three, and to the maxillary sinus in five with subsequent involvement of the orbit in two.

Neoplasms arising primarily in the maxillary sinus spread to the nasal cavity in five, to the orbit in four, and to the hard palate in three.

The nasopharyngeal tumours spread to the nasal cavity in two cases, to the palate in two, and to the orbit in one.

Systemic spread was known to have occurred in eight cases, all of which were of mucosal gland origin. The organs involved included the lungs, heart, brain, liver, and skin though histological confirmation was often lacking. Lymph node metastasis occurred in three cases, two being mucosal and one of parotid origin.

Perineural infiltration was found in six of the mucosal gland tumours. Two of the patients died of their disease within five years, one survived for five years without recurrence before dying from an unrelated cause, and another has survived seven years without recurrence. Of the remaining two cases, one has been lost to follow-up, and in the other neural involvement was first observed in a recurrence after 22 years.

Discussion

ANATOMICAL DISTRIBUTION

The literature now contains many reports on these neoplasms and some, such as those of Smout and French (1961) and Smith *et al.* (1965), have dealt exclusively with this type. The greater number, however, have formed part of larger series including all varieties of mucosal or salivary gland tumours. In the mucosal gland group alone, major series published between 1935 and 1973 include those of Ahlbom (1935), Ringertz (1938), McDonald and Havens (1948), Russell (1955), Ranger *et al.* (1956), Fine *et al.* (1960), Chaudhry *et al.* (1961), Stuteville and Corley (1967), Potdar and Paymaster (1969), and Spiro *et al.* (1973), while during the same period smaller series were reported by Harvey *et al.* (1938), Hoboek (1949), Lampe and Zatzkin (1949), Smith *et al.* (1954), Bhaskar and Weinmann (1955), Edwards (1960), Smith (1962), and Bergman (1969). These major and minor series gave a total of 1712 mucosal gland tumours of all types, of which 557 (32·5%) were cribriform adenocarcinomas. Table 5 shows the anatomical distribution and relative frequency of this type of neoplasm based on the above-mentioned series. It is apparent that the anatomical distribution in the present series fits into the general pattern.

It is generally accepted that this type of adenocarcinoma is more commonly found in mucosal as compared with major salivary glands but precise assessment of the relative frequency is difficult because most series, like the present one, are biased.

Table 5 *Mucosal gland tumours: anatomical distribution and frequency of cribriform adenocarcinomas*

	Anatomical location								
	Palate	*Oro-pharynx mouth*	*Tongue*	*Tonsil*	*Nose and sinuses*	*Naso-pharynx*	*Larynx*	*Trachea*	*Lachrimal gland*
Totals (all types)	716	437	124	34	300	48	22	11	20
Cribriform tumours	210	106	67	9	113	26	7	9	10
Cribriform tumours % all types	29	24	54	26	37	54	32	82	50
Cribriform tumours Anatomical distribution (%)	38	19	12	1·5	20	5	1	1·5	2

On the other hand, the series reported by Russell (1955), consisting of 42 mucosal and 25 major salivary gland tumours, probably has the smallest element of selection since it is based on attendance at the Holt Radium Institute and, in the context of cribriform adenocarcinoma, the ratio of mucosal to major salivary gland origin was nearly 4:1.

STRUCTURE

The light microscopical features have been well documented by many authors, especially Thackray and Lucas (1960). However, it is worth emphasising not only the division into four main patterns (cribriform, tubuloglandular, solid cellular, and hyaline or cylindromatous) which emerged quite clearly in the present series but also the most characteristic of these patterns, the classical cribriform structure. The latter is of sovereign importance not only because its presence is essential to the histological diagnosis but because its pathogenesis offers a clue to the natural clinical behaviour. The evidence of both light and electron microscopy suggests that the cells in such areas are often behaving as though they were partly epithelial and partly connective tissue in type. The PAS negative, hyaluronidase labile metachromatic material in the pseudolumina, originally demonstrated by Azzopardi and Smith (1959), is a product of connective tissue type activity. On the other hand, the tendency of many cells to retain firm intercellular anchorage through the medium of desmosomal attachments is essentially an epithelial characteristic. The occurrence of basement membrane-like material and collagen within the pseudolumina (Friborsky, 1965; Eneroth et al., 1968; Tandler, 1971) also suggests a dual function, as does myoepithelial differentiation. Apposite in this context is the suggestion of Hamperl (1970) regarding the ability of cells to cross the embryological boundary between ectoderm and mesoderm.

It has become a convention to recognise a solid cellular variant of this tumour but in the present series this type of structure was less common than the cribriform pattern, and it is the present author's view that an exclusively solid type of growth with no true cribriform areas should be classified as a malignant basal cell tumour and is probably akin to the solid variant of basal cell cancer of the trachea described by Krompecher (1918) and to the oat cell tumour of Koss et al. (1972). Eneroth et al. (1967) studied adenoid cystic carcinomas arising in the submandibular gland and suggested that the cribriform pattern was associated with a better and the solid pattern with a worse prognosis. In the present series, analysis of those cases ultimately dying of their disease provided no adequate confirmation of such a relationship.

The hyaline or cylindromatous pattern is not always present, thus providing an argument in favour of abandoning the term 'cylindroma'. Furthermore, such a pattern may sometimes be encountered in pleomorphic tumours and hence, striking though this feature may be, it cannot be regarded as a specific one in relation to the cribriform adenocarcinoma. The occasional positive PAS reaction and the electron microscopic appearance are consistent with the possibility that the hyaline material is in part the product of epithelial, basal cell-like activity forming basement membrane substance.

RESEMBLANCE TO TUMOURS IN OTHER SITES

Occasionally, tumours of skin appendages may produce a cribriform pattern identical with that in neoplasms of mucosal or salivary glands (Molesworth, 1927; Willis, 1948). When occurring in this location they have often been referred to as cystic basal cell carcinomas and probably have their origin in sweat glands. The so-called adamantinoma of the tibia may well be of similar type, arising in ectopic tissue as originally suggested by Fischer (1913). Occasionally such tumours are seen in the locations of modified sweat glands, comprising breast (Geschickter, 1945; Willis, 1948; Nayer, 1957; Symmers, 1966) and ceruminous glands (Dockerty and Mayo, 1943; Dancot, 1953; Berdal and Mylius, 1954; Smith et al., 1965). Tumours in all these sites probably have a common pathogenesis, but, when

occurring in the maxillary sinus, the cribriform adenocarcinoma is sometimes confused with the ameloblastoma (Tauxe *et al.*, 1962), and one case in the present series had been initially so diagnosed. The presence of the spider-like cells of the so-called stellate reticulum in the latter tumour is a valuable distinguishing feature.

BEHAVIOURAL CHARACTERISTICS
The malignant nature of these cribriform tumours is no longer in doubt although their behaviour is variable and data on recurrence, spread, and survival are somewhat confusing. Most published series have recorded systemic involvement though the incidence has varied greatly. Beck and Guttman (1936) reviewed 40 cases with tumours of respiratory tract origin, finding systemic spread in only two patients (5%). Dancot (1953) found four in 19 cases involving various sites (21%), Struben and Hampe (1959) reported five out of 21 cases of diverse origin (24%), while Eneroth *et al.* (1967) claimed 15 out of 25 submandibular tumours (60%). Two of the larger series are less specific on this point. Thus Smout and French (1961) found remote spread in at least 15 of their 65 cases of mixed origin (23% or more) while Smith *et al.* (1965) reported systemic involvement in at least 18 of their 58 cases from divers sites (31% or more). The largest series, however, is that of Spiro *et al.* (1973), who recorded remote spread in nearly 40% of 174 cases of mucosal gland origin and stated that 62% of distant metastases from all varieties of malignant mucosal gland tumours were from primaries of this particular type. In the present series, the incidence of less than 20% is undoubtedly an underestimate, having regard to cases lost to follow-up and the fact that necropsies were rarely performed.

Reports on metastases to regional lymph nodes have also shown great variation. Beck and Guttman (1936) reported none among their 40 cases, as did many other authors of smaller series. The highest incidence has been reported in connection with tumours of submandibular origin. Thus, Dockerty and Mayo (1942) recorded an incidence of 26% of their 15 cases while Eneroth *et al.* (1967) found lymph node involvement in 32% of their 25 cases. Among those series of mixed origin, Smout and French (1961) reported an incidence of 10·7% while Smith *et al.* (1965) found 17%. Spiro *et al.* (1973) found 13·9% among their 174 mucosal tumours, and it is noteworthy that this was the lowest incidence of lymphatic spread in all types of malignant tumour in their series, contrasting sharply with the high incidence of bloodstream dissemination. Struben and Hampe (1959) drew attention to the minor role of lymphatic spread, a fact also

indicated in the present series.

Data on the ultimate fate of this neoplasm often suffer from lack of precision and uniformity, reflecting underlying problems such as size of series and difficulties of follow-up. It is no part of the present study to assess patterns of treatment and, in making comparisons, therefore, one is necessarily working on the premise that therapeutic differences have not been sufficiently profound to cause total invalidation of the attempt to measure malignancy. One kind of such an estimate is apparent in the number of cases dying of their tumour. Eneroth *et al.* (1967) found 80%, Smout and French (1961) reported 56%, Smith *et al.* (1965) recorded 59%, while Tauxe *et al.* (1962) claimed 96%. In the present series, the comparable figure is currently 38% but none of these percentages can have any precise meaning unless specifically related to time intervals. The same argument would apply to the recurrence rate which, in the present series, now stands at 49% as compared with 67% reported by Smith *et al.* (1965) or nearly 100% found by Tauxe *et al.* (1962).

Eneroth *et al.* (1967) expressed the view that five-year survival rates were too optimistic. This could well be concluded from the present series in which the crude survival rates at three, five, and 10 years were respectively 67%, 56%, and 38%, and also from the pattern of recurrence shown in Table 4. Spiro *et al.* (1973) reviewed 129 of their cases after 10 years and found a survival rate of 21·7%. These authors also found that 12 out of 52 cases exhibiting recurrence (with secondaries) survived for five years or more, and comparable figures in the present series would be 10 out of 14 cases, giving a five-year survival rate among recurrent cases of 68%. Although the numbers are small, they serve to emphasise the point made by the previously mentioned authors regarding the tendency of many cases of this type of neoplasm to survive in spite of recurrence.

An unequivocal feature of malignancy in these tumours is the perineural infiltration (Fig. 8) which has been reported by many workers (Leroux and Leroux-Robert, 1934; Dockerty and Mayo, 1942; Belsey and Valentine, 1951; Berdal and Mylius, 1954; Smout and French, 1961). The last-mentioned authors reported an incidence of over 40% and emphasised the frequency with which this feature could be demonstrated if searched for with diligence. In the present series, only six cases (14%) had neural involvement and all were of mucosal gland origin. Notwithstanding the significance of this event, the prognosis is clearly difficult to assess.

The higher incidence of malignancy among mucosal as compared with major salivary gland tumours is largely a reflection of a differing frequency pattern in histological type in which the cribriform
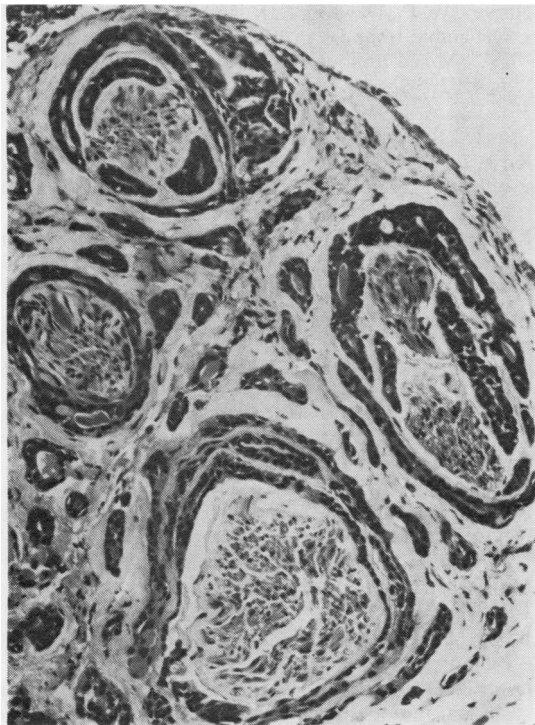
Fig. 8 *Case 186. Cribriform adenocarcinoma of maxillary sinus. Perineural infiltration. H and E × 200.*

or adenoid cystic carcinomas play an important part, but there is no reason to suppose that they have a higher grading of malignancy in the mucosal gland group. The results of the present analysis conform to the general pattern of published series in so far as comparison is possible. The five-year crude survival rate (56%) is loaded adversely in so far as no correction has been made for cases lost to follow-up or for patients dying from unrelated causes. While such a figure may be optimistic in relation to the pattern of recurrence, it nevertheless serves to achieve one of the objectives of this study. Malignant though they are, these cribriform adenocarcinomas appear to be less so, in terms of survival, than other types of carcinoma arising in similar locations. Their less malignant behaviour as compared with other forms of bronchiogenic carcinoma is generally accepted and merits no further comment here. In the upper respiratory tract one may usefully compare the five-year survival rate with that for squamous (17%) or even the transitional type (36%) carcinoma of the paranasal sinuses (Osborn, 1970). In the commonest site of origin, namely, the palate, the contrast is again evident. Of 31 cases of primary carcinoma of the palatal epithelium collected

between 1948 and 1965, only seven have survived for five years or more (22·5%).

Conclusions

Central to the structural theme and essential to the histological diagnosis is the classical cribriform pattern which appears to represent a tumour, partly epithelial and partly connective tissue in type as regards its development and behaviour. Probably, tumours with a predominant solid cellular growth and an absence of the true cribriform structure do not belong to this type, and the prognostic significance of relative proportions of these two patterns is speculative. The hyaline stromal pattern from which the original name of this neoplasm was derived is not always present nor is it an exclusive feature.

This unquestionably malignant tumour is associated with a survival pattern which does not relate entirely to its histopathological nature and behaviour. Predilection for perineural infiltration must be an important factor in local recurrence but, paradoxically, it does not appear to lead necessarily to a reduction in survival prospects. Comparison with other forms of carcinoma in similar locations indicates better survival of the adenocarcinoma though the recurrence pattern (Table 4) emphasises a not inconsiderable morbidity rate. Tendency to spread via the bloodstream rather than the lymphatic system may be a reflection of its partly mesodermal character while the capacity of recurrent cases to survive suggests the possibility of an immunological response reminiscent of the behaviour of malignant melanomas.

No other neoplasm has acquired so many different labels—basalioma, pseudoadenomatous basal cell carcinoma, adenomyoepithelioma, and cystic adenocarcinoma, to mention but a few additional names. Such a plethora of terms is a sure measure of the uncertainty which has existed concerning the nature of this glandular tumour. While too much time and space should not be wasted in arguments over terminology, there is a case for the retention of the expression cribriform adenocarcinoma on the grounds that, by emphasising the essential histological feature, it may contribute more to the understanding of this intriguing tumour.

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