THE HISTOLOGY OF LUNG CANCER

BY

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With the great advances in thoracic surgery, radical excision for pulmonary carcinoma has become a relatively safe and frequent operation, offering to the patient new hope of cure. However, if the results of operative treatment are to be accurately assessed, the ordinary gross pathology must be carefully and fully recorded, for it is of little use comparing survival rates unless attention is paid not only to the different histological types of growth, but also to anatomical factors such as location, size, and site of origin, which can seriously affect the outcome.

At present there is no uniformity in histological nomenclature and the site of origin is a matter of dispute. This paper gives our views on histology after a recent study of 207 surgical specimens and 159 necropsies.

MATERIAL AND METHODS

The material was derived from the lung resections for bronchial carcinoma at Harefield Hospital (161 cases), the Middlesex Hospital (35 cases), and the London Chest Hospital (11 cases), during the period 1950 to 1953. The specimens were unselected and consecutive, with the exception of some which had been destroyed and three from patients who had received pre-operative radiotherapy, and the operations were performed by many surgeons.

The specimens were inflated with formol saline and after fixation sectioned by thin slices in the parasagittal plane. Each tumour was examined with special reference to its size, anatomical location, and site of origin. The number of blocks taken for microscopy depended upon the size of the tumour; from some small growths only one block was taken, but from large tumours as many as 12 pieces of tissue were sectioned. A necropsy series of pulmonary carcinoma was also examined histologically. This consisted of all the necropsies on lung cancer during the period 1948 to 1953 at the Middlesex Hospital (102 cases) and those for 1952 at St. Mary's Hospital (57 cases).

HISTOLOGICAL CLASSIFICATION

The histological classification of malignant epithelial tumours of the lung presents many difficulties and numerous classifications have been put forward in the past. It is generally recognized that the vast majority of tumours arise in the epithelium lining the bronchi and bronchioles. It appears that they arise in the basal layer, and, as in many non-malignant conditions these cells are capable of differentiation into cells of different function and structure, it is not surprising that this adaptability is mirrored in tumour formation.

The simpler classifications recognize two groups. Ormerod (1937) divided his cases into squamous and non-squamous carcinomata, while Rienhoff (1947), regarding the small-cell and cylindrical-cell tumour as forms of adenocarcinomata, divided his cases into squamous and adenocarcinomata. Other authors (O'Keefe, 1948; Björek, 1947; Graham, 1941) have also found difficulty in separating small-cell carcinomata from adenocarcinomata.

In most classifications the squamous-cell tumour is described as an entity and it is the non-squamous types which have caused the most difficulty. Koletsky (1938) divided the non-squamous tumours into small-cell and adenocarcinoma, and Gebauer (1941) added another group, carcinoma simplex, which formed five of his 158 proved cases. The terms anaplastic, undifferentiated, large-cell, small-cell, oat-cell, and carcinoma simplex have all been used to describe growths which were not obviously either squamous or adenocarcinomatous, and it is evident that there is no agreed classification. Even those authors who use similar terms give such divergent percentages of the various types that comparison is difficult and in some cases impossible.

Bryson and Spencer (1951) recognized five groups in their 866 necropsy cases (Table 1), while Buchberg, Lubliner, and Rubin (1951) classified their series of 320 cases into three groups. Both used the term adenocarcinoma, but whereas this growth was the most common in Buchberg's series, constituting
TABLE I  
PUBLISHED CLASSIFICATIONS OF NECROPSY MATERIAL*  

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* Figures are expressed as a percentage, and adenomata are excluded wherever possible.

TABLE II  
PUBLISHED CLASSIFICATIONS OF CLINICAL OR SURGICAL MATERIAL*  

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<td>19-0</td>
<td>849</td>
<td>115</td>
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<td></td>
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<td>64-3†</td>
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<td></td>
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<td>9-9</td>
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</tbody>
</table>

* Figures expressed as a percentage, and adenomata are excluded wherever possible. † Series of resected specimens. ‡ Stated to include oat-cell growths.

39.4%, Bryson and Spencer found it to be the least common (4.9%). Similarly the incidence of squamous-cell carcinomata in necropsy material varies from 6.9% (Bryson and Spencer) to 61.2% (Fried, 1938).

Published classifications of surgical or clinical material show equally divergent results (Table II). McDonald, McBurney, Carlisle, and Patton (1951), McBurney, McDonald, and Clagett (1951), Carlisle, McDonald, and Harrington (1951), and Patton, McDonald, and Moersch (1951a and b) from the Mayo Clinic recognized four groups—small cell, large cell, squamous, and adenocarcinoma; Kreyberg (1952) adopted a similar terminology except that a fifth group of mixed adenocarcinoma and squamous-cell carcinoma was added. However, the large-cell group constituted 40.2% in the Mayo Clinic figures, but only 9.9% in those of Kreyberg. Aufses (1953) did not use this term “large-cell carcinoma,” but had an anaplastic group which formed 20.6% of his 710 cases. Small-cell tumours were grouped separately, and this is of interest in view of Barnard’s inclusion of the oat-cell carcinoma amongst his anaplastic tumours (Barnard, 1938).

There are many possible explanations of these divergent figures; local factors influencing selection of cases, geographical, and racial variations may all play some part. Christiansen (1953) has produced evidence that of recent years there has been a change in the incidence of the various histological types of carcinoma. It is impossible to be certain about the relative importance of these various factors, but we consider that much of the variation is due to different interpretations by individual histologists. In a recent survey of lung cancer in eight London hospitals, Galluzzi and Payne (personal communication, 1955) found that amongst the non-squamous tumours the incidence of adenocarcinoma varied from 6.0% at the Royal Marsden Hospital to 31.0% at St. Mary Abbots Hospital. It seems likely that even when the same terms are used by different pathologists an identical tumour might be put into different categories. Thus an adenocarcinoma containing squamous elements...
might be included with the adenocarcinomata by
one author, in a mixed group by another, and unless
an adequate number of sections is examined, even
with the squamous group. It is obviously important
that not only should the morphological types be
clearly described and defined, but that the manner
in which the classification is worked must be
clearly indicated.

In view of the confusing histological picture
which lung cancer presents, some authors have
attempted simplification in the terminology by
adopting the view that there is only one entity,
cancer of the lung, but that this may show con-
siderable variation in structure. Barnard (1938),
while dividing his 400 cases into squamous-cell
carcinomata (29.5%), columnar-celled (16.5%),
mixed (10%), and anaplastic carcinomata (44%),
marked, that, although the histological picture in
any one case may be simple and consisting of only
one type of growth, the more complex tumours con-
sisting of two or more elements were more common.
According to Willis (1948) individual tumours
show various structural combinations, and great
pleomorphism is possible in one tumour. His
findings in 86 necropsy cases were:

<table>
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<th>Type</th>
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<tr>
<td>Squamous carcinoma only</td>
<td>12</td>
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<tr>
<td>Combined squamous and adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic carcinoma only</td>
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<tr>
<td>Combined anaplastic and adenocarcinoma</td>
<td>8</td>
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<tr>
<td>Combined anaplastic and squamous carcinoma</td>
<td>5</td>
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<tr>
<td>Combined anaplastic, squamous and adenocarcinoma</td>
<td>4</td>
</tr>
</tbody>
</table>

Such classification is legitimate, for the appearance
of each tumour is described and the interpretation of
these findings is left to the reader. Some
tumours certainly present a complex histological
picture, but by adopting certain criteria we found
that all our cases could be classified into one of the
following types: (1) Oat-cell carcinoma,
(2) squamous-cell carcinoma, (3) adenocarcinoma,
(4) polygonal-cell carcinoma, and (5) invasive and
metastasizing “adenoma.”

The terms used in this classification do not differ
from those used by many previous authors, and it
is only in the practical interpretation of histological
findings that our classification can be at variance
with that used by many histologists.

The difficulties encountered, however, are depend-
ent not only upon the basic appearances of the
growth but upon certain secondary, possibly
degenerative, changes which may obscure the
picture. These are squamous metaplasia, clear cell
formation, and giant cell formation. Since these
changes are not peculiar to any one type of growth,
it is convenient to describe them later.

(1) OAT-CELL CARCINOMA.—The epithelial origin
of the “oat-cell tumour” was first propounded by
Barnard in 1926, but since that time many authors
have avoided the term (for example, Ewing, 1940).
We think that the oat-cell carcinoma is an entity
and that the term should be retained. The charac-
teristic feature of these tumours is the relatively
small cells with round, oval or oat-shaped hyper-
chromatic nuclei and scanty, ill-defined cytoplasm
(Fig. 1). They undoubtedly arise from the bron-
chial or bronchiolar epithelium (Fig. 2).

Barnard (1926) noted the occasional occurrence of
tubules in oat-cell carcinomata and regarded
this as evidence of the epithelial nature of the
growth. In a subsequent publication (Barnard,
1938) attempted tubule formation is again noted.
On the other hand many histologists have been
impressed by the uniformity of the oat-cell growths
(Bryson and Spencer, 1951; Fried, 1938) and they
appear to have placed in other groups those tumours
showing tubular shapes. It is likely therefore
that the oat-cell tumours have variously been classified
as adenocarcinomata (Rienhoff, 1947), small-cell
(Jakobsen, 1953), anaplastic (Barnard, 1938),
undifferentiated (Bogardus, Adams, and Phillips,
1950) or even, where squamous metaplasia is
present, as squamous, squamoid, or polygonal.

In 52% of the surgically removed oat-cell car-
cinomata in our series, the growth was uniform and
conformed to the appearances generally regarded as
typical of oat-cell tumours. In the remaining
48%, however, the histological picture was not
uniform and definite evidence of differentiation was
present. This consisted of the formation of tubules
and rosettes. In two tumours, one from each
series, differentiation was so extraordinarily well
marked in places that they would be classified by
most observers as adenocarcinomata (Figs. 3 and
4). Nevertheless the cells in both differentiated
and undifferentiated parts were hyperchromatic and
typically oat type. In other cases, differentiation
was not so marked; tubules were less well
formed and appeared as rosettes (Fig. 5). In all
these differentiated oat-cell tumours, staining for
mucus was negative.

The appearance of these tumours is reminiscent of
that seen in neuroblastoma or retinoblastoma,
but since nearly half the oat-cell tumours in the
surgical series showed rosettes or tubules, it is
unreasonable to think that they could all be secon-
dary to unidentified primary growths elsewhere in
the body.

(2) SQUAMOUS-CELL CARCINOMA.—Tumours were
included in this group only if two criteria were
fulfilled: (i) The tumours showed keratinization or
Fig. 1.—Haematoxylin and eosin. Undifferentiated oat-cell carcinoma, × 590.

Fig. 2.—Haematoxylin and eosin. Oat-cell carcinoma arising from bronchial epithelium, × 320.

Fig. 3.—Haematoxylin and eosin. Well-differentiated oat-cell carcinoma showing tubule formation, × 190.
FIG. 4.—Haematoxylin and eosin. Well-differentiated oat-cell carcinoma (same case as Fig. 3) showing that the cells lining the tubules are of oat type, × 435.

FIG. 5.—Haematoxylin and eosin. Oat-cell carcinoma showing rosettes, × 520.

FIG. 6.—Haematoxylin and eosin. Squamous-cell carcinoma, × 190.
Fig. 7.-Haematoxylin and eosin. Well-differentiated adenocarcinoma showing tubule formation and mucus production, × 320.

Fig. 8.-Haematoxylin and eosin. So-called "alveolar cell" carcinoma showing regular columnar cells lining thickened alveolar septa, × 270.

Fig. 9.-Haematoxylin and eosin. Poorly differentiated adenocarcinoma. Other parts of this tumour showed occasional tubule formation, × 1,200.
HISTOLOGY OF LUNG CANCER

It is most common in the adenocarcinomata (Fig. 11), but although this was not mentioned by some authors (Patton and others, 1951a), Phillips, Basinger and Adams (1950), using a whole section technique, found squamous metaplasia to be present in all their nine adenocarcinomata. In our series it was found in about 19% of the surgical and 12% of the necropsy adenocarcinomata. Two of the latter were of special interest: in both the primary tumour appeared to be squamous while the secondaries were mainly adenocarcinomatosus. It is evident that squamous metaplasia may be so extensive that the parent type of growth is largely obscured by this secondary change.

Squamous metaplasia was also found in polygonal and oat-cell growths. In the latter it was uncommon to find frank keratinization, this being present in only 6% of our cases. A squamous appearance with occasional prickle-cell formation was, however, less uncommon and has been noticed by others (Bryson, personal communication).

Clear Cell Formation.—It was not uncommon to find clear cells laden with glycogen in an otherwise typical adenocarcinoma (Fig. 12). In a few cases this cell type predominated and the appearances bore a striking resemblance to those seen in Grawitz tumours. The cells contained no fat and there was no evidence that they were secondary to renal neoplasms. Clear-cell areas were also found in squamous growths, whilst some clear-celled tumours were undifferentiated and therefore included in the polygonal group.

Giant Cell Formation.—Giant cells were found in some examples of all types of growth, being least conspicuous in the oat-cell tumours. In some squamous-celled tumours pleomorphic growth with spindle and giant cells was confined to intrabronchial snouts and it appeared that this was the result of growth under adverse conditions. In other cases giant cell formation was not restricted to any one part of the growth.

RESULTS

The results of the histological classification of the surgical and post-mortem series are shown in Table III.

Squamous metaplasia was found in six (19%) of the surgical adenocarcinomata and in 10 (22%) of the necropsy group. There are some observations with regard to the oat-cell carcinomata which are of interest; nearly half (48.5%) of the surgical group showed evidence of tubular differentiation, while this was present in only 18.6% of the necropsy series. With post-mortem material the growth was
**FIG. 10.**—Haematoxylin and eosin. Polygonal cell carcinoma, × 960.

**FIG. 11.**—Haematoxylin and eosin. Adenocarcinoma with tubule formation showing an area of squamous metaplasia with keratinization, × 170.

**FIG. 12.**—Haematoxylin and eosin. Poorly differentiated adenocarcinoma showing clear cell formation: these cells contain glycogen, × 270.
Histological Classification of 207 Surgical and 159 Necropsy Specimens of Lung Cancer

<table>
<thead>
<tr>
<th>Surgical Series</th>
<th>Necropsy Series</th>
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<tbody>
<tr>
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<td>%</td>
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<td>Squamous-cell carcinoma</td>
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<tr>
<td>Adenocarcinoma</td>
<td>32</td>
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<tr>
<td>Oat-cell carcinoma</td>
<td>33</td>
</tr>
<tr>
<td>Polygonal-cell carcinoma</td>
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<tr>
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</tr>
<tr>
<td>Unrecognizable owing to poor histology</td>
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</table>

Often necrotic and the cell details obscured; recognition of differentiation was more difficult under such circumstances, but nevertheless we think that the difference is significant. Table IV shows the correlation between differentiation and tumour size, and although the numbers are small the results suggest that the differentiated oat-cell tumours are more liable to remain localized and therefore removable.

Discussion

There seems little doubt that the confused histological nomenclature of lung carcinoma is due to difficulties in interpretation of histological appearances rather than any intrinsic complexities in the growths themselves. A purely descriptive classification like that used by Willis is more useful than one in which the limits of each group are not defined; Willis and Barnard have both emphasized the fact that if sufficient care is taken several cell types may be found in many lung cancers. In those classifications which do not recognize such "mixed" growths, it must be assumed that either the predominant cell type is accorded preference or that insufficient material was examined. With such systems the classification of a tumour is dependent upon individual bias or upon the thoroughness with which the tumour is searched.

In our study of lung cancer we have encountered "mixed" tumours, but we think that the appearances are due either to secondary changes such as squamous metaplasia or to differentiation in the oat-cell tumours.

We are convinced that the main difficulty in classifying carcinoma of the lung is connected with the oat-cell growths. Most authors, including Barnard, have simply called them anaplastic; we maintain that this is a mistake and that the oat-cell tumour is a definite entity. It has a characteristic appearance and should therefore be kept separate from the undifferentiated members of the other types of carcinoma. The oat-cell growths, as shown by Barnard, are sometimes differentiated and show the formation of tubules; these structures are lined by oat-cells, and the tumours in which they are found should still be classified as oat-cell growths. They do not secrete mucus and may be of central type (Walter and Pryce, p. 117). The ordinary adenocarcinoma, whether differentiated or undifferentiated, is quite unlike these oat-cell tumours; secretion of mucus is generally evident and the origin almost invariably peripheral. The differentiated members of this group are often columnar-celled, while the undifferentiated members are polygonal-celled, usually with large vesicular nuclei and cytoplasm which is granular or foamy.

There has never been any difficulty in classifying squamous tumours in which there is no evidence of glandular or oat-celled structure. However, some adenocarcinomata and oat-cell tumours show squamous areas and we consider that this is merely metaplasia and should not be allowed to confuse the issue. Other appearances, such as the formation of clear cells or giant cells, should also be regarded as secondary change, which, like squamous metaplasia, may be so widespread as to make true identification difficult.

Summary

The conflicting features of some published histological classifications of lung cancer are briefly reviewed. The view that the tumours are so pleomorphic that classification serves no purpose has not been confirmed. A consecutive series of 207 resected lung cancers has been divided into five distinct types:

- Oat-cell carcinoma: 15.9%
- Squamous-cell carcinoma: 60.4%
- Adenocarcinoma: 15.5%
- Polygonal-cell carcinoma: 7.7%
- Malignant "adenoma": 0.5%

The oat-cell tumours are described as forming a distinct group, and in nearly half the cases there was definite differentiation with the formation of tubules and rosettes; these differentiated oat-cell tumours have not been generally recognized in the past, and it is suggested that they have frequently been confused with the ordinary adenocarcinoma
even though the cells are of typical oat type. In no case was mucus production found, although this was usual in the ordinary adenocarcinoma. There is some evidence that these differentiated oat-cell tumours are more amenable to surgical removal than are the undifferentiated members.

Squamous metaplasia, clear cell formation, and giant cell formation are regarded as secondary changes liable to occur in any histological type of growth. Any tumour showing glandular function or structure (excluding differentiated oat-cell growths) is classified as an adenocarcinoma regardless of any secondary changes: the value of specific staining for mucus is described. Similarly any tumour showing oat-celled areas is placed in the oat-cell group, while, if squamous growth only is present, the tumour is classified as squamous-cell carcinoma. Tumours showing neither squamous nor glandular differentiation and which were not oat-celled are described as polygonal cell carcinomata. No truly "mixed" growths have been encountered, and it is concluded that the main difficulties in classifying cancer of the lung are due either to secondary changes such as squamous metaplasia or to differentiation in the oat-cell growths.

A series of 159 necropsy specimens was examined histologically and the following incidence found:

<table>
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<th>Type of Tumour</th>
<th>Incidence</th>
</tr>
</thead>
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<td>Oat-cell carcinoma</td>
<td>37-1%</td>
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<tr>
<td>Squamous-cell carcinoma</td>
<td>20-1%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>28-3%</td>
</tr>
<tr>
<td>Polygonal-cell carcinoma</td>
<td>10-7%</td>
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<td>Unrecognizable (due to poor histology)</td>
<td>3-8%</td>
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</tbody>
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REFERENCES