

# Alveolar carcinoma: a review

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Alveolar carcinoma of the lung has always been surrounded by controversy. Morphological criteria for its diagnosis are ill defined, its distinction from adenocarcinoma is often arbitrary,<sup>1</sup> and it is encumbered by a multiplicity of synonyms, reflecting its uncertain histogenesis.<sup>2,3</sup> Its very existence has been questioned,<sup>4,5</sup> though most authorities accept it as an entity<sup>6-12</sup>—and yet tumours of this type are not rare, comprising up to 9% of all pulmonary cancers.<sup>13</sup> The first case was reported over a century ago<sup>14</sup> and currently there are more than 1000 in published reports.<sup>13</sup>

During the last decade or so some new facts have emerged about the nature, aetiology, and natural history of alveolar carcinoma. In particular, it now appears that this is a heterogeneous group of tumours which appear similar on gross examination and by light microscopy but which differ at the ultrastructural level<sup>15</sup>—a concept leading to difficulties in communication between histopathologists and clinicians. This paper therefore falls into two broad sections. In the review of clinical and radiological features, gross pathology, and light microscopy alveolar carcinoma is treated for practical purposes as a single entity; while histogenesis and aetiology are discussed in the light of more recent developments.

## Definition and nomenclature

The accepted diagnostic criteria of alveolar carcinoma on the basis of gross examination and light microscopy are: (1) absence of a primary adenocarcinoma elsewhere; (2) absence of a demonstrable central bronchogenic origin; (3) a peripheral location in the lung parenchyma; (4) intact interstitial framework of the lung; (5) a histological appearance setting it apart from other lung tumours and characterised by the growth of malignant cells along alveolar walls.<sup>1,2,4,6,9</sup>

Over the years many descriptive terms have been used for this tumour, including pulmonary

adenomatosis, bronchiolar carcinoma, alveolar cell carcinoma and many others.<sup>3</sup> The currently preferred name is bronchioloalveolar carcinoma, which was coined in 1960 by Liebow,<sup>2</sup> the implication being that the cell of origin was uncertain. For the purposes of this article I use the term alveolar carcinoma, emphasising that it refers to the histological pattern and has no histogenetic connotation. "Bronchioloalveolar carcinoma" is clumsy to write and difficult to say aloud.

## Historical background

The first published account of alveolar carcinoma is attributed to Malassez,<sup>14</sup> who in 1876 described in detail a multinodular tumour in a woman aged 47, and more briefly a localised tumour in a man of 50 years, "*chez lequel on ne trouvait aucune trace de syphilis antérieure.*" Reports of a pneumonic variant,<sup>16,17</sup> multinodular tumours confined to the chest,<sup>18</sup> and a further example of the localised type<sup>19</sup> appeared during the years 1903-9. Skorpil<sup>20</sup> carried out the first lobectomy for alveolar carcinoma in 1936 and the patient survived for five years despite secondary deposits in hilar lymph nodes.

In 1949 Swan<sup>21</sup> was able to find only 52 published cases, but in the ensuing two decades many more were published.<sup>5,22-32</sup> The question of histogenesis, however, remained unresolved<sup>2</sup>; some authors believed that the origin of the tumour was multicentric,<sup>22,33,34</sup> whereas others favoured a unicentric origin with spread via bronchi and lymphatics.<sup>23</sup> Another school of thought doubted the place of alveolar carcinoma as a primary lesion of the lung; it was pointed out that secondary carcinomas sometimes mimic its appearance exactly.<sup>35</sup> Nevertheless, alveolar carcinoma was generally accepted as an entity and it was noted that surgical treatment of the solitary form was associated with an excellent prognosis.<sup>23,28</sup>

In parallel with these developments, similar tumours were being reported in animals.<sup>2</sup> Of particular interest was *jaagsiekte*, a contagious pulmonary disease of sheep, which is characterised by proliferation of alveolar lining cells in its early stages and later by the development of a malignant lesion

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identical to human alveolar carcinoma.<sup>36</sup> This condition was studied initially in South Africa, but subsequently cases appeared in Peru, Iceland, and the United States. Its aetiology is clearly viral, but its relationship to human disease remains uncertain.

### Clinical features

Alveolar carcinoma accounts for about 5% of all lung cancers, but the actual figure quoted varies from 1.1%<sup>9</sup> to 9.0%<sup>37</sup> in published reports. An incidence as low as 0.4% was cited in an early paper,<sup>23</sup> probably because of difficulties in distinguishing this tumour from adenocarcinoma. Although some workers have noted a female preponderance,<sup>1 28 31 38</sup> the overall sex incidence among published cases is 58.5% in men and 41.3% in women.<sup>13</sup> Solitary resectable lesions appear to be more common in women,<sup>13</sup> and it is noteworthy that alveolar carcinoma is more equally distributed between the sexes than other forms of lung cancer.<sup>1</sup> Patients at presentation are generally in their sixth or seventh decade, but the youngest recorded case occurred in a boy of 15<sup>39</sup> and Donaldson's group reported a further case in a man of 20.<sup>40</sup> Liebow<sup>2</sup> and Storey and his colleagues<sup>23</sup> also found that alveolar carcinoma tended to develop in younger patients. A history of smoking is less evident than in more central tumours,<sup>8 9 30 32</sup> although it does appear to play a part in many cases.<sup>6</sup>

Up to 45% of patients present with an asymptomatic peripheral opacity discovered on a routine chest radiograph,<sup>7 8 41 42</sup> and in some an apparently stable radiological lesion is followed for years before a diagnosis is made.<sup>27 29 31 43</sup> Other symptoms, as with any pulmonary tumour, include chest pain, dyspnoea, weight loss, and cough.<sup>1 6 8-11 41 42 44</sup> Haemoptysis is less common than in bronchogenic carcinomas.<sup>10</sup> In two published cases there was massive venoarterial shunting and hypoxaemia that resolved after surgery.<sup>45 46</sup> The classical massive bronchorrhoea is rare and tends to be a late manifestation.<sup>1 8-10 42 44</sup> When present it may be severe enough to cause electrolyte imbalance<sup>47-49</sup> as well as respiratory embarrassment.

A past history of previous chest disease is often elicited and a high percentage of these tumours arise in damaged lungs or in areas of scarring.<sup>2 7 32 42 50</sup> Apart from those cases associated with asbestosis,<sup>51</sup> there are no occupational factors of relevance, although Dvořáková<sup>52</sup> reported one patient who had been exposed to aflatoxin. Beaumont and his associates<sup>53</sup> found six cases in a single family, arising as a complication of fibrosing alveolitis; and alveolar carcinoma in identical twins has also been recorded.<sup>54</sup>

### Radiology

Radiologically a variety of changes may be seen, and the differential diagnosis includes oedema, pneumonia, haemorrhage, sarcoidosis, alveolar proteinosis, and secondary tumour.<sup>6 7 9 44 55 56</sup> Early lesions consist of a single peripheral shadow 1–10 cm in diameter, which may be well defined but is usually irregular with spicules of fibrous tissue radiating from its periphery. Hilar lymphadenopathy is rare at this stage.<sup>1</sup> Prominent strands, best seen on tomography, often extend to the pleural surface, giving rise to the "rabbit ear" or "tail" sign.<sup>7 41 57</sup> This sign is not pathognomonic and has been described in tuberculosis, *Nocardia* infection, and North American blastomycosis, as well as other types of inflammation and tumour.<sup>7 58</sup>

Radiological appearances in such cases may be misleading: an apparent single nodule may be accompanied by others which are only found at thoractomy.<sup>7</sup> Preoperative computed tomography has proved of value in detecting small lesions of this nature.<sup>59 60</sup> Later in the course of the disease multiple radiologically apparent nodules appear, often in both lung fields—an appearance which implies widespread dissemination and is associated with a poor prognosis.<sup>10</sup> Cavitation and calcification are rare; but there may be a central lucent area, presumably due to the presence of unaffected airways.<sup>7</sup> Occasionally alveolar carcinoma presents with multiple cavitating lesions.<sup>61 62</sup>

The lobar pneumonic type of change is a relatively late manifestation, although in some earlier series it accounts for over 30% of the total.<sup>7</sup> The infiltrate need not extend to include a whole segment or lobe and may have a soft, ill defined edge.<sup>55</sup> One of the characteristic features of this type of lesion is the presence of an "air bronchogram" on tomography and a "leafless tree" appearance on bronchography.<sup>1 6 7</sup> Because alveolar carcinoma is a peripheral lesion, atelectasis and obstructive change due to large airway obstruction is rare. Pneumothorax has been described, and there may be a massive pericardial effusion.<sup>63 64</sup>

Any opacity which does not resolve or progresses and is associated with pre-existing lung disease should therefore be regarded with suspicion. Certainly a persistent type of infiltrate is sufficiently characteristic to warrant a presumptive diagnosis of alveolar carcinoma.<sup>7</sup>

### Diagnosis

There are few published data on changes in respiratory physiology in alveolar carcinoma. In many cases there is no change, whereas in some lung

volume and diffusing capacity are reduced, but with minimal evidence of airway obstruction. Arterial desaturation may be a primary clinical manifestation in patients with venoarterial shunting.<sup>45 46 65 66</sup> A few cases of alveolar carcinoma associated with a high level of S type serum and urinary amylase have been reported, but this phenomenon may also occur in small cell carcinoma.<sup>67</sup>

The results of cytological investigation vary from study to study. Some authors have been unable to diagnose a single case cytologically, whereas others report success rates of up to 80%.<sup>12</sup> Tao *et al*<sup>12</sup> found that cytological examination of sputum, pleural fluid, and bronchial brushings was of little value in solitary lesions, whereas in patients with disseminated tumour a diagnosis could be made by the use of these techniques in 88%. Percutaneous fine needle biopsy, however, was diagnostic in 92% of patients with a solitary lesion and in all patients with multiple lesions. Lobar lavage also appears to be a promising technique.<sup>68</sup> Spriggs *et al*<sup>69</sup> have underlined the difficulties in distinguishing between non-neoplastic, non-ciliated epithelial cells and well differentiated adenocarcinoma. They also advise that no attempt should be made to differentiate alveolar carcinoma and adenocarcinoma in cytological material, although such a distinction has been made by others.<sup>70 71</sup>

Because of the peripheral location of alveolar carcinoma, bronchoscopy and bronchial biopsy are usually unrewarding.<sup>5 32</sup> Diagnosis from lymph node biopsy specimens is not possible and a specimen of lung tissue showing the characteristic alveolar spread is required.<sup>9</sup> In our laboratory we have found transbronchial biopsy diagnostic when the tumour is present in its multinodular or diffuse form, but not when there is only a single peripheral nodule. In the latter type of case, however, percutaneous needle biopsy under radiographic control has yielded diagnostic material in every case. Many patients are still diagnosed only at thoracotomy, and Donaldson and his colleagues advocate an aggressive multidisciplinary approach to diagnosis in any patient with features suggestive of alveolar carcinoma.<sup>7</sup>

### Treatment

Alveolar carcinoma is relatively slow growing, is more often resectable than other pulmonary and bronchial tumours, and carries a better prognosis.<sup>1 6 9 10 25 28-31 44</sup> The treatment of choice for localised, nodular lesions is lobectomy or pneumonectomy, even if the tumour is large.<sup>10 12</sup> The prognosis appears to depend on localisation rather than size,<sup>9</sup> and tumours which are situated centrally in the lung parenchyma have a better

outlook than those which are subpleural or hilar. In patients with localised disease the five year survival rate is 50% or better after surgery,<sup>44</sup> but disease of hilar lymph nodes reduces this appreciably. It must be emphasised, however, that five year survival does not necessarily imply a cure as new lesions may arise from five to 10 years after operation.<sup>11</sup> When there is more widespread disease, palliative procedures may be considered with the aim of reducing bronchorrhoea, but in such cases the outlook is poor. Arterial desaturation, for the reasons already stated, should not be considered a contraindication to resection—other criteria must be taken into consideration.<sup>44 46</sup>

Unfortunately, alveolar carcinoma is resistant to radiotherapy and chemotherapy, so that treatment can be only symptomatic in patients unsuitable for surgery.<sup>6 9</sup> Several methods have been advocated for treating bronchorrhoea: encouraging results have been reported with atropine, with adrenocorticotrophic hormone, and with stellate ganglion block; but some authors have found these measures to be ineffective.<sup>72</sup> Procaine, radiotherapy, steroids, and cytotoxic drugs do not appear to ameliorate this distressing complication.<sup>72</sup>

In general, there is a poor prognosis in the elderly, in patients with tumour affecting central airways, and in those with haemoptysis, dyspnoea, or evidence of mediastinal lymph node disease.<sup>1</sup> The response to surgery is good, so long as a lobectomy at least has been carried out; the results of segmental resection, or resection of the tumour alone, are poor.<sup>1</sup>

### Gross pathology

In necropsy or surgical material alveolar carcinoma manifests itself as either an isolated nodule, as multiple and often widely disseminated nodules, or as diffuse "pneumonic" consolidation.<sup>2 5 7 41-2 44 56</sup> Edgerton and colleagues<sup>13</sup> found that the tumour originated in an upper lobe in about 35% of published cases and in a lower lobe in 22%. In the remainder the site of origin was uncertain.

The isolated nodular form appears to be more common in the upper lobes and is frequently associated with a scar.<sup>2 50</sup> The tumour may be minute or may be over 10 cm in diameter<sup>2 10</sup> and is often circumscribed and roughly spherical, with a greyish white, mucoid cut surface.<sup>2</sup> Others are less well defined and may be difficult to recognise as neoplastic.<sup>2</sup> The adjacent pleura is frequently puckered, particularly in those cases associated with a scar. Cavitation is rare, but occurs sometimes in larger specimens. The cavity frequently contains mucus.

In the disseminated nodular form the individual tumours are similar in appearance to isolated

nodules and vary in size from miliary deposits to small masses 3 or 4 cm in diameter. They may resemble secondary carcinoma, bronchopneumonia, or granulomatous foci. The diffuse, pneumonic form resembles lobar pneumonia in the stage of grey hepatisation; but its texture is finer, its colour has a pinkish cast, on close examination a faint nodular pattern is apparent, and cavitation may occur.<sup>2 16</sup> As with certain types of lobar pneumonia the cut surface is frequently mucoid. Rarely alveolar carcinoma does not conform to any of these patterns, presenting instead as multiple cystic nodules or a large single cystic cavity.<sup>40 61-2 73-7</sup> In a recently described case<sup>62</sup> the necropsy appearances suggested centrilobular emphysema, but on histological examination the spaces were lined by tumour cells: the authors suggest that the walls of terminal bronchioles were thickened by tumour and acted as check valves. There are a few descriptions of single cavitory carcinoma, sometimes associated with previous aspergillus infection<sup>74-6</sup>; and one case arising adjacent to an abscess has also been reported.<sup>40</sup>

The reported frequency of the gross types of alveolar carcinoma has varied over the years, reflecting current trends towards the earlier diagnosis and treatment of lung tumours. For instance in 1962 Belgrad, Good and Woolner<sup>28</sup> found that 62% of their patients had diffuse disease at presentation, whereas in 1978 only 29% of the series published by Miller and his co-workers<sup>44</sup> fell into this category.

### Light microscopy

The microscopic appearance varies from case to case and also from area to area in the same tumour,<sup>2 44</sup> and there is no correlation between histology and gross pattern.<sup>42 44</sup> In well differentiated tumours the alveoli are lined by tall columnar cells, with an amphophilic or eosinophilic, often vacuolated cytoplasm. Nuclei are basally situated, round or oval and bland in appearance with prominent nucleoli; mitoses are rare.<sup>2 4 7 8 10 42 79-80</sup> Mucin is generally present in alveolar lumina, and in such cases the cytoplasm is periodic acid Schiff positive after diastase and stains with alcian blue<sup>4 8 15 41 62 79 81</sup>; but mucin positivity may be absent or confined to the apices of the cells.<sup>4 5 79 80 82-9</sup> Intranuclear inclusions have also been described.<sup>15 39 41 89 90-1</sup>

In other tumours the predominant pattern is less well differentiated, with an alveolar lining of peg shaped, low columnar or cuboidal cells showing less mucin production.<sup>2 4 8 42 78</sup> The nuclei are centrally placed and often hyperchromatic, large, and bizarre. In both well and poorly differentiated tumours the alveolar lining layer is only one cell thick, but foci of papillary infolding are often present and tumour

cells may lie free in the lumen. Occasional tumour giant cells are often seen and there may be foci of squamous metaplasia or small cell anaplastic change.<sup>2 6</sup> Other features include cytoplasmic fat,<sup>2 78 87</sup> occasional ciliated cells,<sup>2 78 85 88</sup> and psammoma bodies.<sup>2 92</sup> The latter are more frequent in less well differentiated papillary tumours.

By definition, the supporting stroma of alveolar carcinomas is formed by the alveolar walls, which in better differentiated examples are apparently unaltered and stain faintly with connective tissue stains.<sup>4 78</sup> Where the lining cells are poorly differentiated the alveolar walls are thickened by fibrous tissue; such thickening is also present towards the central parts of the tumour, regardless of its cytological appearance.<sup>5 41-2</sup> Variable numbers of chronic inflammatory cells are present in the stroma, and sometimes there are non-caseating epithelioid cell granulomas.<sup>15 88 93</sup>

The central part of the tumour frequently contains hyaline or collagenous scar tissue<sup>6 42 50</sup> and areas of necrosis. It also contains a variable amount of tissue with a frankly adenocarcinomatous structure,<sup>2</sup> a feature which immediately raises the question of differential diagnosis between adenocarcinoma and alveolar carcinoma. It must be admitted that the distinction at light microscopy is somewhat arbitrary. In 1960 Liebow<sup>2</sup> stated that no definition had succeeded in separating the two and that the question was unlikely to be resolved without further studies at an ultrastructural and histochemical level.

### Histogenesis

The difficulty in distinguishing between alveolar carcinoma and other tumours has only partially been solved by the advent of the electron microscope. Doubts have been expressed about the existence of alveolar carcinoma as an entity separate from adenocarcinoma<sup>4 5 94-5</sup> and even its status as a primary tumour of the lung has been questioned— notably by Eck,<sup>96</sup> who presented three cases of apparent alveolar cell carcinoma which were in fact secondary deposits from the rectum, pancreas, and bronchus. Other workers have described similar findings and emphasis that in many cases a pancreatic primary was responsible.<sup>97 98</sup> There is now abundant evidence that alveolar carcinoma does arise in the lung, although identical appearances can be produced by secondary tumours. Primary sites in pancreas, large bowel, gall bladder, ovary, thyroid, and breast have all been mentioned in this context and a careful search must always be made for unrecognised primary disease.<sup>6 35 97-9</sup>

Because the histogenesis of alveolar carcinoma could not be ascertained by light microscopy, it was

named bronchioloalveolar carcinoma on the grounds that it was impossible to deny either a bronchiolar or an alveolar origin.<sup>2</sup> To solve this problem, several ultrastructural studies were instituted. The results were wildly conflicting. Some workers were of the opinion that alveolar carcinoma arose from granular pneumocytes or type II cells, others thought that an origin from non-ciliated bronchiolar or Clara cells was more likely, and a third group favoured an origin from metaplastic mucus secreting cells. Dogmatic statements were made, often on the basis of a single case.

It is unthinkable that all these workers were wrong in the interpretation of their findings, and it is now clear that all were correct but had based their conclusions on series which were too small. In fact, alveolar carcinoma is a heterogeneous group of tumours, which may be derived from either type II cells, Clara cells, or bronchial mucus cells.<sup>15 79</sup> The vast majority of alveolar carcinomas arise from bronchial mucus cells and are morphologically identical to mucus secreting adenocarcinomas.<sup>4 78 100-3</sup> At light microscopy they stain positively for epithelial mucins and they secrete mucus into the alveolar lumen. Ultrastructurally there are apical mucin granules showing coarse granularity.<sup>78</sup>

In tumours of type II cell origin<sup>15 82-3 89 90 93 104-5</sup> the cytoplasm contains the characteristic lamellated bodies which are markers for pulmonary surfactant. Short microvilli are present on the luminal surfaces. On light microscopy the cells are cuboid or columnar, with round, oval or convoluted nuclei which may contain eosinophilic inclusions. Stains for mucin are negative.<sup>80 89 105</sup> Hyperplastic, non-tumour type II cells are present at the edge of any pulmonary neoplasm and may be mistaken for intrinsic cells of the tumour,<sup>78 85</sup> but cells with type II characteristics have been described in secondary deposits<sup>105</sup> and analysis of the fluid from a patient with bronchorrhoea indicated that it was of alveolar origin.<sup>72</sup> The presence of surfactant apoprotein in the cytoplasm of the cells of these tumours has also been demonstrated using an immunoperoxidase technique.<sup>15</sup>

The cells of alveolar carcinomas with non-ciliated bronchiolar cell differentiation (Clara cell tumours) contain round electron dense cytoplasmic granules and finger print structures.<sup>4 78 84-5 88 106-7</sup> Vacuoles containing mucin may also be present<sup>88</sup> and short microvilli are present on the free surface. The cells tend to be tall and columnar. An autoradiographic study<sup>107</sup> has demonstrated an association of newly synthesised glycoprotein with the cytoplasmic granules, which has also been seen in normal Clara cells.

It must be emphasised that the three variants

described above are not clear cut. Cells containing lamellar surfactant material as well as Clara cell granules have been described, abortive cilia may also be present<sup>78 85 87-8</sup> and in another case the alveoli were lined by cells without any specific features.<sup>91</sup> It may be that a substantial proportion of alveolar carcinomas arise from a bronchiolar stem cell which is capable of differentiation to type II cells, Clara cells, ciliated cells and goblet cells.

### Multicentric or unicentric origin

There is still no agreement about whether alveolar carcinoma has a multicentric or unicentric origin. An early solitary lesion has an excellent prognosis and it is likely that the multinodular form is due to aerogenous and lymphatic dissemination rather than simultaneous multiple foci,<sup>2 23</sup> but it has been shown that multiple tumours can appear years after surgery.<sup>11</sup> These may be due to previously undetected secondary deposits, but alveolar carcinoma arises in damaged lungs, and possibly this phenomenon is due to the development of further primary tumours in an already metaplastic field of growth. Extensive areas of dysplasia and premalignant change have been demonstrated in damaged lungs by several workers,<sup>108-9</sup> and Miller and his colleagues<sup>44</sup> postulate that there are two clinical types of alveolar carcinoma. In the first type the disease is localised and may metastasise in a fashion similar to any other pulmonary malignancy, while the second type may be diffuse from the onset.

### Benign variants

It is doubtful if a benign variant of alveolar carcinoma, (that is, true pulmonary adenomatosis) exists. There seems little doubt that in some cases the disease progresses through a proliferative stage before a frank neoplasm develops and possibly such proliferative lesions have been mistakenly interpreted as tumours. The slow growth and good prognosis of alveolar carcinoma also may have led to confusion in the past. Furthermore, a benign tumour of type II cells is well documented.<sup>110</sup> It was first thought to be a type of haemangioma, but subsequent studies indicate an origin from the alveolar lining.

### Aetiology

Alveolar carcinoma is frequently associated with localised scars following tuberculosis, infarcts, lung abscesses, or bronchiectasis.<sup>5 6 50 83</sup> In other cases there is preceding diffuse lung disease, including cryptogenic fibrosing alveolitis,<sup>111-3</sup> rheumatoid

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lung disease,<sup>114 115</sup> mitral lung disease,<sup>116</sup> busulphan lung,<sup>117</sup> and even Hodgkin's disease.<sup>118</sup> The epithelial proliferation in fibrotic conditions of the lung appears in some patients to be a prelude to the development of neoplasia.<sup>108-9</sup>

Jaagsiekte is an infective disease of sheep.<sup>119-22</sup> In the early stages there is alveolar epithelialisation, which progresses to a malignant tumour identical to human alveolar carcinoma.<sup>121-2</sup> There is no doubt about its contagious nature: multiple cases in a flock are well documented and the disease has been induced in experimental animals by inoculation of infected material.<sup>122</sup> Viruses resembling the RNA tumour viruses (retroviridae) appear to be responsible. Although first described in South Africa, outbreaks have now been reported from other countries, including Iceland and Peru.<sup>2 122</sup>

Direct animal to man transmission of jaagsiekte has not yet been established, but alveolar carcinoma has been reported in patients exposed to affected sheep.<sup>123</sup> No virus has been isolated from human cases, although intranuclear inclusions have been seen.<sup>15 90 124-5</sup> Some workers are of the opinion that these inclusions are not virus like<sup>15</sup> whereas others are struck by their resemblance to paramyxovirus,<sup>90 124</sup> and in a recent paper papovavirus like structures were described.<sup>126</sup> On the other hand, intranuclear bodies of a non-viral nature may be seen in various neoplastic and non-neoplastic conditions.<sup>83</sup> An infective aetiology, therefore, is not proved in human alveolar carcinoma, but it is of interest that cell free extracts of tumour are cytopathic in cultured cell lines.<sup>124</sup>

Specific tumour associated antigens and lymphocyte associated antigens have been demonstrated in alveolar carcinoma, but the exact significance of this finding is uncertain.<sup>127-9</sup> More recently Langerhans cells have been reported in patients with this tumour, together with serum precipitating antibodies to *Aspergillus* species and thermophilic actinomycetes.<sup>130</sup> The authors of this paper suggest that there may be a link between alveolar carcinoma and pulmonary eosinophilic granuloma.

**Conclusions**

Alveolar carcinoma as defined from gross and light microscopic appearances is not a single entity. Most of these tumours are morphologically identical to adenocarcinomas arising elsewhere; but some consist predominantly of type II cells and some of Clara like cells, while others contain a mixture of all three elements; possibly the ultimate derivation is from uncommitted bronchiolar stem cells. Secondary tumours, particularly those originating in the gas-

trointestinal tract and pancreas, can produce an identical appearance. In all cases of suspected alveolar carcinoma a careful search for a primary tumour outside the lung is mandatory.

The differential diagnosis between adenocarcinoma and alveolar carcinoma is often arbitrary and is in any event an artificial distinction in most cases. Nevertheless, the term remains a useful label which can be applied to peripheral lung tumours showing the characteristic spread along alveolar walls, with the proviso that the exact cell type may be uncertain on the basis of light microscopy. Such tumours carry a better prognosis than bronchogenic neoplasms. They present as small peripheral masses and often appear to grow slowly. The classic pneumonic and multinodular lesions are late manifestations. Bronchorrhoea is rare.

Further work is required on the possible viral aetiology of alveolar carcinoma, and the natural history of the various subtypes needs to be investigated.

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