THE LOCAL FACTORS WHICH DETERMINE THE SPREAD OF GROWTH IN CARCINOMA OF THE LUNG

By Alak Kumar Gupta

Presented in accordance with the regulations governing the award of the Degree of Doctor of Philosophy in the University of London

Department of Pathology
St. Mary's Hospital Medical School
London, W.2.

August, 1962

ABSTRACT

During the last fifty years lung cancer has emerged from its obscurity as a rare disease to be the most common malignant disease in man. With the recent phenomenal advances in anaesthesia, respiratory physiology and surgical techniques, this disease has been enthusiastically attacked by surgeons. The early hopes of clinicians have not been fulfilled because of the poor salvage rate of this disease.

In spite of the recent publicity and intensive study of this disease, many aspects of it still require clarification. It is clear that a greater understanding of metastases, their modes of spread and the possible factors which determine them in primary pulmonary carcinoma is of diagnostic, prognostic and therapeutic importance and deserves serious study.

The salient macroscopic and microscopic observations in 114 surgically resected primary peripheral lung carcinomas constitute the main substance of this thesis. An attempt has been made to correlate the tumour cell type, differentiation, and such local factors as vascular invasion, fragmentation, necrosis and stromal reaction, with tumour size and dissemination, in order to discover whether, by these means, it is possible to predict the probable clinical course.

CONTENTS

		Page
I	PREFACE	8
II	INTRODUCTION	10
III	METHODS	14
IV	MATERIAL	21
V	RESULTS	
	Metastatic spread	23
	Histological appearances	31
	Influence of local factors on lymph node metastasis	48
VI	DISCUSSION	57
VII	PROGNOSTICATION ON THE 'M' TUMOURS	66
VIII	CONCLUSION	69
IX	TABLES giving salient features of 114 peripheral lung carcinomas	71
X	DIAGRAMMATIC ILLUSTRATIONS of 114 peripheral lung carcinomas	100
XI	APPENDIX	118
	Appendix I (A)	
	The pre-operative duration of symptoms with central and peripheral bronchial carcinoma	119
	Appendix I (B)	
	Survival studies of central and peripheral bronchial carcinoma	126
	Appendix II	
	Presence of scars in peripheral carcinomas	135
	Appendix III	
	Cavitation in peripheral lung carcinoma	140
XII	ACKNOWLEDGEMENT	143
XIII	REFERENCES	144

LIST OF FIGURES

Figure		Page
1	Diagrammatic representation of the distribution of peripheral lung tumours arranged according to size and metastasis of lymph glands.	14
2	Squamous carcinoma, well differentiated, with keratin and cell nests and showing lymphocytic infiltration of the stroma.	17
3	Adenocarcinoma, tubulated and mucus secreting, with scanty stroma.	17
4	Oat cell carcinoma, undifferentiated. No stromal reaction.	18
5	Polygonal cell carcinoma. Alveolar strands thickened. No stromal reaction.	18
6	114 peripheral lung carcinomas. Distribution according to size and lymph node metastasis.	25
7	17 peripheral oat cell carcinomas of lung. Distribution according to size and lymph node metastasis.	26
8	35 peripheral squamous carcinomas of lung. Distribution according to size and lymph node metastasis.	27
9	37 peripheral adenocarcinomas of lung. Distribution according to size and lymph node metastasis.	28
10	25 peripheral polygonal cell carcinomas. Distribution and size of lymph node metastasis.	29
11	Artery showing infiltration by oat cell carcinoma.	32
12	Vein occluded by polygonal cell carcinoma.	32
13	Oat cell carcinoma. Lymph channel invasion.	33
14	Oat cell carcinoma showing fragmentation (alveolar exfoliation) at the periphery of tumour.	38

Figure		Page
15	Adenocarcinoma showing marked fragmentation (alveolar exfoliation) at the periphery of tumour	38
16	Well differentiated squamous carcinoma showing stromal reaction.	40
17	Differentiated and undifferentiated oat cell tumours. Distribution according to size and lymph node metastasis.	41
18	Oat cell carcinoma. Cell size related to lymph node metastasis.	42
19	Squamous carcinoma showing invasion of artery. Tumour shows central necrosis and mitotic figures.	44
20	Squamous carcinoma. Distribution of keratinising tumours related to lymph node metastasis.	45
21	Polygonal cell carcinoma. Stromal reaction related to lymph node metastasis.	47
22	Distribution of microscopic blood vascular invasion in 114 peripheral tumours.	50
23	Distribution of obvious lymph channel invasion in peripheral lung tumours.	51
24	Distribution of tumours showing fragmentation (alveolar exfoliation) in 114 peripheral tumours.	53
25	Distribution of tumours showing conspicuous stromal reaction.	54
26	The only oat cell tumour (O 14) showing good stromal reaction.	55
27	High power view of the dense lymphocytic infiltration at the periphery in O 14).	55

LIST OF FIGURES TO APPENDICES

Appendix I (A)

Figure		Page
1	Pre-operative duration of symptoms of 110 peripheral lung carcinomas.	122
2	Pre-operative duration of symptoms of 65 central lung carcinomas.	122

Appendix I (B)

1	Post-operative survival in 81 cases of peripheral lung cancers arranged according to size.	128
2	Post-operation survival in 43 squamous carcinomas of central type.	129
3	Post-operation survival in 30 cases of peripheral squamous carcinoma.	130
4	Post-operation survival in 12 cases of central oat cell carcinoma.	131
5	Post-operation survival in 11 cases of peripheral oat cell carcinoma.	132
6	Post-operation survival in 28 cases of peripheral adenocarcinoma.	133
7	Post-operation survival in 12 cases of peripheral polygonal cell carcinoma.	134

Appendix II

Figure		Page
1	Small peripheral tumour (adenocarcinoma) in the dorsal segment of the lower lobe showing a central scar and with the pleura puckered over the tumour.	137
2	Section of tumour shown in Appendix II: Fig. 1. The pigmented scar is plainly seen. The growth reaches the adherent and retracted pleura.	139

Appendix III

1	Lower lobe showing cavitating tumour (squamous carcinoma.	141

PREFACE

It has been said that the important thing in research is to ask the right questions. The question which this thesis sets out to answer is: what are the characteristics of a lung tumour which does relatively well and those of a growth which does badly? This appears to be a proper question, not only because it has stimulated some answers but also because the investigation has provided new information in related fields.

The investigations on lung cancer carried out during my association with Professor D.M. Pryse (which we intend to publish later in separate papers) are:

1. A graphic demonstration of the difference between central and peripheral tumours when the length of pre-operation history is plotted against tumour size. Peripheral tumours attain an operability ceiling (12 cm.) nearly twice that of central tumours. This greater size range was one of the reasons for using peripheral tumours in the titular investigation.

2. A graphic demonstration for peripheral and central lung tumours of the lack of correlation between tumour size and survival time. A similar paradox was found by Kreyberg and Christiansen (1953) in surgical breast cancer. The probable explanation is that highly malignant tumours are operable only when small while less malignant tumours remain operable when large. Strong evidence in support of this is provided by the following investigation.

3. A graphic demonstration from a study of 114 peripheral tumours that the metastasising rate is constant over the whole range of tumour sizes.

4. A correlational study of histological appearances and malignancy which is the subject of the present thesis.

INTRODUCTION

Carcinoma of the lung has been known to pathologists and clinicians for a long time. Agricola[+] mentioned it in the 16th century in the miners of Joachimsthal (Jachymov), Bohemia, although he did not understand the disease as it is now known. Laennec (1819) mentions the medullary cancers of the lung in his treatise. The subject is also discussed, although meagrely by present standards, in the classical text-books on pathological anatomy by Hasse (1846) and Rokitansky (1842). Both these morbid anatomists regarded it as rare and, in spite of the truth that man sees only what he knows, it would be presumptuous to question Rokitansky, who personally performed about 30,000 autopsies. He regarded the primary tumour as rare though secondary tumours were not uncommon in his experience.

In English literature there are numerous references to the disease in the 19th century (Cmuigbo, 1959). It is sufficient to mention only a few pioneers. Among these, Stokes (1837) discusses the difficulty of diagnosis in life in his treatise on chest diseases. Cockle (1865) wrote the first monograph on intrathoracic cancer. He was one of the early observers to note the frequent metastases to the brain. Bennett (1872) also spoke of the difficulty in diagnosing lung cancer in life. It is easy to understand how difficult the position must have been without the modern aids of radiology, bronchoscopy, biopsy and cytology.

[+] Extensively quoted by Weller (1956).

Indeed an early diagnosis is still the goal most sought after.

As late at 1912 Adler was unable to find more than 374 cases of lung cancer in the world literature. Since then the disease has reached epidemic proportions and the literature has become voluminous. In the past 50 years lung cancer has emerged from comparative obscurity to be the most common malignant disease in men (Rigdon and Kirchoff, 1961). It is, after coronary disease, the second most frequent cause of death in adult men. The Registrar-General's figures are ample proof of this increase.

		1950	1955	1960
Death from malignant neoplasms of trachea, bronchus and lung	M	10,219	14,761	18,882
	F	1,978	2,438	3,118
	Total	12,197	17,199	22,000
Death rate per million all neoplasms	M	2,099	2,309	2,419
	F	1,890	1,913	1,975
Death rate per million from neoplasms of trachea, bronchus and lung	M		445	582
	F		67	89

Though a comparison with earlier figures shows a much more spectacular rise, figures only from 1950 are quoted as it is thought that misdiagnosis in lung cancer cases would be comparatively eliminated or lessened. Even so an 80 per cent increase in the total number of deaths is seen which can hardly be ascribed to enhanced awareness of the disease. It is, therefore, difficult to concur with doubts expressed by Fried (1959)

and Willis (1961) on this increased incidence.

Great advances have been made in the aetiological aspect of this disease. Smoking and air pollution by industrial fumes are factors with which definite correlation has been found (Campbell, 1936; Hammond and Horn, 1954; Kotin, 1956; Doll and Hill, 1950, 1952, 1954, 1956). It was surprising, therefore, how incomplete the clinical notes of the present series of cases were in this respect. It was common to find "retired" stated as a patient's occupation, and for no mention to be made of smoking habits.

It is only since 1933, when Graham performed the first successful pneumonectomy for carcinoma of the lung, that pathologists have been able to study lung tumours before post-mortem changes occur. In this we are much more fortunate than the older generation of pathologists. It is now possible to see primary tumours of the lung in all stages of evolution - from metaplasia and atypia to frank malignancy and metastases. In autopsy cases one is often handicapped by distortion of the gross anatomy due to overgrowth of the tumour and extensive metastasis. Often the site of origin is irretrievably obscured. Undoubtedly this is one of the reasons why the oat cell carcinoma masqueraded under the name of mediastinal sarcoma until Barnard (1926) established its epithelial origin.

During the past three decades the disease has been attacked enthusiastically by surgeons and radiotherapists. Surgical

resection is the only form of treatment available at present which offers the suitable patient any chance of cure.

With the great improvement in operative technique and advances in anaesthesia the immediate operation mortality has been greatly reduced. Yet the overall survival rate has not shown the expected rise. Where in all this does pathology stand? According to Fried (1959) "the microscopic or macroscopic classification of primary carcinoma of the lung has not yet provided dependable criteria applicable to prognosis or treatment ..... In the surgical treatment what progress has been made is due essentially to improved technical methods rather than to better understanding of the morphological character of the cells or of the patterns of the tumour." There is undoubtedly some truth in this criticism, and it constitutes a challenge which should be met.

The purpose of this thesis is to re-examine without prejudice the relative malignancy of the various tumour types and search for special points in the histology which might help in prognosis.

METHODS

The problem which has been stated before was to correlate in the surgically resected specimens of lung cancer the histological appearances associated with malignant and relatively benign tumours. Surgical rather than post-mortem material was preferred for this purpose because of the better histology and less advanced state of the tumours.

There are several ways in which tumours may be arranged in order of malignancy. The method employed in this investigation was to arrange the tumours in order of size above and below a line according to whether they were or were not associated with lymph node metastases (Fig. 1).

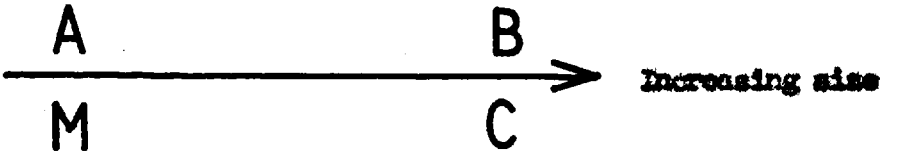


Fig. 1
(see text above)

Arranged in this way tumours A (small tumours with lymph node metastases) are obviously the most malignant and tumours C (large tumours without metastases) the least malignant. The tumours B are of intermediate malignancy and the M tumours are mixed. One would expect those tumours to do best which are of size M but have the histology of C.

In the resected specimens of lung tumours lymph node metastases are more conveniently studied with peripheral tumours than with central tumours, because with the latter the tumour arises in too close proximity to the hilar glands and one is too dependent on the surgeon for the provision of the mediastinal glands. The peripheral lung tumours were more satisfactory also for two other reasons. They remain operable longer than central tumours (Appendix I, Fig. 1) so that they provide a wider range of tumour size. Peripheral tumours also include all histological types whereas in central tumours the adenocarcinomas are rare and the polygonal types common. There is one possible drawback, i.e., metastatic tumours from other parts of the body are more likely to masquerade as peripheral lung tumours than when central. Special care was taken against this possibility however (not only by the clinicians but also in the macroscopic examination of the specimen). All clinical notes were scrutinised to exclude all cases which had a previous malignant tumour.

The tumours were all thoroughly examined histologically. No more attention was paid to the contrasting histological groups

A and C than to the other groups B and M, i.e. the examinations, often tedious and prolonged, were carried out without prejudice.

The histological classification adopted was that of Walter and Pryse (1955). The histological types are shown in Figs. 2, 3, 4, 5. This is essentially the same as the classification followed at the Mayo Clinic (Moersch and McDonald, 1953).

Apart from histological typing the points selected for special consideration were:

1. Blood vascular infiltration. Only those cases were considered positive which showed tumour cells infiltrating through the intima or thrombi of tumour in the lumen of the vessels. Care was taken to exclude any "carrys." No distinction was made between the size of the vessels, microscopic vessels being included.

2. Lymph vascular infiltration. This was undoubtedly present in a much larger number of cases than described but all cases which showed obvious lymph channel infiltration are presented.

3. Peripheral fragmentation. All cases where there was exfoliation of tumour cells in the alveoli were carefully noted. It is thought that this is an expression of the loss of mutual adhesiveness of tumour cells and their mobility.

4. Mitotic activity.

5. Necrosis of tumour.

6. Stromal reaction.

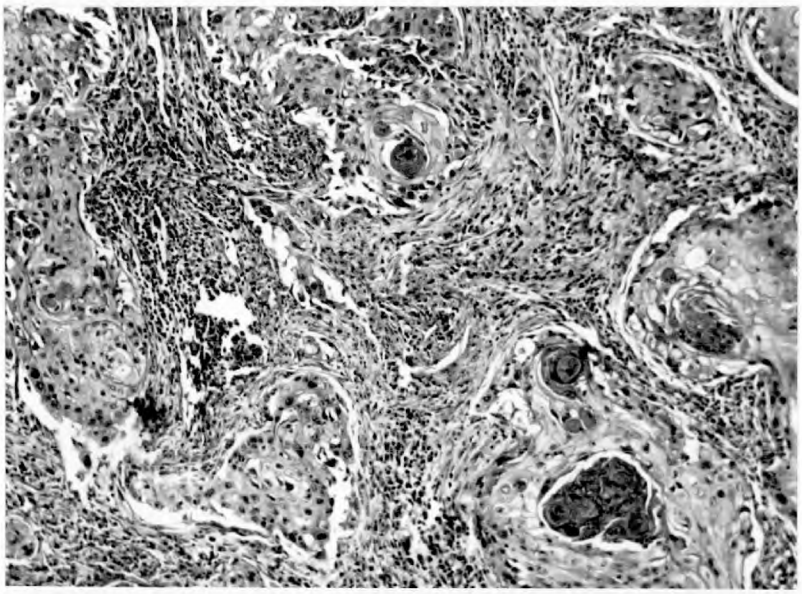


Fig. 2. Squamous carcinoma, well differentiated, with keratin and cell nests and showing lymphocytic infiltration of the stroma.
H & E x 100

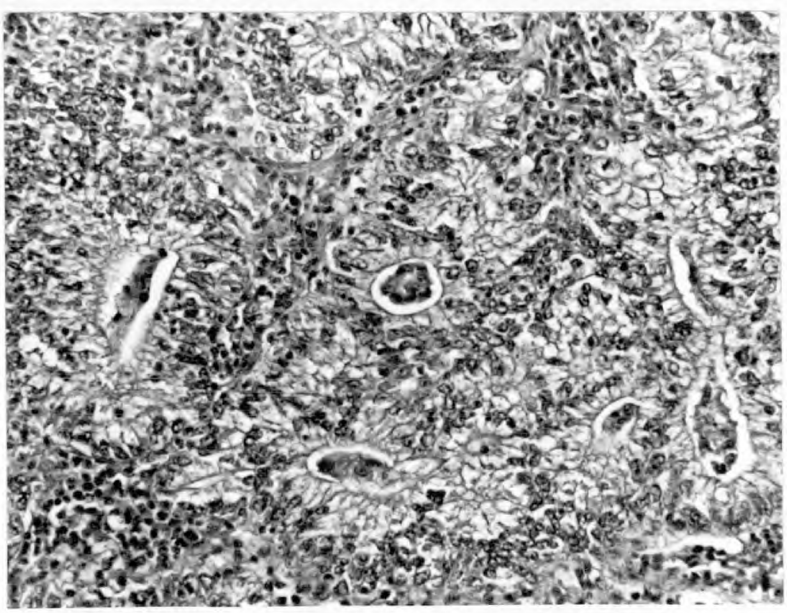


Fig. 3. Adenocarcinoma, tubulated and mucus secreting, with scanty stroma.
H & E x 100

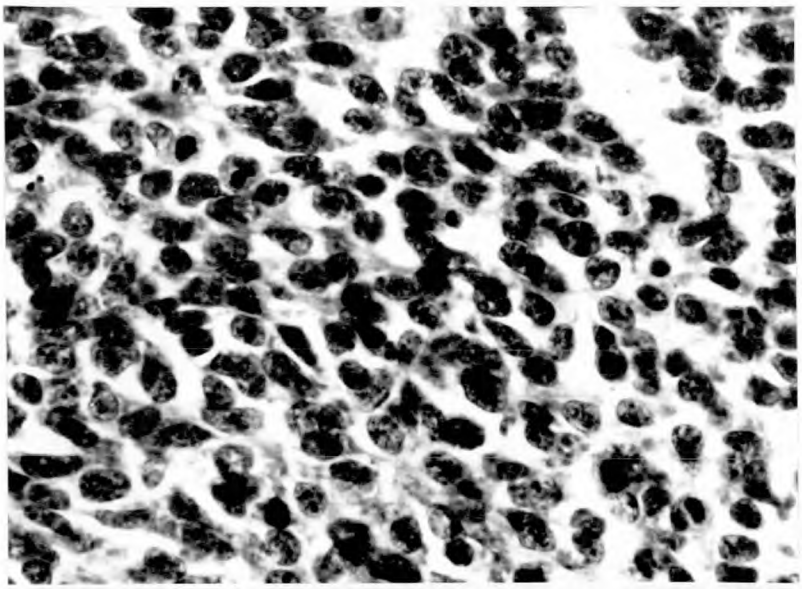


Fig. 4. Cat cell carcinoma, undifferentiated. No stromal reaction. H & E x 510

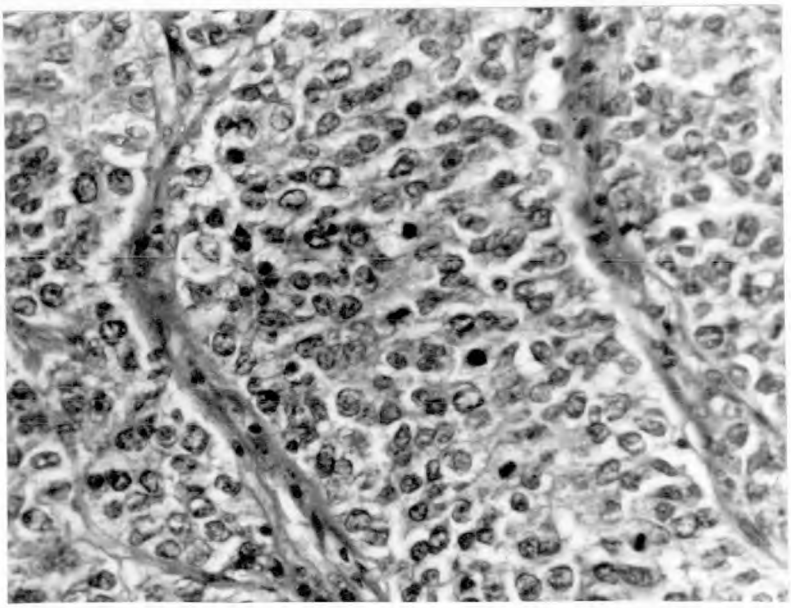


Fig. 5. Polygonal cell carcinoma. Alveolar strands thickened. No stromal reaction. H & E x 250

The specimens were fixed by filling with formol saline in the manner which is widely practised in thoracic pathology, and after fixation excised by parasagittal slicing. In all cases photographs were taken or diagrams made of the tumours and the anatomical and gross structure was described.

Tissue was taken from representative areas of the tumour for histological study. The routine stains used were haematoxylin and eosin, Weigert's elastic and Southgate's mucicarmine. The Hurdfield specimens were also stained with Masson's trichrome. Many sections of tumour were also stained with Alcian blue and periodic acid schiff for mucin, Lendrum's picro-Mallory for fibrin and Unna-Pappenheim for plasma cells.

All available lymph nodes were sectioned and microscopically examined - a total of 997 nodes, or an average of 8.75 per specimen. Serial sectioning of macroscopically negative nodes was done in 20 cases but the practice was discontinued because of negative results.

Note was always taken to make a distinction between metastatic and direct encroachment in a lymph node. A tumour was considered positive whether one or more nodes were metastatically involved.

Attempts were made to trace the presence of fibrin in and around pulmonary tumours with the help of Coons' fluorescent technique (Coons and Kaplan, 1950). O'Meara (1958, 1960) has suggested that fibrin is laid down by tumour cells as a

scaffolding or matrix on which they can grow. Extravascular fibrin has been demonstrated in some human tumours by Hiramoto et al. (1960). Crawford and Woolf (1960) showed that the fluorescent antibody method was much more sensitive for the detection of fibrin in the tissue sections than conventional histological stains. Our results, however, were not promising and O'Meara's findings could not be confirmed.

MATERIAL

The series of tumour studied comprised 114 specimens (101 specimens from Harefield Hospital[+] and 13 from St. Mary's Hospital). These cases were selected from a consecutive series. Twenty-two of the cases were pneumonectomies, 86 were lobectomies, and 6 were segmentectomies.

The salient features of the cases are presented in tabular form on page

Site of tumour

Right		Left	
Upper lobe	41	Upper lobe	31
Lower lobe	25	Lower lobe	13
Middle lobe	4		44
	70		

In the lower lobe the dorsal segment on the right side contained 17 tumours and the left dorsal segment contained 10 tumours.

The upper lobes and the dorsal segments of the lower lobes were the sites of tumour in 99 cases. There were only 13 cases in the basal segments of the lower lobes. Histology of the cases is shown in Table I.

[+]It is doubtful if the project would have been possible without access to the wealth of material at Harefield of peripheral lung tumours recently forthcoming as the result of mass radiography.

Histology of 114 Resected Peripheral Lung Cancers Compared with Walter and Pryce's Peripheral Group

Table I

Histological type	Present Series No.	%	Walter & Pryce 1955 No.	%
Adenocarcinoma	37	32	27	31
Squamous cell carcinoma	35	31	35	41
Polygonal cell carcinoma	25	22	13	15
Oat cell carcinoma	17	15	11	13
Total	114		86	

RESULTS

METASTATIC SPREAD

The observations showed that histological type was of the first importance (Fig. 6). As is generally accepted the oat-called type was the most malignant. The least malignant was the squamous-called type. The adenocarcinomas were of intermediate malignancy but were associated with much wider degrees of differentiation. The dispersal of metastasis was more widespread. The polygonal cell tumours (which are the undifferentiated adenocarcinomas and squamous carcinomas) are considered separately.

Oat cell carcinoma

The average size and dispersal was smaller than any other group. The average size was 4 cm. and the scatter between 2-6 cm.

The metastatic rate to lymph nodes was highest. Eleven of a total of 17 tumours were positive, i.e. 65 per cent (Fig. 7).

Squamous carcinoma

The average size was 6.2 cm. The tumours were scattered over a wide range (2-11 cm.).

The metastasising rate to lymph nodes was less than any other group. Eleven out of 35 tumours showed positive glands, i.e. 31.5 per cent.

It should be noted that below 5.2 cm. there were 13 tumours devoid of any metastases. Even above this size the metastasising rate was only 50 per cent: 11 tumours with and 11 tumours without

metastases. It should be carefully noted that this benign type of growth when of large size does metastasise, (Fig. 8).

Adenocarcinoma

The tumours varied in size from 1.5 cm. to 10 cm., the average size being 4.25 cm. It was quite obvious from a consideration of size alone that these tumours varied widely in malignancy. The average size was close to the oat cell tumours while the size range corresponded to that of the squamous tumours. The metastasising rate was intermediate. There were 15 tumours with and 22 tumours without metastases, a rate of 40.5 per cent. (Fig. 9).

Polygonal cell carcinoma (Undifferentiated squamous and adenocarcinomas)

The tumours varied in size from 2.5 cm. to 12 cm., the average size being 5.4 cm. The average size was intermediate between that of the squamous carcinomas and the adenocarcinomas, while the size range was even greater than that of the squamous carcinomas. The overall metastasising rate was 40 per cent, which is similar to that of the adenocarcinomas. The metastatic behaviour of this group, however, requires comment. The numbers thinned out between 4 cm. and 7 cm. so that the group appeared possibly to be composed of two separate entities. This is a conception which we had previously entertained about the group from purely morphological considerations, (Fig. 10).

The essential findings are presented in Table II.

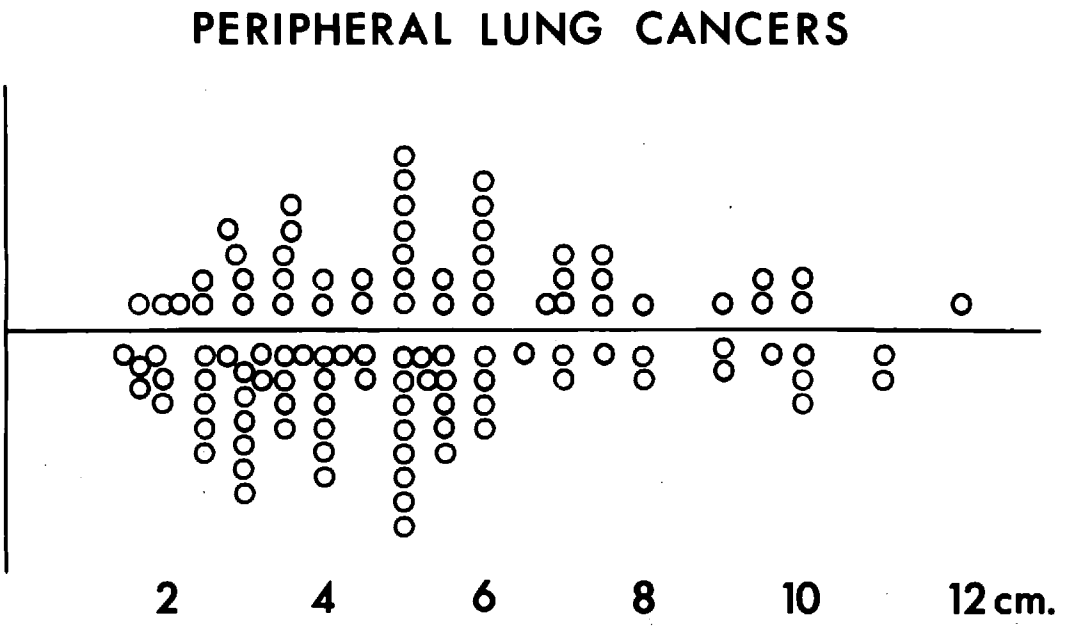


Fig. 6. 114 peripheral lung carcinomas. Distribution according to size and lymph node metastasis (tumours above the line showed lymph node metastasis).

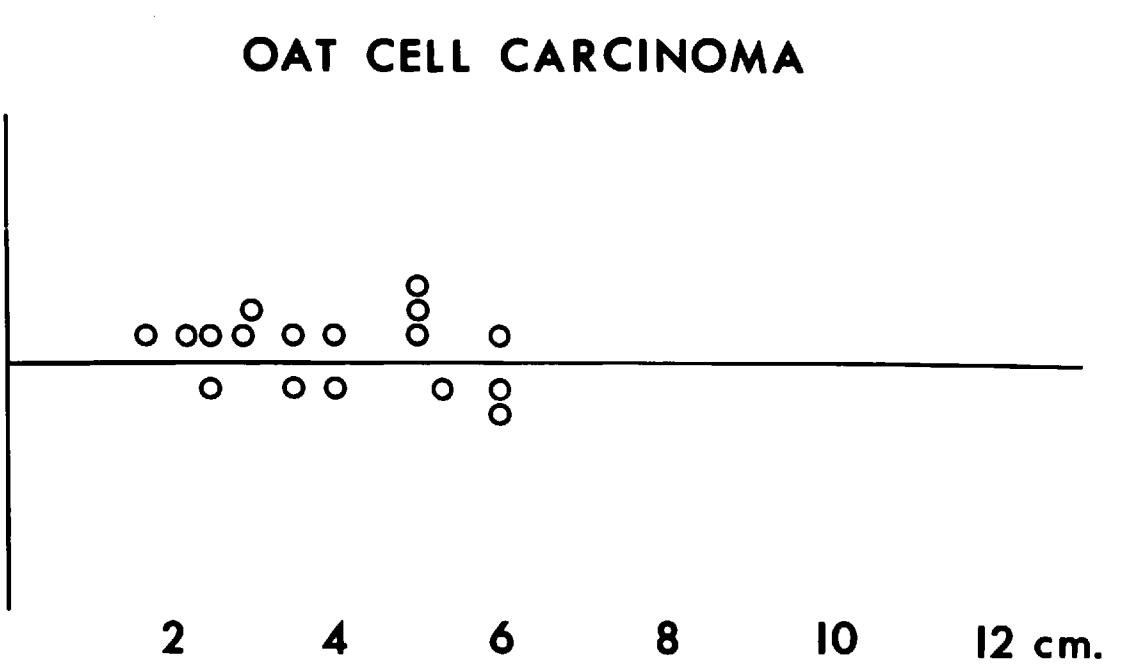


Fig. 7. 17 peripheral oat cell carcinomas of lung. Distribution according to size and lymph node metastasis.

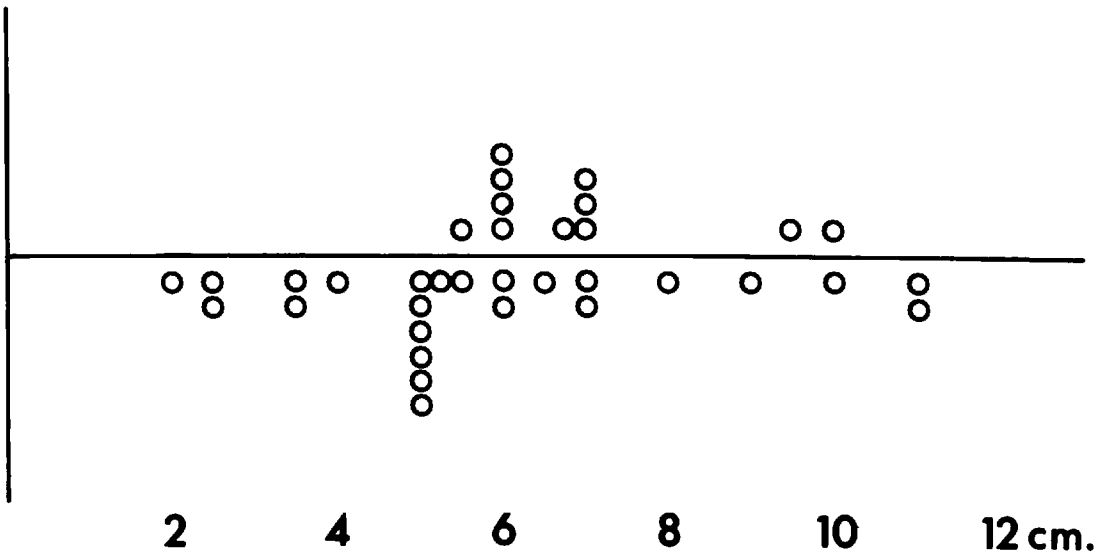


Fig. 8. 35 peripheral squamous carcinomas of lung. Distribution according to size and lymph node metastasis.

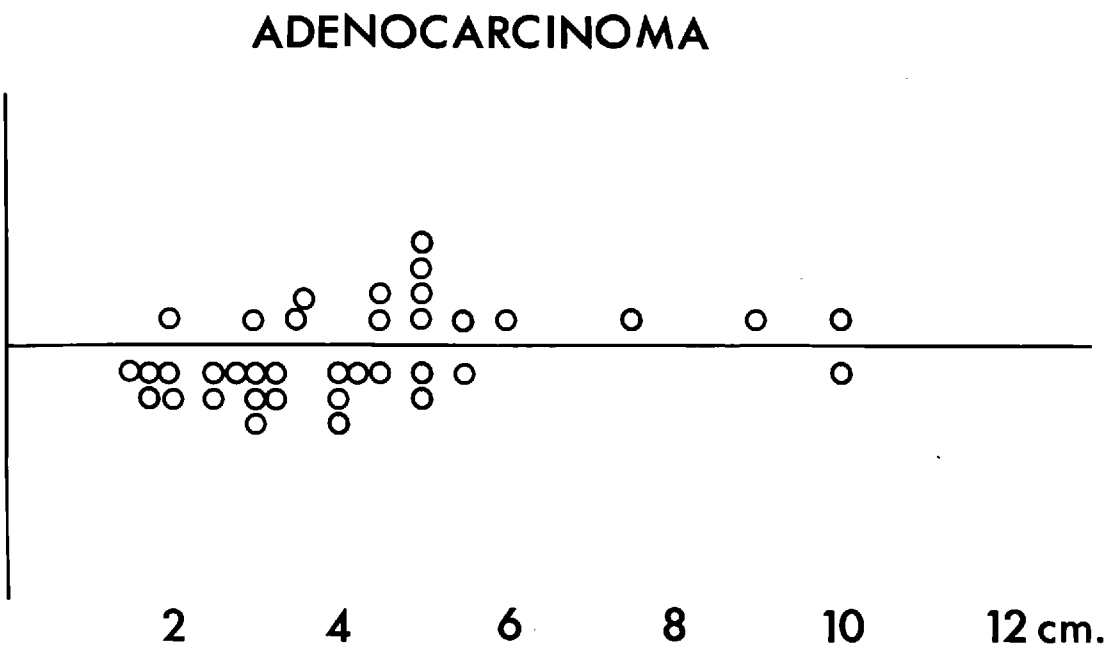


Fig. 9. 37 peripheral adenocarcinomas of lung. Distribution according to size and lymph node metastasis.

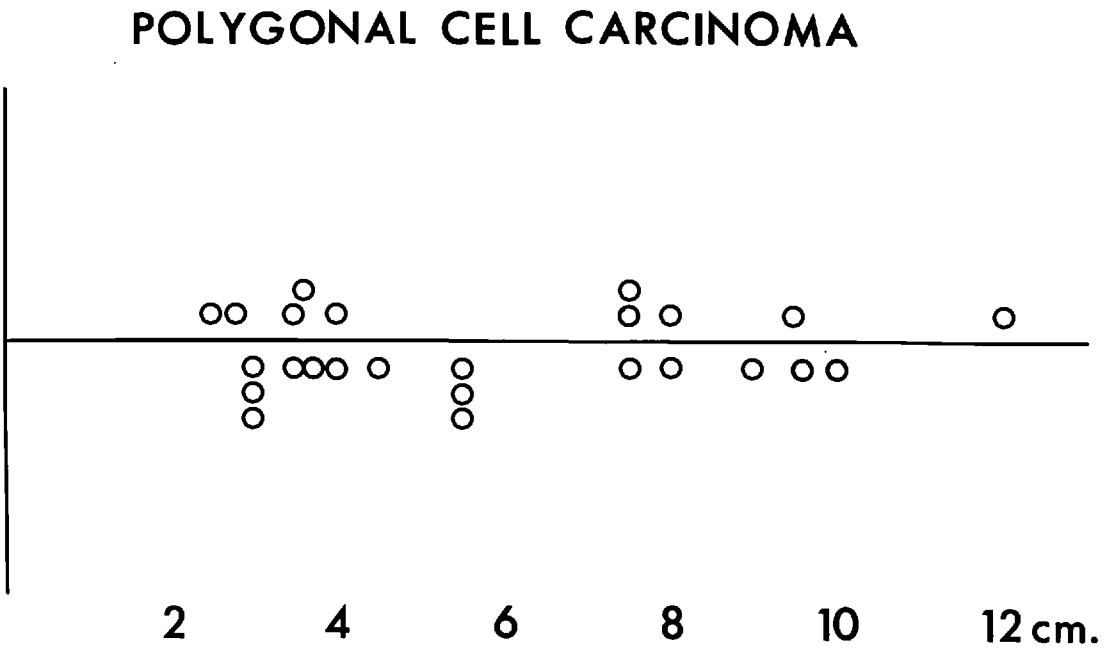


Fig. 10. 25 peripheral polygonal cell carcinomas. Distribution and size of lymph node metastasis.

Table II

Metastatic rate, average size and size range of the different histological types

Histological type	Metastatic rate	Average size	Size range
Adeno-carcinoma	40.5%	4.25	1.5 - 10 8.5 cm.
Squamous carcinoma	31%	6.2	2 - 11 9 cm.
Polygonal cell carcinoma	40%	5.4	2.5 - 12 9.5 cm.
Oat cell carcinoma	65%	4.2	2 - 6 4 cm.

HISTOLOGICAL APPEARANCES

With each tumour type attention was directed particularly to the following histological features which it was considered might be of importance in cases with metastases:

Vascular infiltration (of veins and/or arteries).

Similar infiltration of lymphatic channels,

differentiation of growth, fragmentation of the advancing edge (? nature of advancing edge, i.e. peripheral fragmentation or compression).

Mitotic activity and necrosis.

The reactivity of the host cells was also carefully scrutinised.

Vascular invasion

This was so common as to be of doubtful significance. One got the impression that if seriously searched for this would be present in almost every case. Actually it was observed in 96 cases, i.e. 84.2 per cent. The data is more fully presented in Tables 3 and 4. (See Figs. 11 and 12).

Lymphatic channel invasion

This was undoubtedly present in a larger number of cases than the number in which it was seen. But as an obvious feature it definitely appeared to have significance so far as lymph node metastasis was concerned, (Fig. 13).

The data is presented in Table V.



Fig. 11. Artery showing infiltration by oat cell carcinoma. Elastic stain x 40

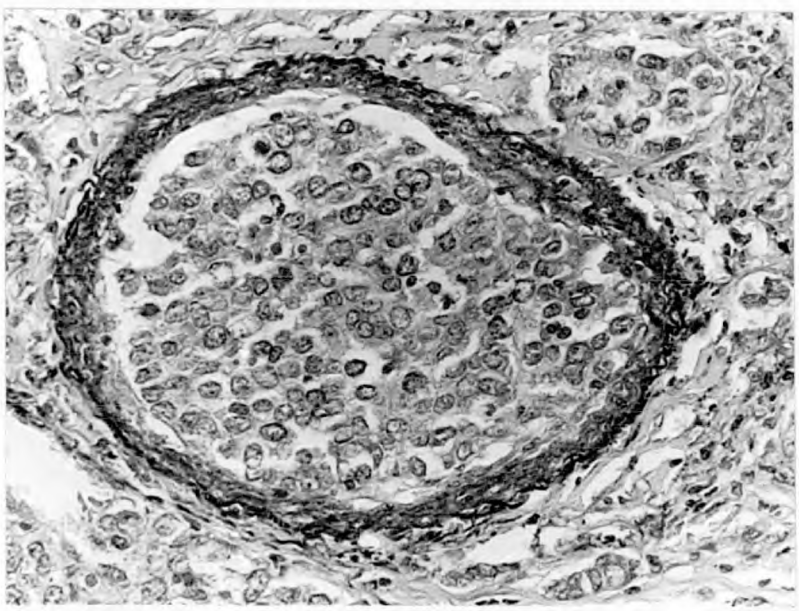


Fig. 12. Vein occluded by polygonal cell carcinoma. Elastic stain x 250



Fig. 13. Oat cell carcinoma. Lymph channel invasion. H & E x 100

Incidence of Vascular Invasion in the Histological Types of Peripheral Lung Cancer

Table III

Histological type		Arteries alone	Veins alone	Arteries & veins	Nil	% of vascular invasion
Adeno ca.	37	6	6	16	9	75.6%
Squamous ca.	35	9	12	8	6	82.8%
Polygonal cell ca.	25	2	12	8	3	88%
Oat cell ca.	17	8	2	7	0	100%
Total	114	25	32	39	18	84.2% (61%)

The figure in brackets indicates % of gross vascular invasion as observed by Walter and Pryce (1960) in peripheral tumours.

Table IV

Vascular invasion and lymph node metastasis
in 114 peripheral pulmonary carcinomas

Number of cases	Percentage	Arteries invaded	Veins invaded	Glandular metastases
12	10.5	+	-	-
13	11.4	+	-	+
19	16.5	+	+	+
20	17.5	+	+	-
20	17.5	-	+	-
12	10.5	-	+	+
3	2.6	-	-	+
15	13.2	-	-	-
114	99.7			

Table V

Relationship of lymph channel invasion and metastases

Histological type	Cases with lymph channel invasion	Cases without invasion
Adeno-carcinoma	7 cases (mets. in 57%)	30 cases (mets. in 37%)
Squamous carcinoma	6 cases (mets. in 50%)	29 cases (mets. in 20%)
Polygonal cell carcinoma	3 cases (mets. in 66%)	22 cases (mets. in 41%)
Oat cell carcinoma	9 cases (mets. in 88%)	8 cases (mets. in 38%)
	25 cases (mets. in 68%)	89 cases (mets. in 33.7%)

Differentiation

The importance of this with regard to malignancy has long been recognised.

In lung cancer it is an obvious feature in the squamous and the adenocarcinomatous tumours. Only recently however (Walter and Pryce, 1955 and 1960; Aszopardi, 1959) has the differentiation of rosettes, tubules and foliated sheets been recognised as a marked feature in many cases of oat cell tumour, even though its occurrence was well described as far back as 1926 (Shennan). The undifferentiated members of the squamous carcinomas and adenocarcinomas are often not easy to distinguish and are grouped together as polygonal tumours.

Fragmentation

Alveolar exfoliation of tumour cells at the periphery is a feature of lung carcinoma. It is undoubtedly helped by the spongy structure of the lung and the constant movement. Fragmentation is probably due to loss of adhesiveness between the tumour cells. This appears to be of significance in the A - C contrast. Data is presented in Table VI. (See Fig. 14 and 15).

Mitotic activity

This varied widely in the different groups and no correlation with metastases was observed.

Necrosis

Necrosis of tumour was present in a large number of cases. Data is presented in the results.

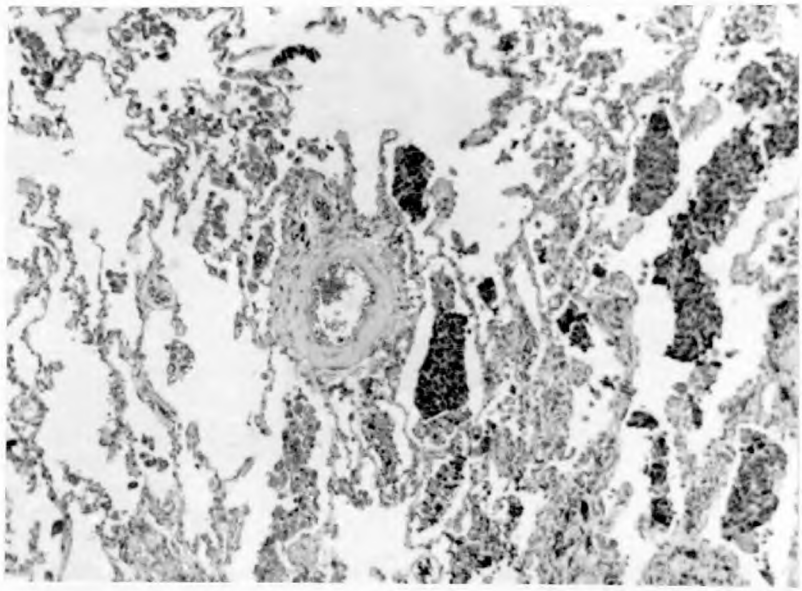


Fig. 14. Oat cell carcinoma showing fragmentation (alveolar exfoliation) at the periphery of tumour. H & E x 100

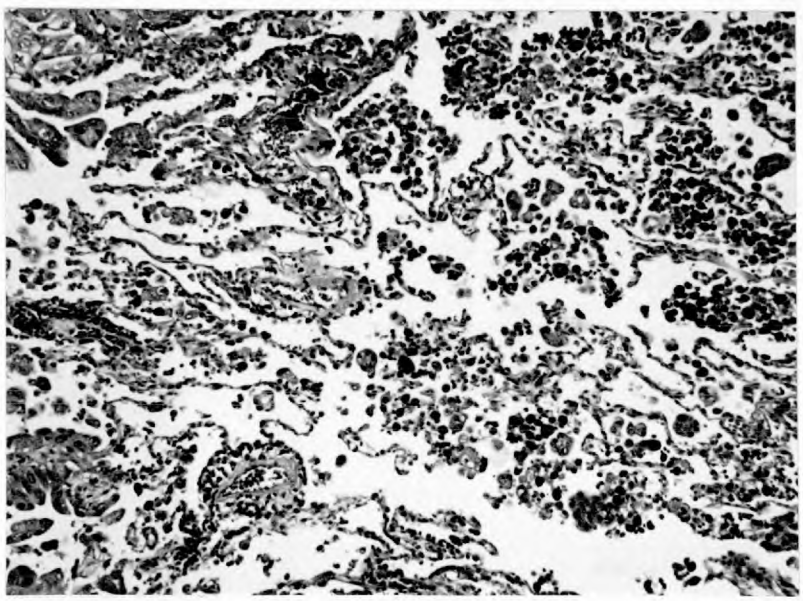


Fig. 15. Adenocarcinoma showing marked fragmentation (alveolar exfoliation) at the periphery of tumour. H & E x 100

Stromal reaction

Cellular infiltration of the tumour, especially at the margin, was studied. This was characterised by a predominance of lymphocytes and plasma cells; some sprinkling of eosinophils and polymorphs was also present. In a few cases giant cell reaction was observed. Scirrhous reaction in the tumour and fibrosis at the periphery were also studied (Fig. 16).

1. Oat cell carcinoma

As can be seen in Fig. 17, of the 11 cases with metastases 4 were differentiated (36 per cent).

Of the 6 cases without metastases 5 were rosetted (i.e. 83 per cent).

It will be noted that all but one of the 8 undifferentiated tumours (88 per cent) had given rise to lymph node metastases.

The cell size also seems important (see Fig. 18). Only 2 of the 11 tumours with metastases were of the large cell type (i.e. 18 per cent), while of the 6 tumours without metastases 4 were of the large cell type (i.e. 66 per cent).

Fragmentation was present in all 17 cases.

Mitotic activity: No correlation was found between the frequency of mitosis and metastasis.

Necrosis was a prominent feature in 8 of the 17 cases. Of these 4 showed metastases. It is possibly related to a factor (extrinsic or intrinsic) which influences metastasis. Thus, in the 9 cases showing no obvious necrosis, metastases were present in 7 cases (77 per cent).

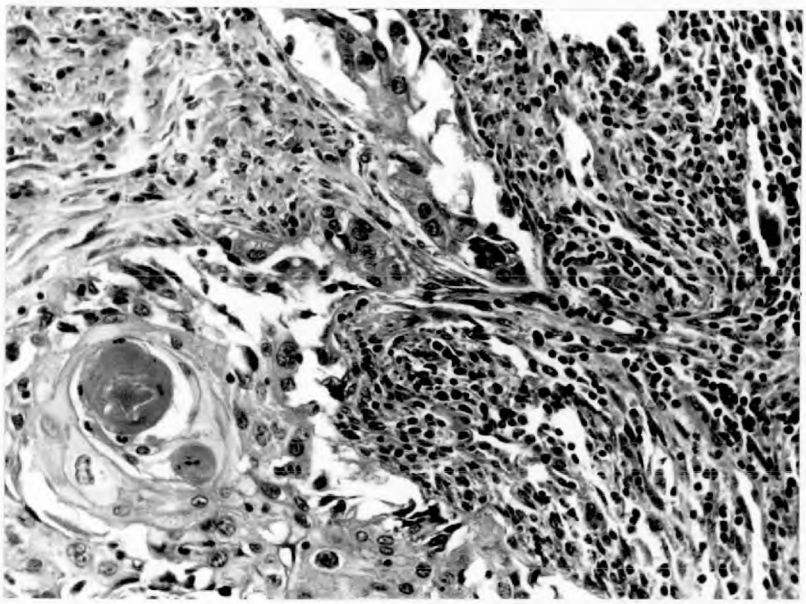


Fig. 16. Well differentiated squamous carcinoma showing stromal reaction.

H & E x 250

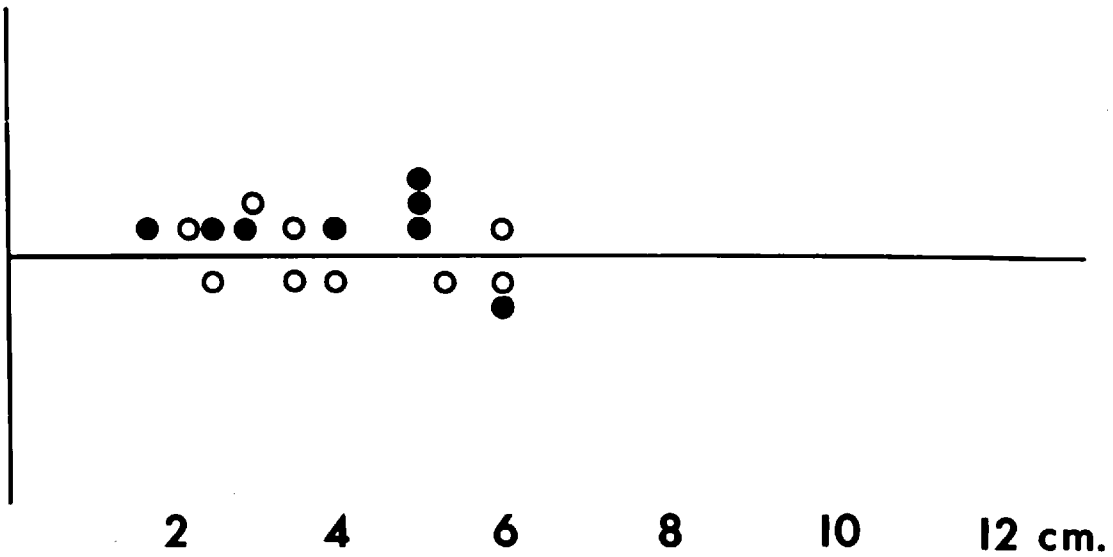


Fig. 17. Differentiated and undifferentiated oat cell tumours. Distribution according to size and lymph node metastasis.

Dark circles = undifferentiated tumours
Open circles = differentiated tumours (rosettes or tubules etc.)

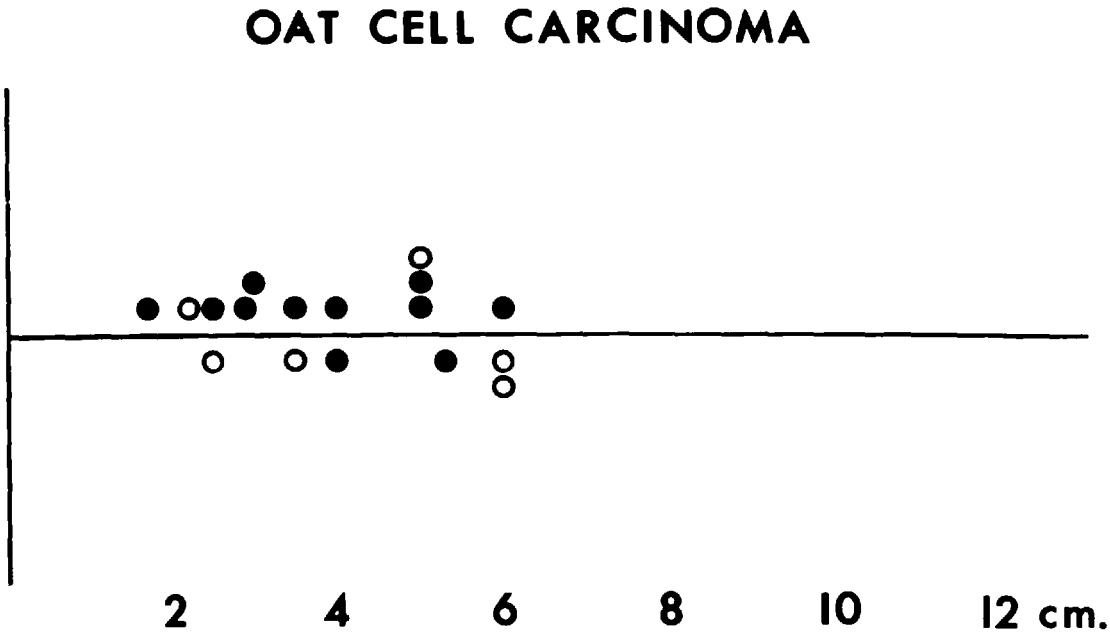


Fig. 18. Oat cell carcinoma. Cell size related to lymph node metastasis.

Dark circles = small celled tumours
Open circles = large celled tumours

2. Squamous carcinoma

Vascular invasion was present in 29 of 35 cases (see Fig. 19 and Table III in which the incidence is separately given for arteries and veins).

Eighteen of the 35 squamous tumours were well differentiated and keratinised. In these, lymph node metastasis was present in 5 (28 per cent).

The only observation of note was a slightly greater tendency to keratinisation with increasing tumour size. Thus, in the 6 tumours below 5 cm. it was not a feature, while in the 29 tumours of this size and over it was present in 18 cases (62 per cent) and in the 7 tumours of 8 cm. and over it was present in 5 cases (71 per cent).

It is doubtful, however, if this has any influence on the metastasising rate to lymph nodes (Fig. 20).

All that could be concluded was that increasing tumour size in surgical material goes with decreasing malignancy and also with increasing keratinisation.

3. Adenocarcinoma

There were at least 6 tumours which could be recognised as A's but only 1 C was available and a satisfactory comparison is not possible.

Actually, however, there is nothing in this data which in any way supports the generally accepted view (and our own preconceived ideas) that differentiation is associated with lesser malignancy. Of the 6 A tumours all but one were well differentiated.

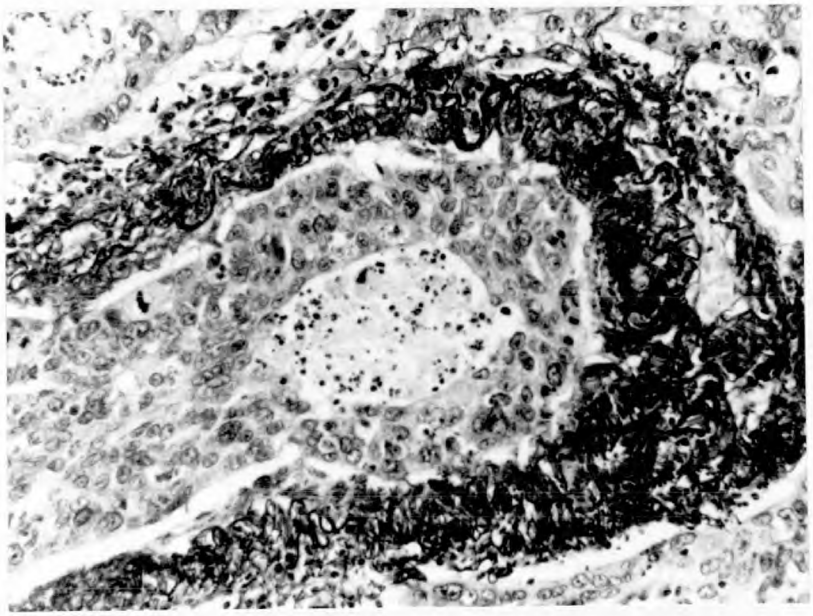


Fig. 19. Squamous carcinoma showing invasion of artery. Tumour shows central necrosis and mitotic figures.
Elastic stain x 250

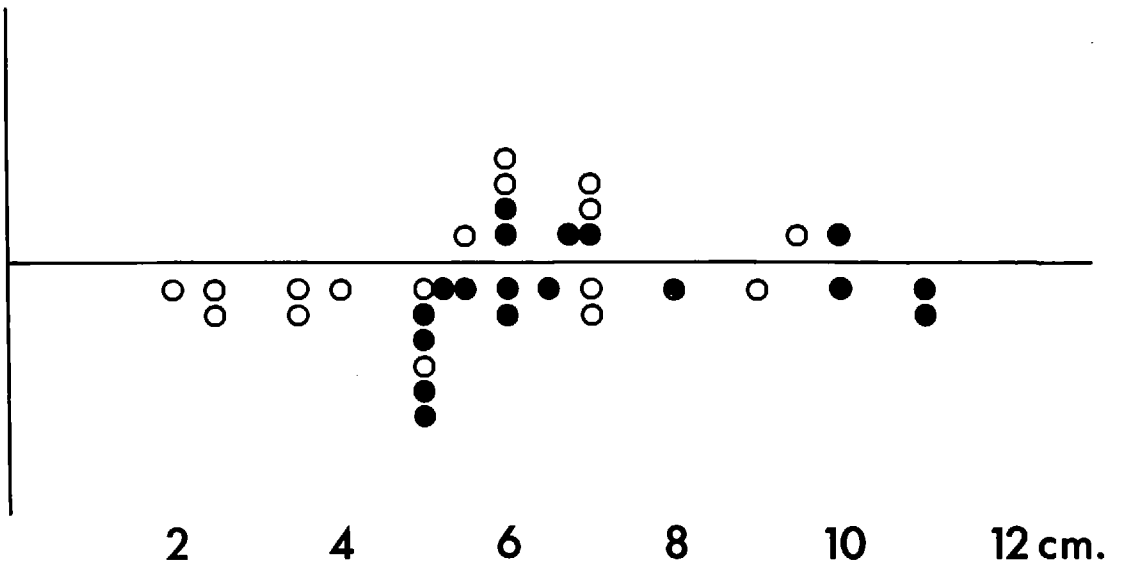


Fig. 20. Squamous carcinoma. Distribution of keratinising tumours related to lymph node metastasis.

Dark circles = keratinising tumours

4. Polygonal cell carcinoma

These tumours presented a complex and interesting picture. From the accompanying graph (Fig. 21) it can be seen that there was a group of tumours (A) which metastasised even when small and a group (C) which did not metastasise even when large. It is the mixed (M) group which is of particular interest because, of these, some are going to metastasise or have already had occult metastasis and the rest will have a comparatively benign course and end up as the C group.

Differentiation: They were probably undifferentiated members of the squamous carcinomas and adenocarcinomas.

Fragmentation was not a prominent feature in the polygonal cell carcinomas. It was present in 6 of the 25 cases. Metastasis in lymph nodes was present in 4 of these cases.

Mitotic activity: No correlation with metastasisability was observed.

Necrosis: Fifteen tumours showed necrosis of growth. Four cases showed metastases - a rate of 27 per cent.

Stromal reaction: Cellular infiltration of the tumour stroma and cellular reaction at the periphery of the tumour was observed in 13 cases. Only one of these cases showed lymph node metastasis, (Fig. 21).

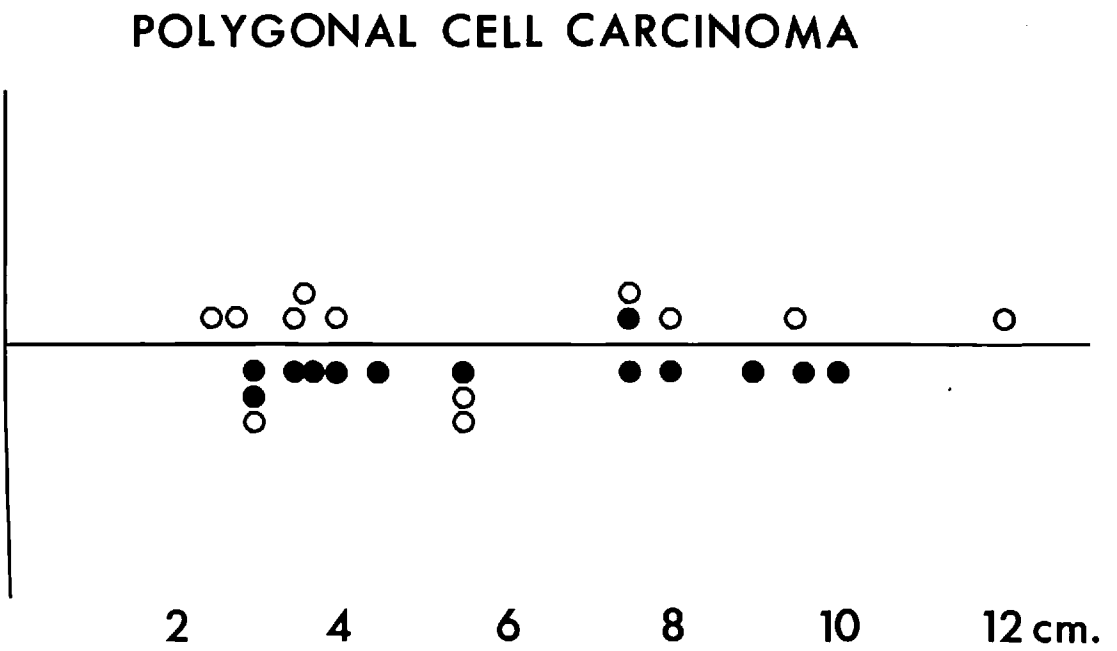


Fig. 21. Polygonal cell carcinoma. Stromal reaction related to lymph node metastasis.

Dark circles = tumours showing good stromal reaction

INFLUENCE OF LOCAL FACTORS ON LYMPH NODE METASTASIS

Inspection of the composite graph (Fig. 6) shows that the metastasising rate of the lung cancers studied varied little from the general average of 41 per cent when the different sizes were considered. The tumours which were 4 cm. and below showed a metastasising rate of 34 per cent, the tumours of 8 cm. and above 41 per cent, and the tumours between 4 and 8 cm. a slightly higher rate of 48 per cent. It is apparent that the lymph node metastasing rate for peripheral tumours which is acceptable to the surgeon is about 50 per cent.

Only with the polygonal tumours are all 4 groups (A, B, C and M) represented. The impossibility of making an A - C contrast with the 3 definitive histological types is not due to the paucity of cases but to the intrinsic characteristics of these tumours.

Histological types

The separate graphs for the different histological types (Figs. 7, 8, 9 and 10) show very striking differences from the composite graph and from each other. The highly malignant oat cell tumours in surgical specimens tend to be small, and in the present series of cases there are no B or C tumours. The squamous tumours are spread out over a wide size range but there are no A tumours. The adenocarcinomas, which are of intermediate malignancy, have an equally wide distribution but have only one representative of group C. Only with the polygonal tumours are

all 4 groups (A, B, C and M) represented.

The frequency and distribution of blood vascular infiltration is shown in Fig. 22 and Table III. It was so common that we had the impression that if sufficiently searched for it would be found in almost all cases. It is obviously of importance in haematogenous dissemination but, as it is as frequent in cases with as in cases without lymph node metastases, it cannot be of any importance in the present investigation.

Lymph channel invasion is clearly of more importance. Undoubtedly it would have been found more often if the investigation had been more prolonged but the recorded results (demonstrated in the composite graph, Fig. 23, and in Table V) show that it is most frequent in A tumours and very much less apparent in C tumours.

Tumour differentiation as a factor in lymph node metastasis could not be adequately studied by the methods used in the present investigation, because in the definitive histological types it was not possible, as previously stated, to make an A - C contrast.

With increasing size (which in surgical material means diminishing malignancy) the squamous tumours show a greater tendency to be keratinised (whether they are positive or negative with regard to lymph node metastases).

In the oat cell tumours it might be noted that of the

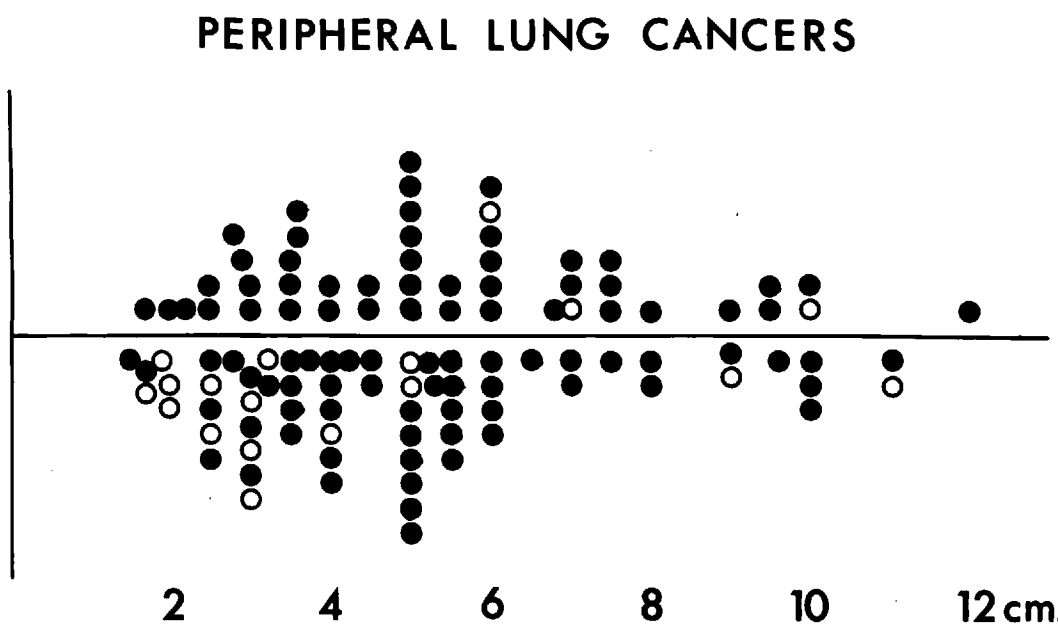


Fig. 22. Distribution of microscopic blood vascular invasion in 114 peripheral tumours.

Dark circles = arterial invasion or venous invasion or both

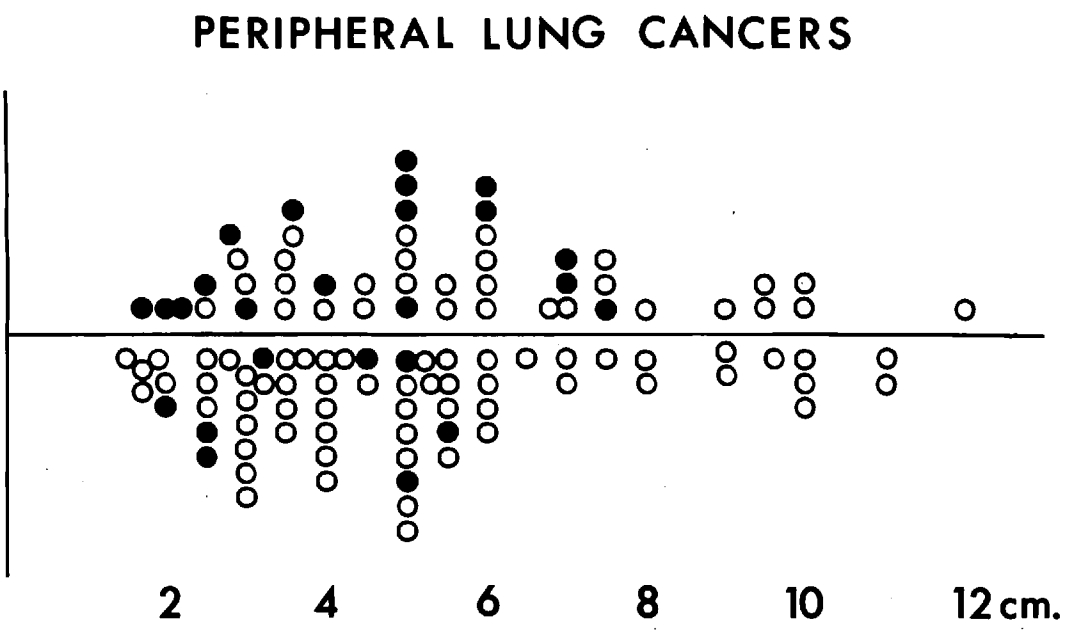


Fig. 23. Distribution of obvious lymph channel invasion in peripheral lung tumours.

Dark circles = lymph channel invasion

9 cases showing rosettes 4 showed positive nodes (44 per cent).

With the adenocarcinomas we were surprised to see how many of the tumours in group A were well differentiated. Even though we had previously encountered cases of well differentiated adenocarcinomas with metastases and cases which had shown only a short post-operation survival time, it was still surprising that this should be so frequent.

The fragmentation results are also significant. As can be seen in Fig. 24 the process is most common in A tumours and very uncommon in C tumours.

Nothing of any interest emerged from the observations of mitotic activity.

In the oat cell carcinomas gross necrosis of the tumour was present in 8 cases and of these 4 had positive nodes. In the 9 cases showing no necrosis 7 showed lymph node metastases.

Stromal reactivity has a distribution in the composite graph which is the reverse of that of the lymph channel invasion and fragmentation (Fig. 25) and it is possible that it is more important. This is suggested by case O 14 (Figs. 26 and 27), the only case of oat cell tumour with a marked stromal reaction alive and well 2 years after operation. This is remarkable for an oat cell tumour.

If group A is defined as those tumours with metastases which are 4 cm. or less in diameter, and group C as those without metastases which are 8 cm. and over, then these 2 groups are made up as follows (Table VI).

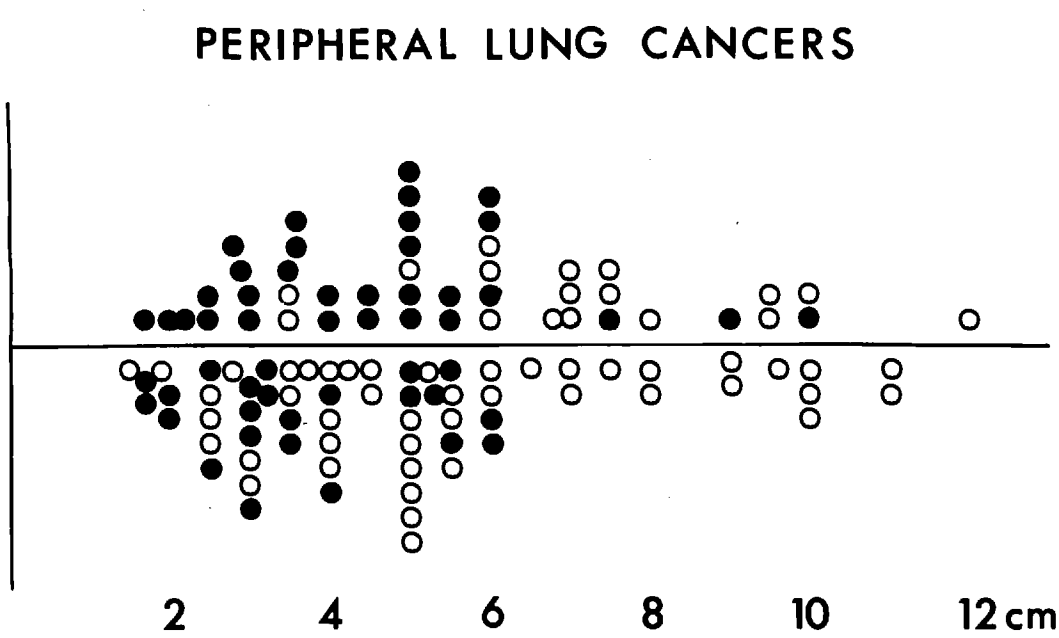


Fig. 24. Distribution of tumours showing fragmentation (alveolar exfoliation) in 114 peripheral tumours.

Dark circles = tumours showing fragmentation

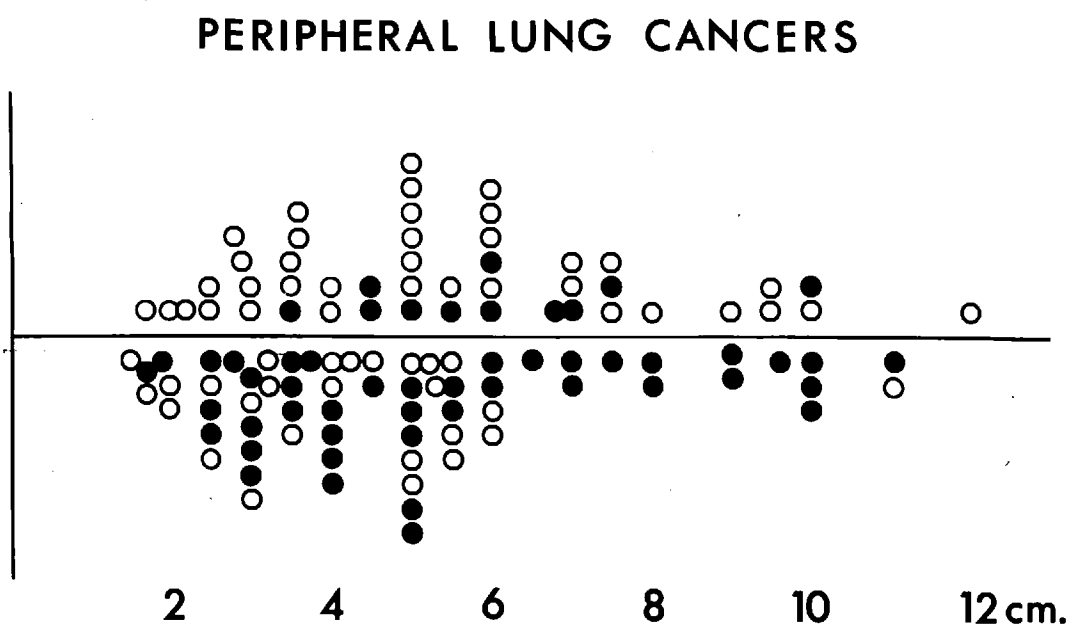


Fig. 25. Distribution of tumours showing conspicuous stromal reaction.
Dark circles = tumours showing stromal reaction

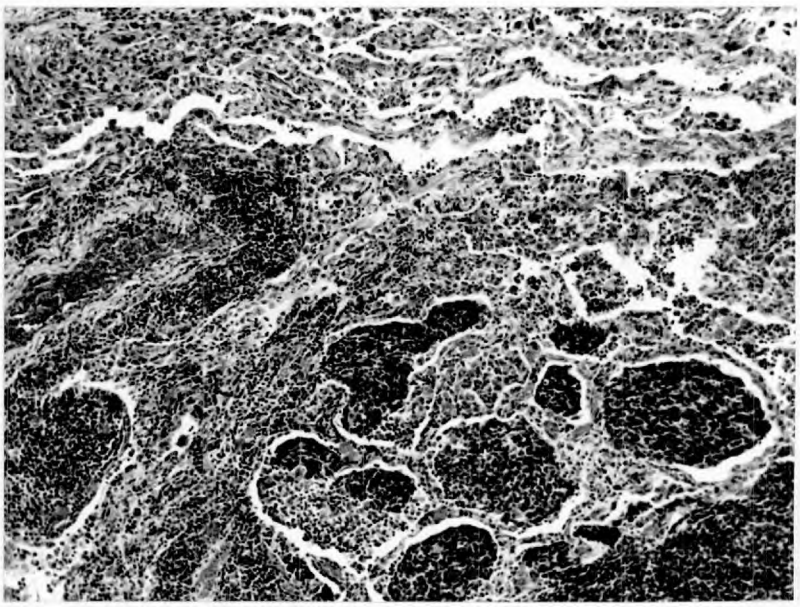


Fig. 26. The only oat cell tumour (O 14) showing good stromal reaction. H & E x 100

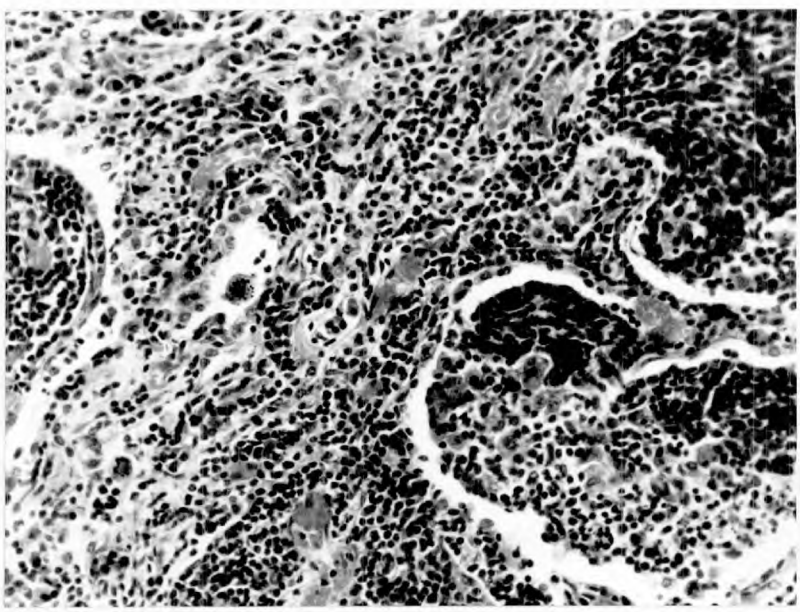


Fig. 27. High power view of the dense lymphocytic infiltration at the periphery in O 14. H & E x 250

Table VI

Histological characteristics of 16 group A tumours (early metastasising) and 10 group C (less malignant) tumours

GROUP A	Number of cases	Lymph channel invasion	Fragmentation	Stromal Reaction
Adenocarcinoma	4	2	3	1 (?)
Squamous carcinoma	0	-	-	-
Polygonal cell carcinoma	5	2	4	0
Oat cell carcinoma	7	4	7	0
	16	8	14	1 (?)
GROUP C				
Adenocarcinoma	1	-	-	1
Squamous carcinoma	5	-	-	4
Polygonal cell carcinoma	4	-	-	4
Oat cell carcinoma	0	-	-	-
	10	0	0	9

DISCUSSION

The reason for the relatively poor surgical results in lung cancer is not merely the malignancy of many of the tumours but also the very great vascularity of the organ. Provided the regional growth is successfully excised ultimate survival depends on the occurrence of distant metastases. In the lung the vascularity is so great and cancerous invasion of arteries and veins so common that the chances of haematogenous dissemination are always high. Much of this dissemination apparently takes place during the operation itself, and better results may be expected with preliminary ligation of the hilar veins, as advocated by Aylwin (1951). The scale on which venous invasion occurs appears to be important. Mohl's (1962) figures are: cases with gross venous invasion had an 18 per cent 4 year survival; cases without gross venous invasion had a 40 per cent 4 year survival. The importance of particle size in the formation of metastases has been emphasised by several other authors, e.g. Pryce and Heard (1956) in speculating on their results with experimental emboli, and Zeidman et al. (1950) in tumour transplantation experiments in mice which showed that it was the size of the tumour embolus and not the number of cells injected that mattered in the formation of metastases, also seen by Watanabe (1954). The vast numbers of circulating cancer cells which have been described in malignant disease

obviously must nearly all die (e.g. Engell, 1955; Moore, 1957). When one considers the great frequency of vascular invasion in lung cancer and the limited number of visceral metastases at post-mortem in the average case it is almost equally certain that the great majority of embolising clumps also perish. The occasional survival of such fragments and the development of metastases appears to be a complex process involving factors inherent in the tumour cells and factors in the host.

The distribution of metastases in the body is influenced by the differential blood supply and various other mechanical factors such as muscle contractility, and also by the metabolic environment provided by the different viscera. The present paper deals only with metastases in the regional lymph nodes but the factors dealt with (infiltration, cohesiveness, necrosis and stromal reaction) are factors which influence the development of metastases at any site.

Infiltrability: In lung cancer this is most strikingly instanced by the invasion of arteries and veins - which is so frequent as to be almost constant. It is a factor which is directly concerned only with visceral metastases but it is indicative of the probable presence of the process by which lymph node metastasis occurs, viz., infiltration of lymphatic channels. It is almost certain that if sufficiently searched for invasion of lymph channels would be found in all cases, but it seems likely that it was recorded only in those cases in

which it was very obvious. The recorded results show a direct correlation with lymph node metastasis and, as in the case of haematogenous metastasis, point to the importance of a quantity factor. Gross venous invasion is important in haematogenous dissemination; gross lymph channel invasion is important in lymph node metastasis. Hukill and Stern (1962) observed that lymphatic invasion was one of the factors associated with a poor prognosis.

Cohesiveness: The separation of cells from the periphery of a growth is of fundamental importance in connection with the present problem. Loss of cohesiveness in many lung cancers shows up histologically in the exfoliation of tumour cells into the adjacent lung. This appearance, which we have referred to previously as peripheral fragmentation is the same process as leads to the separation of malignant cells in the lymph and the blood. It leads to the occurrence of tumour cells in the sputum, which is regarded by Hukill and Stern (1962) as another of the factors associated with a poor prognosis. The cohesiveness of normal cells is remarkable. Although the subsequent inflammatory changes may later induce much exfoliation, the most delicate epithelial surfaces, such as that of the stomach and bronchi, often withstand the most vigorous friction without much cellular loss. The cohesiveness of malignant cells has been studied and actually measured and has been found to be significantly less than that of corresponding normal cells (Coman, 1944; McCutcheon et al., 1948).

Necrosis: Tumours differ greatly with regard to this factor which presents many aspects. In the squamous tumours the cells have a tendency to die as part of the keratotic process. This takes place away from the vascular stroma but sometimes extends right up to it. Necrosis due to anoxia begins suddenly at a depth of 160 - 180 μ from the capillary stroma (Thomlinson and Gray, 1955). Then, quite apart from infarctive and infective and therapeutic necrosis, there is also sometimes seen a necrosis which may affect the whole of a large tumour and which may be due to a defence mechanism of an essential sickness of the cells. This lack of viability, which is usually associated with tumours devoid of metastases, appears to be intrinsic. In the investigation of the present series of lung tumours conscientious regard was given to this process but no definite conclusions were reached, except possibly in the oat cell tumours. Here an A - C contrast was not possible but comparing the A with the M tumours it is seen that necrosis was an obvious feature: oat cell tumours showing no obvious necrosis - metastases in 77 per cent; cases showing necrosis - metastases in 50 per cent. It seems obvious that impairement of viability would be a potent factor militating against the survival of disseminated tumour cells.

Stromal reactivity: Cellular infiltration of tumours had been observed by MacCarty as far back at 1922. He investigated the longevity in a large series of carcinomas of breast,

rectum and stomach and found that cellular infiltration, hyaline fibrosis and differentiation were important factors in long term survival. Black and Speer (1954, 1958 and 1960) in some recent papers have studied lymph node reactivity as a criterion of host resistance in cases of breast cancer and have found significant correlation with survival. Berg (1956) in a similar study of lymph nodes was unable to repeat Black and Speer's findings, but in a later study Berg (1958) observed that cellular infiltration in the tumour (lymphocytic and plasmacytic) was important and probably an exhibition of host resistance. In my opinion stromal reaction is perhaps the most important factor in the spread of tumour. In this investigation the only oat cell tumour (O 14) to show stromal reaction was from a patient who is alive and well 2 years after operation. Of the A tumours only one case (A 3) was found with a stromal reaction and re-examination of this case showed that the response was absent at the periphery.

Histological tumour types: The present investigation confirms the generally accepted view with regard to the relative malignancy of the different histological types: the oat cell carcinomas are the most and the squamous cell carcinomas the least malignant, while the adenocarcinomas are of intermediate malignancy. But it seems that a closer assessment of malignancy may be possible by taking into account the ancillary factors which have just been considered. All the

oat cell tumours showed peripheral fragmentation and only one showed stromal reactivity; this case, O 14 (see Figs. 26 and 27), was without lymph node metastasis and is still alive and well 2 years after operation. Cure in this case can hardly be expected, but the survival time is remarkable for this type of tumour. There were no squamous tumours of small size with lymph node metastasis. Those of large size without metastasis showed no fragmentation, were well differentiated and exhibited good stromal reaction in 4 out of 5 cases. The adenocarcinomas gave surprising results as far as differentiation is concerned and that point is discussed later. There was only one C tumour among this group so that a proper A - C contrast was not possible, but stromal reaction, lymph channel invasion and fragmentation were obviously significant factors (see Table VI).

One of the great surprises of the present investigation was the lack of uniformity in the results obtained with the undifferentiated large cell polygonal group.[+] It had been expected that the post operation survival in all these cases would be short but (using the peripheral polygonal tumours of the earlier series of Walter and Pryce) it was found that some lived only a short time while others were still alive after a considerable time (see Fig. 7, Appendix I B). And (looking at

[+] This lack of uniformity in the polygonal tumours is a very strong reason for <u>not</u> classifying the undifferentiated polygonal tumours with the oat cell tumours in an "anaplastic type." The frequent differentiation of the oat cell tumours is, of course, an equally strong reason.

the peripheral polygonal tumours of the present series in Fig. 10) it is seen that they also are obviously divided into 2 groups: those of small tumour size with metastases (A tumours) and those of large size without metastases (C tumours). This dual nature of the polygonal tumours has been recorded previously as the result of survival studies (Moersch and McDonald of the Mayo Clinic, 1953). The possibility of making the distinction immediately by the application of the 3 factors dealt with in this paper is a matter of some interest.

Another surprising finding was the lack of parallelism between differentiation and malignancy, which was well seen with the adenocarcinomas. Five of the 6 A tumours were well differentiated. This was also the experience of Moersch and McDonald who state: "The results of early studies that were carried out to classify carcinoma of the lung solely on the basis of grade of malignancy of the tumour according to the method of Broders were soon found to be of little or no clinical, surgical or prognostic value;" and of Fried (1959) who states: "There seems to be no sustained connection between the degrees of cellular differentiation and the tendency to metastasise. It has been found that anaplastic types remained confined to the lungs whereas the differentiated types metastasised." In all groups, but especially in the adenocarcinomas, fragmentation, lymph channel invasion and stromal reactivity

were apparently of much greater value than differentiation. No help was forthcoming from the recorded results of mucous secretion.

Clinical utility: The question remains, how are these various findings to be utilised in practice? Firstly, the surgical lung cancers should be differentiated as to site into central and peripheral tumours. These are so different that it is imperative that they should be considered separately. Strictly speaking the investigation has dealt almost entirely with peripheral tumours but some of the conclusions will apply also to central tumours (and possibly to tumours in general). Next, it is important to take into account the presence or absence of lymph node metastasis in relation to tumour size. As can be seen from a consideration of Fig. 6 the larger the tumour (provided it is still operable) the lesser, by and large, is the malignancy - a conclusion which was similar to that was previously arrived at by Haas (1948) in connection with breast tumours. This clearly divides the operable lung cancers into the 3 groups, A, B and C, of progressively lessening malignancy, and group M, which is a mixture of these 3 groups while they are still of small size. Histological typing should then be taken into consideration together with the ancillary histological appearances described above (gross lymph channel invasion, fragmentation and stromal reaction). Finally, a prognostic assessment of the case should

be committed to writing in order to test later the validity of the process.

In bringing this discussion to a close it may not be out of place to question the logical basis of the Oslo classification of lung tumours (Kreyberg, 1960). This combines the squamous cell tumours with the oat cell tumours and is, therefore, of no use at all to the surgeon in prognostication. It is also doubtful if it will stand the test of time regarding its claim to be of use in aetiology.

PROGNOSTICATIONS ON THE H TUMOURS

It is generally accepted (Overholt and Schmidt, 1949; Churchill et al., 1950; Berrie, 1952; Ochsner et al., 1954; Bignall and Moon, 1955; Gifford and Waddington, 1957, and many others) that cases with glandular metastases do badly with regard to survival. Lymph node metastasis can, therefore, be used to obtain data with regard to other factors affecting malignancy. In the present investigation a series of peripheral tumours has been arranged in order of size above and below a line according according to whether they have or have not metastasised. They were divided into 4 groups: 'A' tumours, which were of small size and showed lymph node metastasis; 'B' tumours, which were of large size with metastasis; and the 'C' tumours, which were of large size without any metastasis. The 'M' group was a mixture of A, B and C tumours when still small and free from metastasis.

By comparing the 'A' tumours with the 'C' tumours the following factors were seen to be significant:

1. Histological type.
2. Fragmentation.
3. Lymph channel invasion.
4. Stromal reactivity.

Taking these factors into account in 'M' tumours we differentiated them and predicted the prognosis.

There were 31 'H' tumours out of a total of 114. In 11 of these tumours adverse appearances were completely absent, i.e. there was no fragmentation or lymph channel invasion and a good stromal reactivity was observed. Of these 11 tumours with a good prognosis, 4 were squamous carcinomas, 3 adenocarcinomas and 4 polygonal cell carcinomas. There were no oat cell tumours among this group.

Complete confirmation of this prognostication must await the passage of another 5 years. If the system does not work, of course, this pragmatic test will reveal its flaws before that time.

A pilot test was also undertaken with the cases shown in Fig. 1 of Appendix I B, in which the survival time was known. The prognosis was arrived at on purely histological characteristics and without any knowledge of tumour size or metastasis. The prognostications were wrong in only 2 out of 20 cases. The first was a small tumour of 1.7 cm. diameter. This was an undifferentiated adenocarcinoma showing mucous secretion. Fragmentation, lymph channel invasion and a good stromal reaction were observed. We considered the patient would soon be dead but he was still alive 3 years after operation. This case had a strong stromal reaction and perhaps more attention should have been given to it. The other case was a well differentiated adenocarcinoma of 3 cm. diameter. This showed alveolar spread, no fragmentation and no vascular

or lymph channel invasion. Although there was no stromal reaction it was considered to have a good prognosis because of its being well differentiated. This patient died 9 months after operation.

It is believed that with the full facts known the prognostications might have been still more reliable and it is with this end in view a prospective study is given.

CONCLUSIONS

The preceding investigations on 114 peripheral lung carcinomas have brought out the following conclusions.

The relatively constant metastasising rate over the whole range of tumour sizes showed that the progressive elimination of bad ones, due to the passage of time, produces an apparent paradox that large tumours and tumours of long duration tend to do better than, or as well as, small and early tumours.

The different metastasising rates of the various histological types confirmed that histological typing has a place in lung carcinoma studies. The differences between the histological types were amplified when the oat-celled tumours and the squamous-celled tumours were compared, there being no C type of tumour among the oat-celled and no A type among the squamous-celled carcinomas.

The studies on the local factors which determine the spread of growth in carcinoma of the lung provided us with 3 factors which we think are of importance in spread of bronchogenic carcinoma. They are:

a) Fragmentation or alveolar exfoliation at the periphery.

b) Stromal reaction.

c) Lymph channel invasion.

Microscopically, blood vascular invasion was almost constantly present (84.2 per cent). The probability is that it is the gross degree of invasion that is of significance in haematogenous dissemination.

These studies, it is thought, might enable reliable prognostications to be made in resected cases of lung cancer. With the M group of tumours in the present series a prospective prognosis has been carried out.

114 peripheral tumours tabulated according to their salient features.

		pages
Adenocarcinoma	1 - 37	72 to 81
Squamous cell carcinoma	1 - 35	82 to 89
Polygonal cell carcinoma	1 - 25	90 to 95
Oat cell carcinoma	1 - 17	96 to 99

PERIPHERAL CARCINOMA OF LUNG

I ADENOCARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
1	M H2389/60	64	Lobectomy	L.U.L.	2	Pigmented scar	-	-	a+ V+	+	-
2	M H1791/59	43	Pneumonec-tomy	L.L.D.	3	Pigmented scar	+	-	V+	+	+
3	M H548/60	58	Lobectomy	L.U.L.	3.5	Pigmented scar	-	-	a+	+	+
4	M H731/61	54	Lobectomy	R.U.L.	3.6	Pigmented scar	-	-	a+ V+	+	+
5	F SD4967/56	37	Lobectomy	L.L.D.	4.5	Pigmented scar	+	+	a+	+	+
6	M SD870/60	50	Lobectomy	L.U.L.	4.5	Pigmented scar	-	-	a+ V+	+	-
7	M H462/59	55	Lobectomy	R.L.D.	5	Pigmented scar	+	+	a+ V+	+	+
8	M H1751/59	66	Lobectomy	R.U.L.	5	Pigmented scar	-	-	V+	+	+

I ADENOCARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
1	-	+	+	-
2	+	+	+	-
3	+	-	-	+
4	+	-	+	-
5	+	-	+	+
6	+	-	+	+
7	+	-	+	+
8	+	-	+	-

ADENOCARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
9	M	62	Pneumon-ectomy	R.L.D.	5	-	+	-	V+	+	-
	SD863/62										
10	M	57	Pneumon-ectomy	L.U.L.	5	Pigmented scar	-	-	a+ V+	+	+
	H1421/61										
11	M	52	Pneumon-ectomy	R.U.L.	5.5	Pigmented scar	+	-	a+	+	+
	H243/61										
12	M	66	Lobectomy	L.U.L.	6	Pigmented scar	-	-	a+ V+	+	-
	H1707/59										
13	M	56	Lobectomy	L.L.L.	7.5	Pigmented scar	-	-	a+ V+	+	-
	H1515/61										
14	M	62	Lobectomy	L.U.L.	9	-	+	-	a+ V+	+	+
	H324/60										
15	M	56	Lobectomy	R.L.D.	10	Pigmented scar	-	-	-	+	+
	H1952/61										
16	M	66	Lobectomy	L.L.D.	1.5	Pigmented scar	-	-	a+	-	+
	H71/62										
17	M	58	Lobectomy	R. upper & middle	1.7	Pigmented scar	-	-	a+ V+	-	+
	H859/59										

I ADENOCARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
9	-	-	-	-
10	-	+	+	-
11	+	-	+	+
12	-	-	-	+
13	-	+	+	-
14	-	-	+	-
15	+	-	+	-
16	-	-	-	-
17	+	-	+	+

ADENOCARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
18	M	63	Lobectomy	R.M.L.	1.7	Scar	+	+	-	-	+
	H617/61										
19	M	65	Lobectomy	R.M.L.	1.9	Pigmented scar	+	-	-	-	-
	H2307/60										
20	M	52	Lobectomy	R.L.D.	2	Scar	-	-	-	-	-
	H1788/60										
21	M	64	Lobectomy	R.U.L.	2.5	Pigmented scar	-	-	a+	-	+
	SD959/61										
22	F	48	Lobectomy	R. upper & middle	2.5	Pigmented scar	-	-	-	-	+
	H2572/61										
23	M	69	Lobectomy	L.U.L.	2.8	Pigmented scar	-	-	v+	-	-
	H917/60										
24	M	63	Lobectomy	R.U.L.	3	Pigmented scar	-	-	a+ v+	-	-
	H526/62										
25	M	59	Lobectomy	L.L.D.	3	Scar	-	-	-	-	-
	H650/59										

I ADENOCARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
18	+	-	+	-
19	-	-	-	+
20	+	-	+	-
21	-	-	+	+
22	+	-	-	-
23	-	-	-	+
24	-	-	+	+
25	+	-	+	-

ADENOCARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
26	M	69	Lobectomy	R.L.D.	3	Scar	+	-	a+	-	-
	H2228/60										
27	M	64	Lobectomy	R.U.L.	3.2	Scar	-	-	-	-	-
	H2030/61										
28	F	66	Lobectomy	R.U.L.	3.2	Pigmented scar	-	-	a+ v+	-	+
	H1390/61										
29	M	57	Lobectomy	R.M.L.	4	Pigmented scar	-	-	v+	-	+
	H323/62										
30	M	58	Lobectomy	R.U.L.	4	Scar	-	-	a+ v+	-	+
	SD3008/57										
31	M	50	Lobectomy	R.U.L.	4	Scar	+	+	v+	-	+
	H1209/59										
32	M	46	Lobectomy	L.L.D.	4.2	Pigmented scar	-	-	a+ v+	-	+
	H946/60										
33	M	60	Lobectomy	L.U.L.	4.5	Pigmented scar	-	-	a+ v+	-	+
	H248/62										

I ADENOCARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
26	+	-	+	+
27	+	+	+	-
28	+	-	+	-
29	-	-	-	-
30	-	-	+	-
31	+	-	-	+
32	-	-	-	-
33	-	+	-	-

ADENOCARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
34	F	65	Lobectomy	R.U.L.	5	-	+	-	-	-	+
	H835/62										
35	M	45	Lobectomy	R.L.L.	5	Pigmented scar	+	-	-	-	-
	H894/60										
36	M	55	Segment-ectomy	L.L.D.	5.5	Pigmented scar	-	-	a+ v+	-	+
	H989/60										
37	M	57	Lobectomy	R.U.L.	10	Pigmented scar	+	-	a+ v+	-	+
	H861/59										

I ADENOCARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
34	+	+	+	-
35	-	-	+	+
36	-	-	+	-
37	+	-	-	+

II SQUAMOUS CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
1	M H255/62	68	Lobectomy	R.U.L.	5.5	Pigmented scar	-	-	a+	+	-
2	M SD1954/56	68	Lobectomy	R.U.L.	6	Pigmented scar	-	-	a+ v+	+	+
3	F H922/60	76	Lobectomy	R.L.L.	6	Scar	+	+	a+ v+	+	+
4	M H1279/60	55	Pneumon-ectomy	R.L.D.	6	-	+	-	a+	+	-
5	M H1351/61	54	Lobectomy	R.U.L.	6	Scar	+	+	-	+	-
6	M H2063/61	70	Lobectomy	L.U.L.	6.8	Pigmented scar	+	-	a+	+	+
7	M H1125/60	64	Lobectomy	R.U.L.	7	Pigmented scar	-	-	-	+	+
8	F H2616/61	60	Pneumon-ectomy	L.U.L.	7	Scar	+	+	a+	+	+
9	M H2263/60	73	Lobectomy	L.L.L.	7	Pigmented scar	+	+	a+ v+	+	+

II SQUALIDUS CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
1	-	-	+	-
2	+	-	+	-
3	+	-	-	+
4	-	-	-	-
5	-	+	+	-
6	+	-	-	+
7	+	-	-	+
8	+	+	-	-
9	+	+	-	-

SQUAMOUS CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
10	M	59	Pneumon-ectomy	L.U.L.	9.5	Pigmented scar	+	+	V+	+	+
	H1658/59										
11	M	64	Lobectomy	R.U.L.	10	-	+	+	V+	+	+
	H823/60										
12	F	68	Segment-ectomy	R.U.L.	2	-	+	-	-	-	-
	SD948/62										
13	M	59	Lobectomy	R.U.L.	2.5	Scar	+	+	V+	-	+
	H1477/59										
14	M	66	Segment-ectomy	L.L.D.	2.5	Pigmented scar	-	-	-	-	-
	H2295/60										
15	M	60	Segment-ectomy	R.L.D.	3.5	Scar	+	-	V+	-	-
	H1583/61										
16	M	64	Lobectomy	R.U.L.	3.5	Pigmented scar	+	-	V+	-	-
	H527/60										
17	M	63	Segment-ectomy	L.U.L.	4	-	+	-	-	-	+
	SD933/62										
18	M	55	Lobectomy	L.U.L.	5	Pigmented scar	+	-	a+	-	+
	H1819/60										

II SQUAMOUS CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
10	+	-	-	-
11	+	-	-	+
12	-	+	+	-
13	+	-	-	+
14	-	+	-	+
15	+	-	-	+
16	-	-	-	+
17	-	-	-	+
18	+	-	-	+

SQUAMOUS CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
19	M	59	Pneumon-ectomy	L.U.L.	5	Pigmented scar	+	+	v+	-	-
	H119/60										
20	M	68	Lobectomy	R.U.L.	5	-	-	-	a+	-	+
	H2316/61										
21	M	68	Lobectomy	R.M.L.	5	Pigmented scar	+	-	v+	-	+
	H1179/61										
22	M	64	Lobectomy	L.U.L.	5	Pigmented scar	+	+	v+	-	+
	H2491/61										
23	M	60	Lobectomy	R.U.L.	5	Pigmented scar	+	-	a+	-	-
	H833/61										
24	M	74	Lobectomy	R.L.D.	5.2	Pigmented scar	+	-	a+	-	+
	H2321/60										
25	M	60	Lobectomy	R.U.L.	5.5	Pigmented scar	-	-	v+	-	+
	H799/62										
26	M	54	Pneumon-ectomy	L.U.L.	6	Pigmented scar	+	-	a+	-	+
	H1305/59										
27	M	54	Lobectomy	L.U.L.	6	Pigmented scar	+	+	v+	-	-
	H1875/59										

III SQUAMOUS CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
19	+	-	-	+
20	+	-	-	-
21	-	+	-	-
22	+	-	-	+
23	-	-	-	+
24	+	-	-	-
25	+	-	-	+
26	+	-	-	+
27	+	-	-	+

SQUAMOUS CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
28	M	71 H2031/61	Lobectomy	R.U.L.	6.5	Pigmented scar	+	+	2+ V+	-	+
29	M	65 H1894/61	Lobectomy	L.U.L.	7	Pigmented scar	+	+	V+	-	+
30	M	72 H382/60	Lobectomy	L.L.L.	7	Pigmented scar	+	+	3+ V+	-	-
31	M	63 H1341/61	Lobectomy	R.U.L.	8	-	+	+	3+ V+	-	+
32	M	56 H1863/59	Lobectomy	R.L.L.	9	Pigmented scar	+	+	V+	-	-
33	F	61 H174/60	Pneumon-ectomy	L.U.L.	10	Pigmented scar	+	-	2+ V+	-	+
34	M	H1384/59	Lobectomy	R.L.L.	11	Pigmented scar	+	+	2+ V+	-	+
35	M	53 H864/61	Pneumon-ectomy	R.U.L.	11	-	+	-	-	-	+

II SQUAMOUS CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
28	+	-	-	+
29	-	-	-	+
30	-	-	-	+
31	+	-	-	+
32	+	-	-	+
33	+	-	-	+
34	+	-	-	+
35	+	-	-	-

III POLYGONAL CELL CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
1	M H510/62	68	Lobectomy	L.U.L.	2.5	Pigmented scar	-	-	v+	+	-
2	M H2533/61	51	Lobectomy	L.U.L.	2.8	Pigmented scar	-	-	v+	+	+
3	M SD683/56	59	Pneumon-ectomy	R.U.L.	3.5	Pigmented scar	+	-	v+	+	-
4	M H860/61	57	Lobectomy	R.L.D.	3.6	Pigmented scar	+	-	v+	+	-
5	M H516/61	66	Lobectomy	R.L.D.	4	Pigmented scar	+	+	v+	+	-
6	M H1548/61	68	Lobectomy	R.L.L.	7.5	Pigmented scar	+	+	a+ v+	+	+
7	M H249/61	49	Lobectomy	R.L.L.	7.5	-	+	+	-	+	+
8	M H244/60	57	Pneumon-ectomy	L.U.L.	8	[illegible]	+	+	a+ v+	+	+
9	F H1557/61	30	Pneumon-ectomy	R.L.L.	9.5	Pigmented scar	+	-	a+ v+	+	+

III POLYGONAL CELL CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
1	-	-	+	-
2	-	+	+	-
3	-	-	-	-
4	-	+	+	-
5	-	-	+	-
6	-	-	-	+
7	-	-	-	-
8	-	-	-	-
9	-	-	-	-

POLYGONAL CELL CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
10	M SD1684/59	67	Pneumon-ectomy	L.U.L.	12	Pigmented scar	+	-	a+ V+	+	+
11	M H471/60	67	Lobectomy	R.U.L.	3	Pigmented scar	+	-	-	-	-
12	F H853/60	48	Lobectomy	L.U.L.	3	Pigmented scar	-	-	V+	-	+
13	M H2545/61		Lobectomy	R.U.L.	3	Scar	-	-	-	-	-
14	M H501/59	62	Lobectomy	R.U.L.	3.5	Pigmented scar	+	+	V+	-	-
15	M H1537/61	60	Lobectomy	R.U.L.	3.7	Pigmented scar	+	-	a+ V+	-	+
16	M H51/62	58	Lobectomy	R.L.D.	4	Pigmented scar	+	-	a+ V+	-	+
17	M H1165/59	54	Lobectomy	R.L.L.	4.5	Pigmented scar	+	-	a+ V+	-	+
18	F H1805/59	45	Lobectomy	L.U.L.	5.5	Pigmented scar	+	+	V+	-	-

III POLYGONAL CELL CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
10	-	-	-	-
11	-	-	-	+
12	-	-	-	+
13	-	-	+	-
14	-	-	+	+
15	-	-	-	+
16	-	-	-	+
17	-	-	-	+
18	-	-	-	+

POLYGONAL CELL CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
19	M	46	Lobectomy	L.U.L.	5.5	Pigmented scar	-	-	a+	-	-
	SD1631/59										
20	M	55	Lobectomy	L.U.L.	5.5	Pigmented scar	+	-	v+	-	-
	H304/62										
21	M	68	Lobectomy	L.U.L.	7.5	Pigmented scar	+	-	a+ v+	-	+
	H2192/60										
22	M	57	Lobectomy	R.U.L.	8	Pigmented scar	+	-	v+	-	-
	SD183/61										
23	M	59	Pneumonectomy	L.L.D.	9	-	+	-	-	-	-
	H2386/61										
24	M	55	Pneumonectomy	L.L.D.	9.6	-	+	+	v+	-	+
	H2537/61										
25	M	43	Pneumonectomy	R.U.L.	10	Pigmented scar	+	-	a+	-	+
	H1731/59										

III POLYGONAL CELL CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
19	-	+	+	-
20	-	-	-	-
21	-	-	-	+
22	-	-	-	+
23	-	-	-	+
24	-	-	-	+
25	-	-	-	+

IV OAT CELL CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
1	M	61 H585/61	Lobectomy	R.U.L.	1.7	Pigmented scar	-	-	a+ v+	+	+
2	M	57 H713/61	Lobectomy	L.U.L.	2.2	Pigmented scar	-	-	a+	+	+
3	M	60 H2385/60	Pneumon-ectomy	R.L.D.	2.5	Pigmented scar	-	-	a+ v+	+	+
4	M	61 H441/62	Segment-ectomy	R.L.D.	2.9	Pigmented scar	+	-	a+	+	-
5	M	58 H198/62	Pneumon-ectomy	L.L.D.	3	Pigmented scar	+	-	a+	+	+
6	F	56 H1280/61	Lobectomy	R.U.L.	3.5	-	+	-	a+	+	-
7	M	64 H994/59	Lobectomy	L.U.L.	4	Pigmented scar	-	-	a+ v+	+	+
8	F	61 H365/60	Lobectomy	R.U.L.	5	Pigmented scar	+	-	a+ v+	+	-
9	M	57 H1180/60	Lobectomy	R.L.D.	5	Pigmented scar	-	-	a+	+	+

IV OAT CELL CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
1	-	+	+	-
2	+	+	+	-
3	-	+	+	-
4	-	-	+	-
5	+	-	+	-
6	+	-	+	-
7	-	+	+	-
8	-	+	+	-
9	-	+	+	-

IV OAT CELL CARCINOMA

No.	sex	age	Operation	Site	Size (cm.)	Scar	Necrosis (Gross)	Cavity	Blood vascular invasion	Lymph node metastasis	Pleura
10	M	53	Pneumon-ectomy	R.U.L.	5	Pigmented scar	+	+	a+	+	+
	H1370/60										
11	F	62	Lobectomy	L.U.L.	6	Pigmented scar	+	-	v+	+	-
	SH122/62										
12	M	59	Lobectomy	R.U.L.	2.5	Hyalinised scar	-	-	a+	-	-
	H1482/61										
13	M	61	Lobectomy	R.L.D.	3.5	Scar	+	-	a+ v+	-	+
	H1182/60										
14	M	57	Lobectomy	R.U.L.	4	Pigmented scar	+	-	a+	-	-
	H791/60										
15	M	59	Lobectomy	R.L.D.	5.3	Pigmented scar	+	-	v+	-	+
	H725/59										
16	M	65	Pneumen-ectomy	R.U.L.	6	Pigmented scar	+	-	a+ v+	-	+
	H768/59										
17	M	60	Lobectomy	R.L.D.	6	Pigmented scar	-	-	a+ v+	-	-
	H451/62										

IV OAT CELL CARCINOMA (continued)

No.	Differentiation	Lymph channel invasion	Fragmentation	Stromal reaction
10	-	+	+	-
11	+	+	+	-
12	+	+	+	-
13	+	-	+	-
14	+	-	+	+
15	+	-	+	-
16	+	-	+	-
17	-	-	+	-

Diagrammatic illustrations of 114 peripheral lung tumours tabulated on pages 72 to 99.

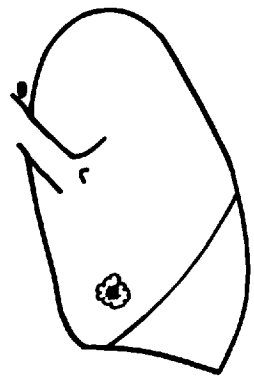
The tumours have been grouped into 4 sections:

37 adenocarcinomas.	pages 101 to 105
35 squamous cell carcinomas.	pages 106 to 110
25 polygonal cell carcinomas.	pages 111 to 114
17 oat cell carcinomas.	pages 115 to 117

Within each section the illustrations are numbered in the same way as in the Tables, in the ascending order of size. The metastasising tumours precede the non-metastasising ones. The following data are illustrated: site of tumour, lymph node metastasis, scarred areas and cavities.

ADENOCARCINOMAS

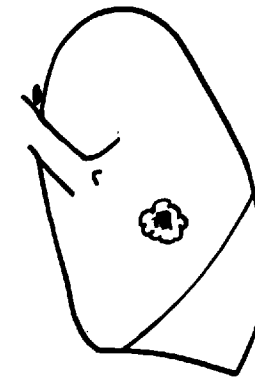
1 - 37



1



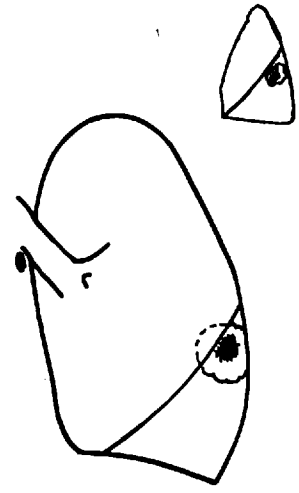
2



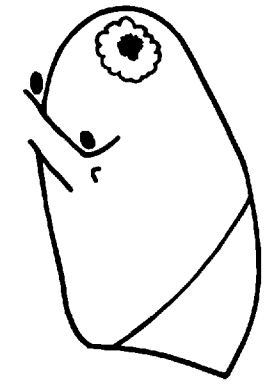
3



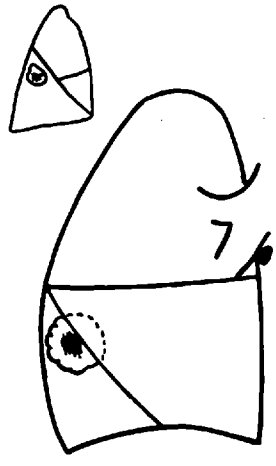
4



5



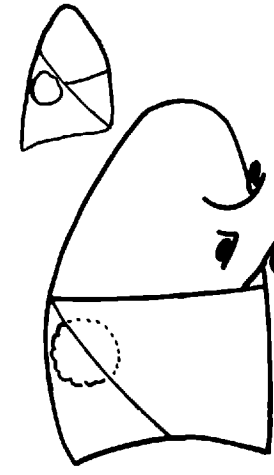
6



7



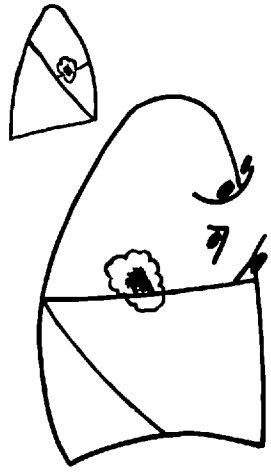
8



9



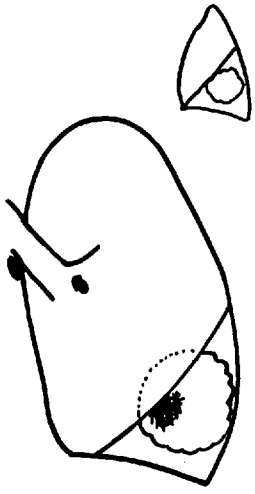
10



11



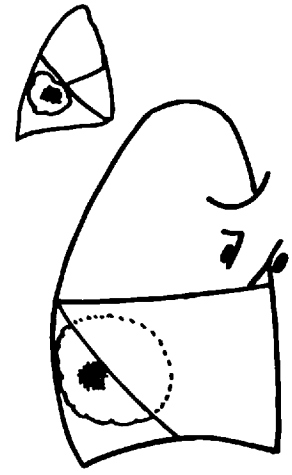
12



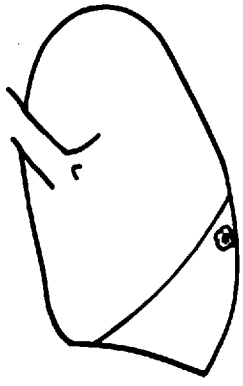
13



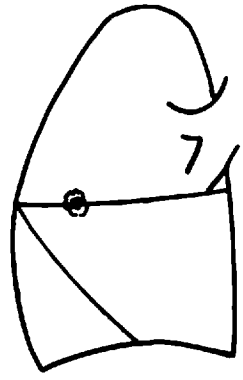
14



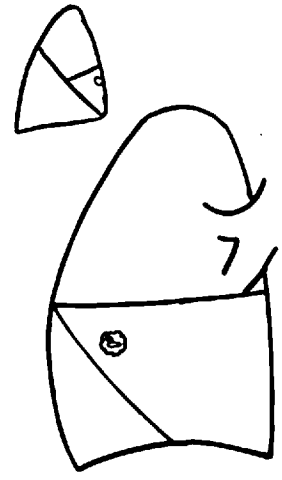
15



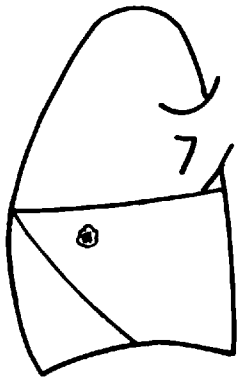
16



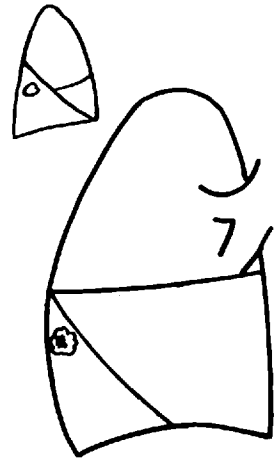
17



18



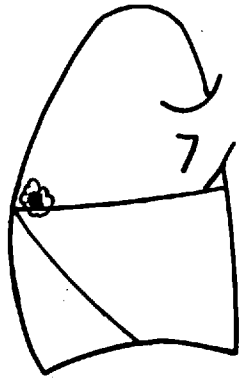
19



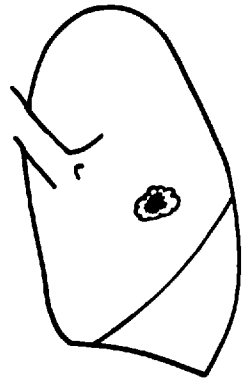
20



21



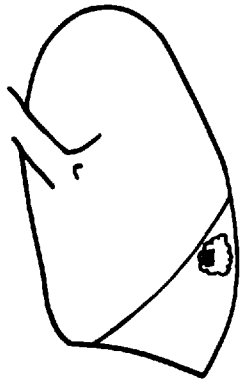
22



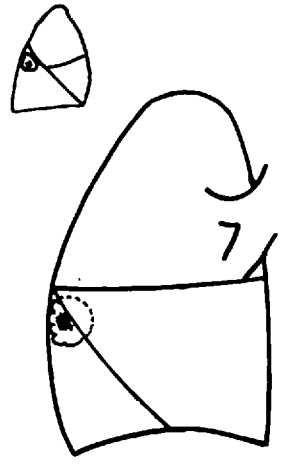
23



24



25



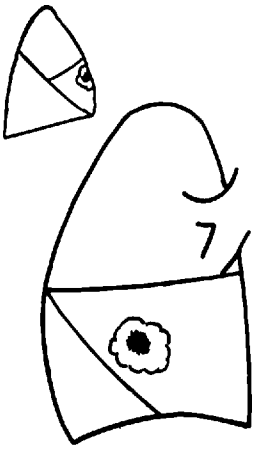
26



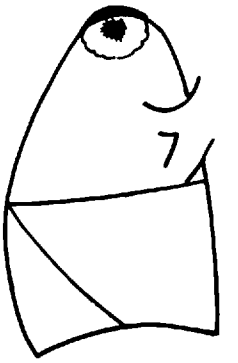
27



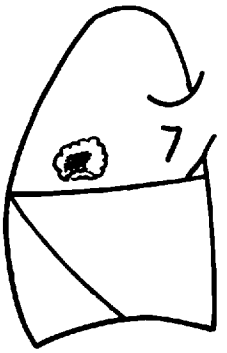
26



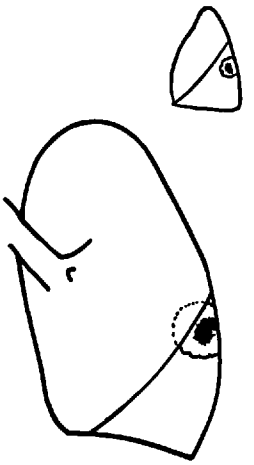
29



30



31



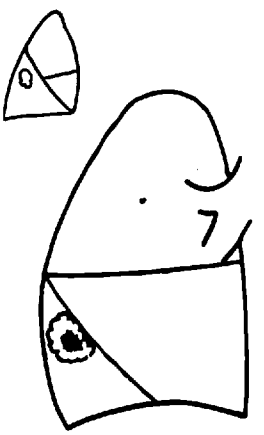
32



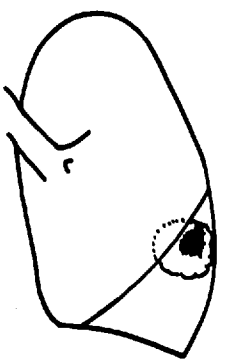
33



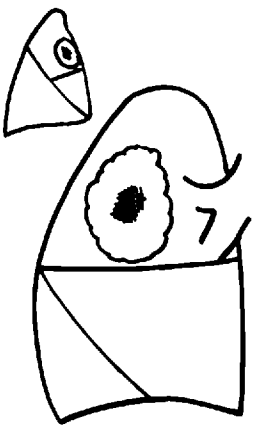
34



35



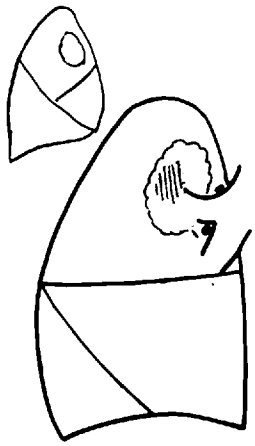
36



37

SQUAMOUS CARCINOMAS

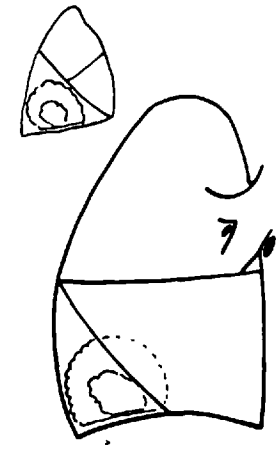
1 - 35



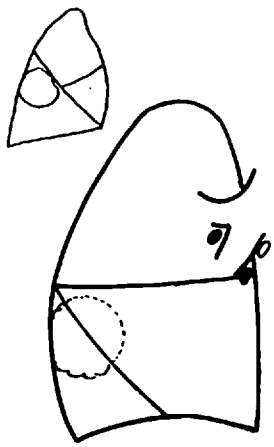
1



2



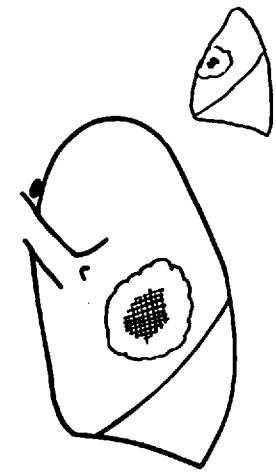
3



4



5



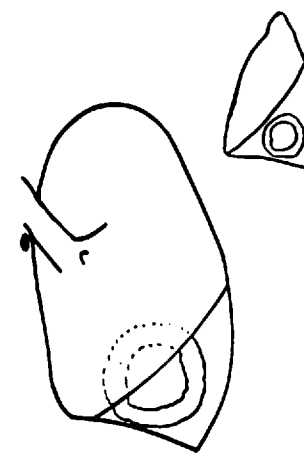
6



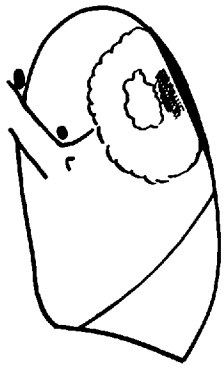
7



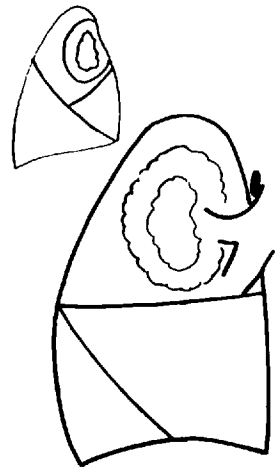
8



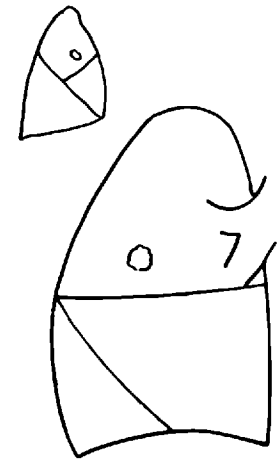
9



10



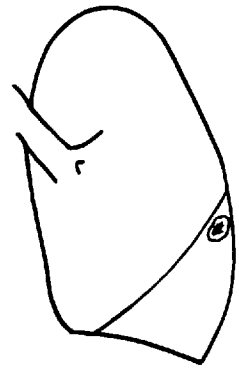
11



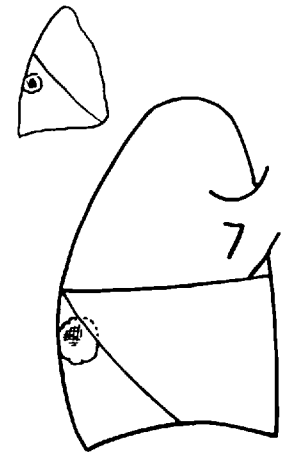
12



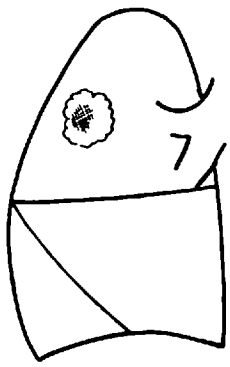
13



14



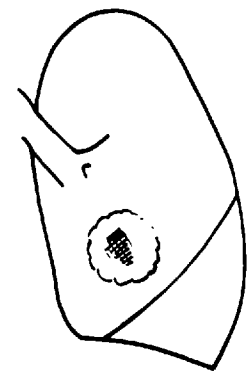
15



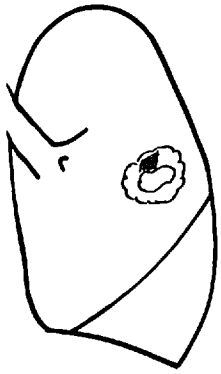
16



17



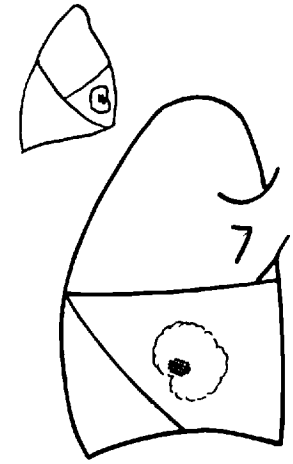
18



19



20



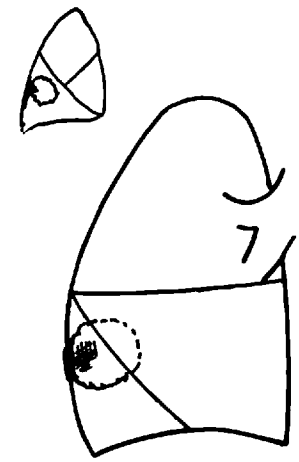
21



22



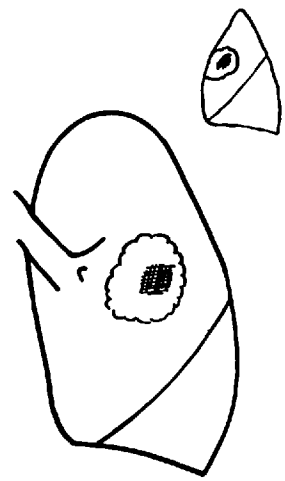
23



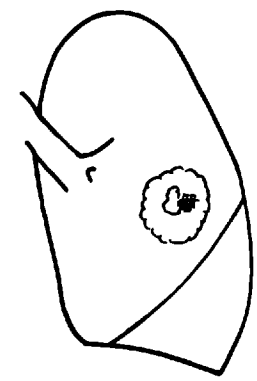
24



25



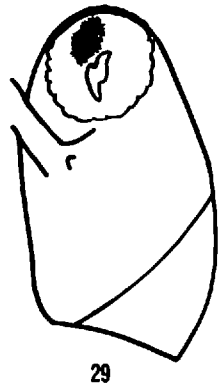
26



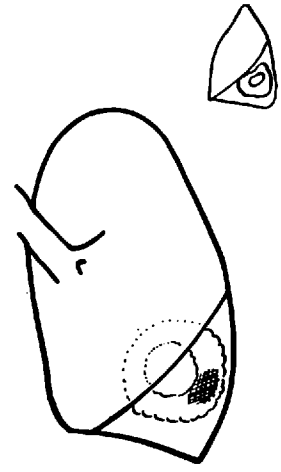
27



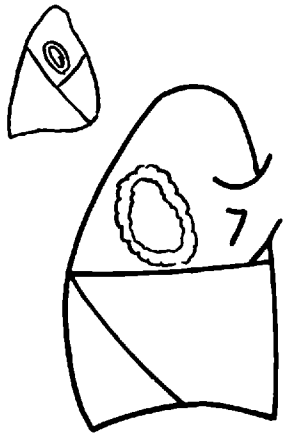
28



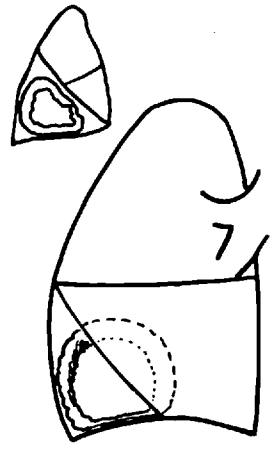
29



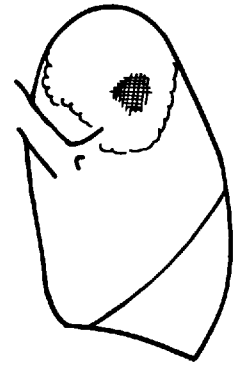
30



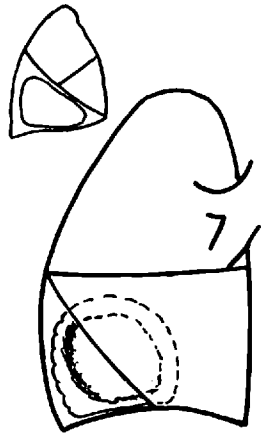
31



32



33



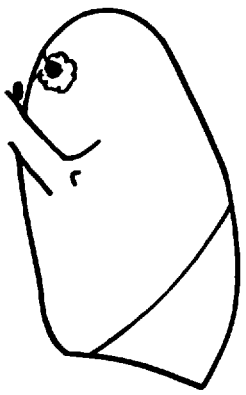
34



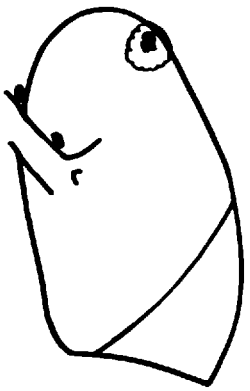
35

POLYGONAL CELL CARCINOMAS

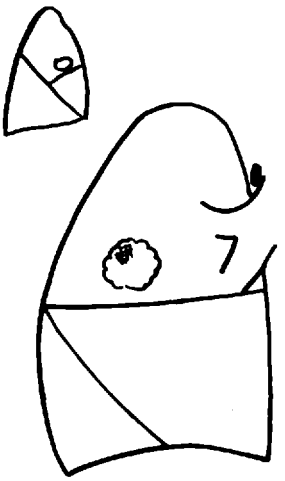
1 - 25



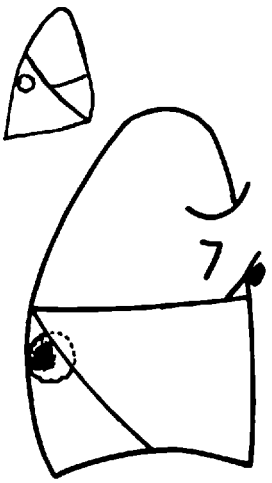
1



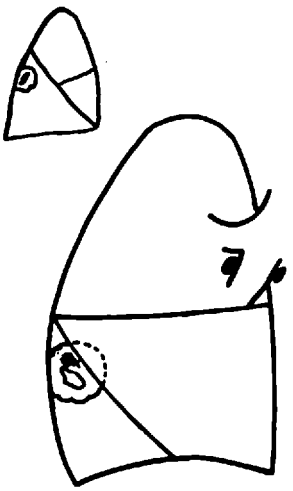
2



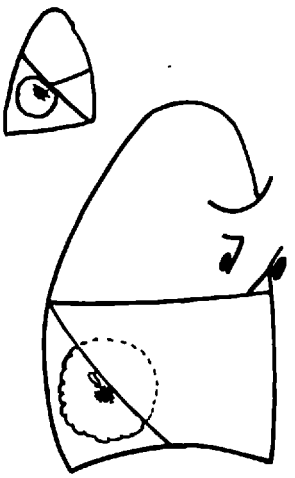
3



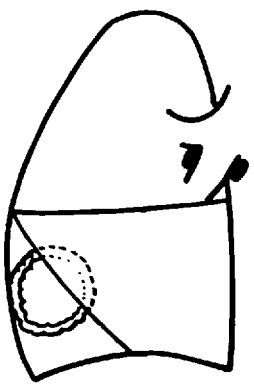
4



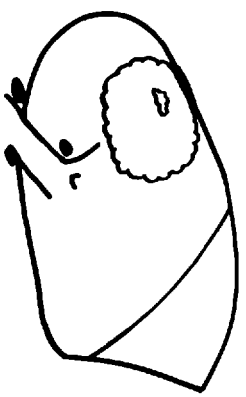
5



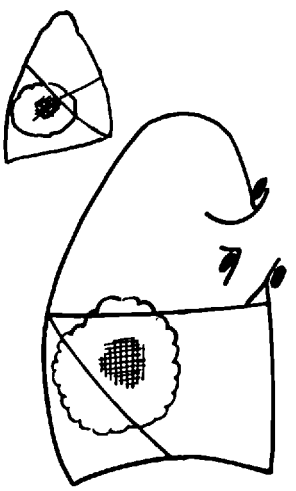
6



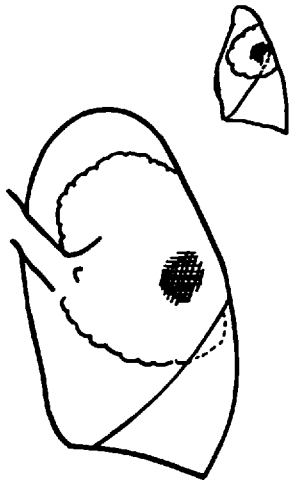
7



8



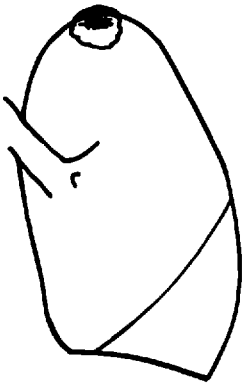
9



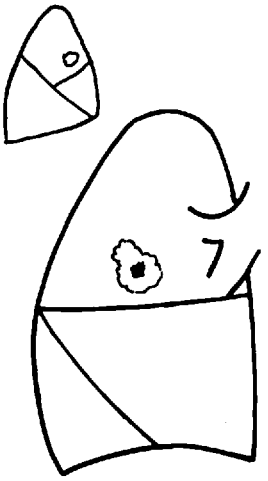
10



11



12



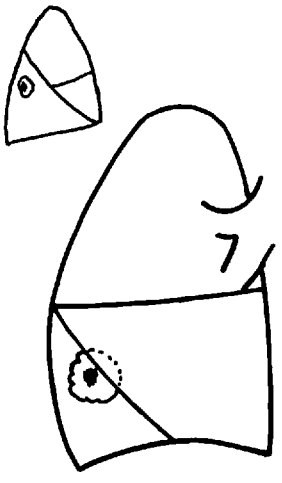
13



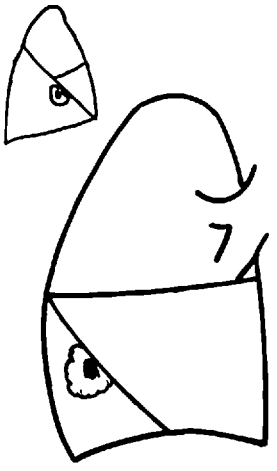
14



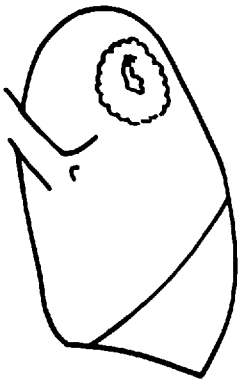
15



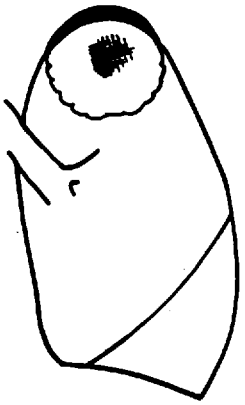
16



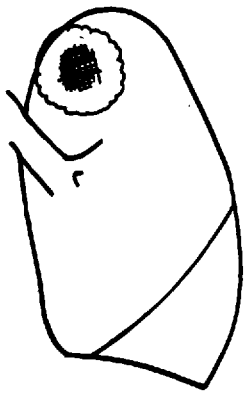
17



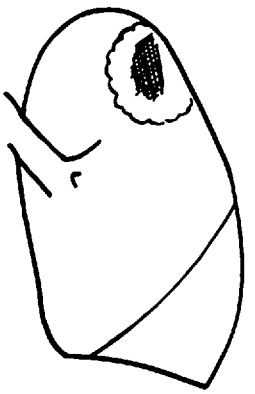
18



19



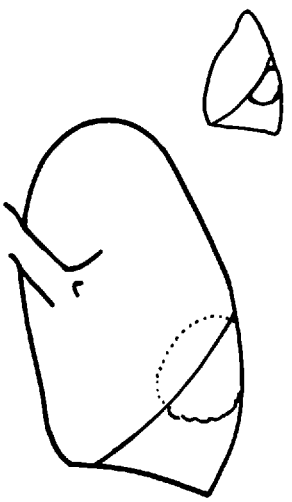
20



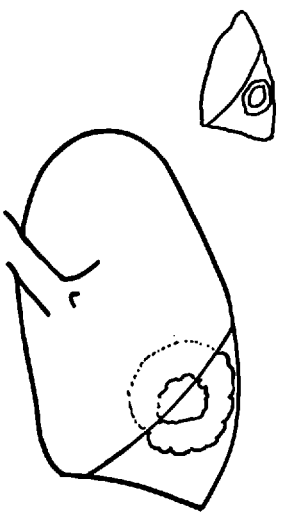
21



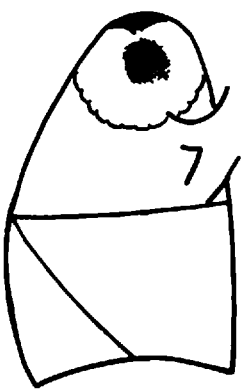
22



23



24



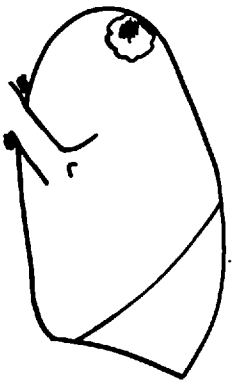
25

OAT CELL CARCINOMAS

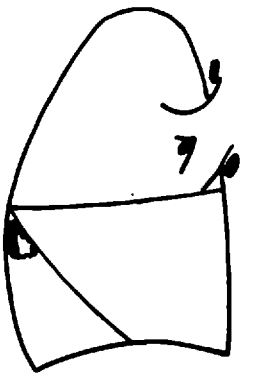
1 - 17



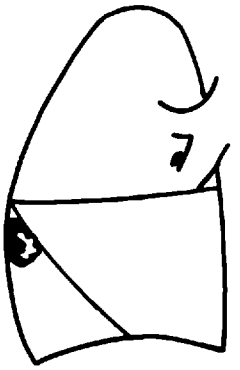
1



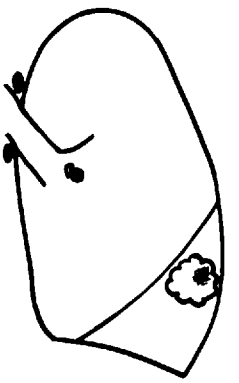
2



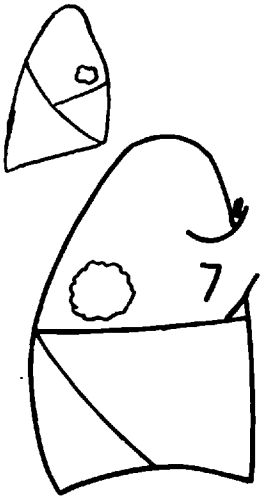
3



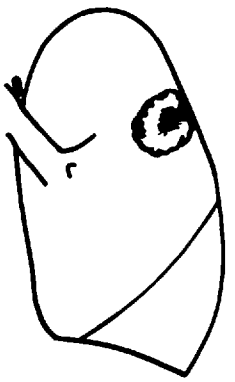
4



5



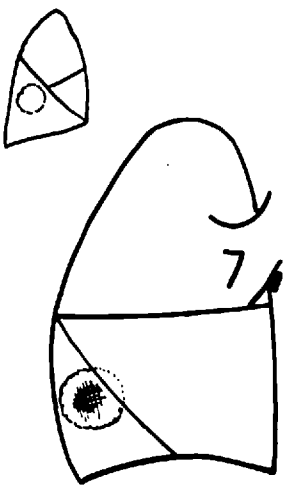
6



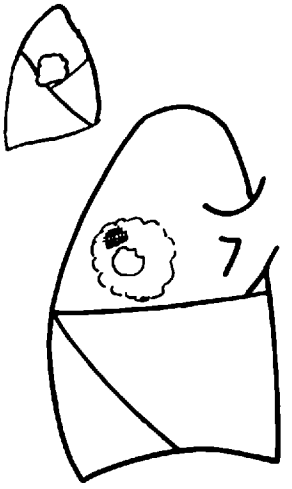
7



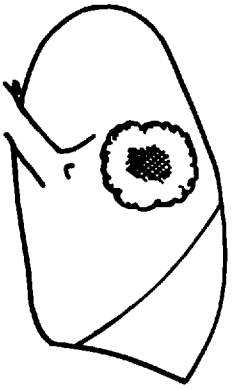
8



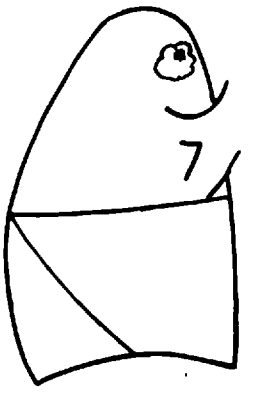
9



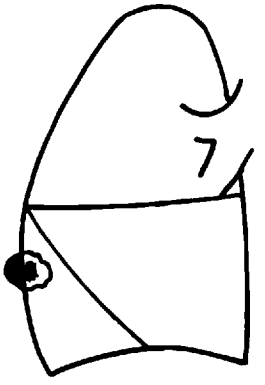
10



11



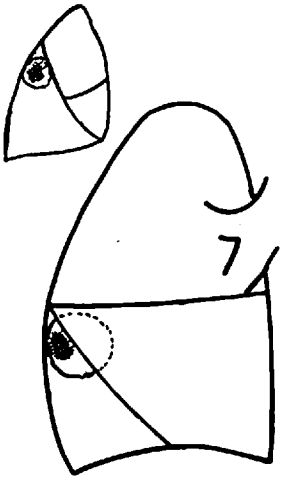
12



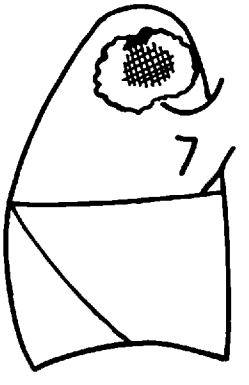
13



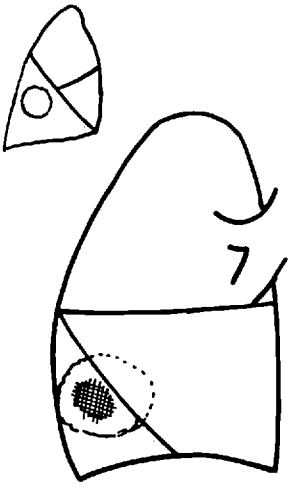
14



15



16



17

The following observations are biproducts of the present investigation. They have only an indirect bearing on the title of the thesis and are, therefore, presented as an appendix.

APPENDIX I (A)

The Preoperative Duration of Symptoms with Central and Peripheral Bronchial Carcinoma

It is well recognised that carcinoma of the lung can arise in any part of the bronchial tree. There does, however, appear to be a special predilection for the largest bronchi and the peripheral, the latter being situated in the hilar or extra-hilar regions of the lung.

The great majority of the tumours arising in the major bronchi are intra bronchial in the early stages and, in this paper, will henceforth be termed as simply central tumours.

It was thought that this investigation would be worth doing as the peripheral type of tumour is not the rarity that is presented in recent literature (Ackerman and Del Regato, 1954; Bignall, 1959; Fried, 1959; Willis, 1960) but in operative cases is more common than the central type (Walter and Pryce, 1955 b).

One might expect symptom histories of central tumours (i.e. tumours arising in the main, lobar or segmental bronchi) to be different from those which are extra-hilar and subpleural. This is logical because the former would more quickly give rise to obstruction.

The site of origin of carcinoma of the lung has an important bearing on the duration of symptoms before diagnosis. This has

been known for some time to people studying lung cancer and has been recently commented on by Walter and Pryce (1955 b) and Mayer (1956). Yet Bignall (1959) states that "the site appears to have little effect on the length of history before diagnosis."

To re-examine this problem it was decided to survey the clinical histories of surgically resected cases of primary carcinomas of lung, only cases where the site of origin was definitely recognisable being included.

Material and Method

Out of a large number of resected specimens (430) 175 cases were studied. This number is composed of cases from several hospitals over a period of 10 years. This is considered to be a fairly representative sample.* No selection was made unless the site of origin was established. The specimens were formalin-fixed and examined by slicing them in the para-hilar plane and looking for bronchial involvement, alveolar spread, retention phenomenon, pleural involvement, scarring, pigmentation, vascular invasion and lymph node metastases. Of the 175 cases studied 116 had been part of previous histological and anatomical studies by Walter and Pryce (1955).

There were, in all, 65 central and 110 peripheral tumours. The length of history was taken from the clinical notes coming from specialised hospitals and departments. It was, however,

* There were as many cases as could be procured. The only criterion in selection was the ability to identify the site as peripheral or central.

rather surprising that in view of the interest being shown in the relationship between smoking and lung cancer it was not possible to analyse smoking from the clinical notes.

Every case that had the remotest chance of being a secondary was excluded.

The tumours were not grouped regionally as has been the usual practice because although the rapidity with which obstruction might occur in the different regions may vary, the purpose was to make a clear-cut comparison between tumours which were likely, on account of their anatomical situation, to cause obstruction and those which were not.

Results

Peripheral tumours tended to be larger tumours with shorter histories as compared to central tumours (Appendix I A, Figs. 1 and 2).

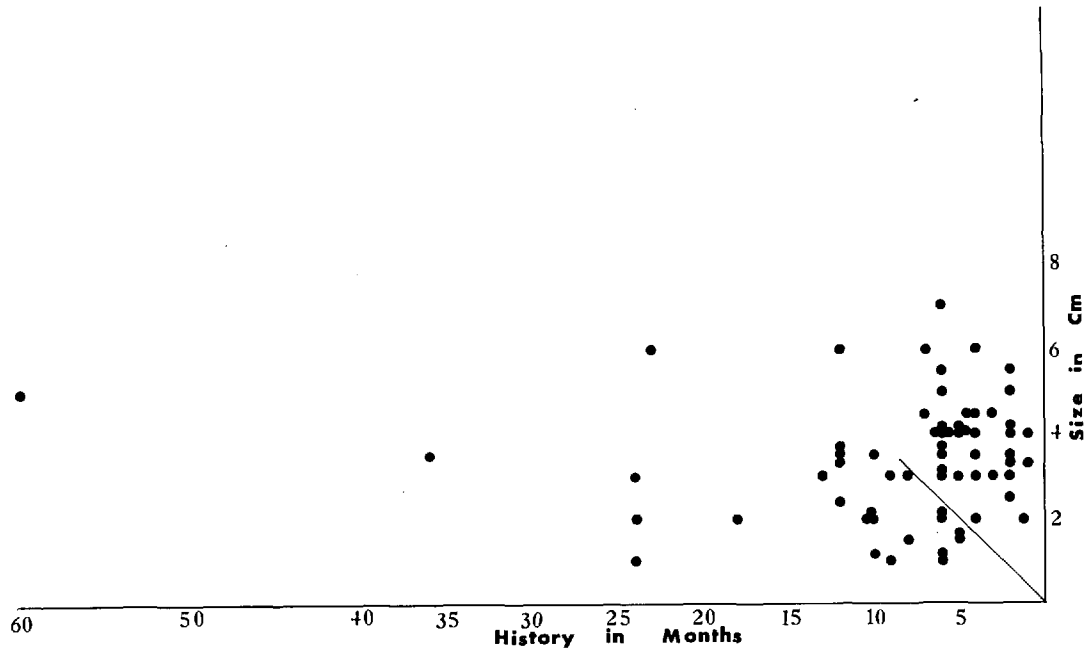
Average size of peripheral tumours	5.897 cm.
Duration of symptoms	3.271 months.
Average size of central tumours	3.385 cm.
Duration of symptoms	8.519 months.
Size difference	2.513 ± 0.354
Time difference	-5.249 ± 0.992

The calculations were made by Dr. C.C. Spicer of the Imperial Cancer Research Fund. The differences were regarded as statistically significant.

There was a difference in the presenting local symptoms.



Appendix IA: Fig. 1. Pre-operative duration of symptoms of 110 peripheral lung carcinomas.



Appendix IA: Fig. 2. Pre-operative duration of symptoms of 65 central lung carcinomas.

With central tumours cough was the predominating presenting symptom. It was present in almost half the cases (47.7 per cent). In the peripheral tumours, however, pain was the most prominent symptom, being present in 28.2 per cent of cases.

If cases with cough and haemoptysis are added the figures vary more markedly.

Presenting local symptoms

	Centrals	Peripherals
Cough	31 (47.7%)	30 (27.3%)
Haemoptysis	19 (29.2%)	19 (17.3%)
Pain	15 (23%)	31 (28.2%)
Acute febrile onset	18 (27.7%)	19 (17.3%)
Dyspnoea	15 (23%)	6 (5.5%)

Chronic bronchitis was present in 13 central and 31 peripheral cases. The total represented 25 per cent of the cases reviewed.

More than 20 per cent of the peripheral tumours had been discovered by mass miniature radiography, or were accidental findings in routine investigations.

Haemoptysis was, as expected, more prominent as the presenting symptom in the central type of tumour, being present in almost 30 per cent of cases. It was seen in less than 20 per cent of the peripheral group.

Dyspnoea as a presenting symptom was more often seen with the central type of case (23 per cent against 5.5 per cent in the peripheral cases).

Discussion

One of the major difficulties in the study of lung cancer is the absence of a uniform classification. Due to the lack of uniform criteria it is not possible to strictly compare series of cases from different centres.

From a review of literature it was found that no such comparison with central and peripheral tumours had been made by previous workers. This has already attracted considerable attention, as Bennet et al. (1959) state: "it is patently unsound to group together as 'resected cases of squamous cell carcinoma' asymptomatic patients with small solitary nodules and patients with haemoptyses and marked weight loss who have fungating lesions that obstruct bronchi producing atelectasis."

Though in necropsy series it is often impossible to assess the origin of growth, due to uninhibited growth of tumours (Budinger, 1958), it is comparatively much easier in the resection cases. Walter and Pryce (1955) assessed the site of origin of a large series of carcinomas of lung and divided them into central and peripheral tumours. They were able to form an opinion on the site of origin of almost 80 per cent (77.8 per cent) of cases.

The results differ from those obtained by Bignall (1958).

The reason for this difference lies in the insistance on the anatomical site of origin and not on their later and grosser manifestations. It was not possible, therefore, to agree with his statement that the site of tumour has no influence on the duration of symptoms before diagnosis. Overholt (1949) in his stimulating article on the silent phase of cancer of the lung also makes this apparent.

Conclusions

There has been some despondency lately due to the phenomenal rise in the incidence of pulmonary carcinoma and the poor operability of most of the cases and the meagre survival rate of patients undergoing surgery. Much of this has been coloured by the misconception that the greater percentage of carcinomas of lung arise in the major bronchi near the hilum, causing later symptoms and casting a non-detectable shadow in the hilar tangle of bronchi, blood vessels and glands, ruling out early diagnosis at an operable stage.

It is thought that a reorientation is needed. A significant number (probably the majority) of neoplasms appear in the lung substance in the smaller bronchioles away from the hilum and are radiologically detectable (Rigler, 1953). It has been conclusively shown by Boucot et al. (1959) that the asymptomatic solitary nodule has not only a greater resectability rate but also has a higher survival rate than the symptomatic patient.

APPENDIX I (B)

It was attempted to study the post operation survival of the above cases. Cases which were resected after 1959 could not be used in this investigation because the maximum possible survival time was not sufficiently long. But 81 peripheral tumours and 56 central tumours were available for study and these gave interesting and significant results. It was seen that survival had no correlation with duration of symptoms. Some tumours with long histories did well whereas some with short histories did poorly. Again, it was seen that the peripheral tumours were technically more resectable and there was greater operative mortality in central tumours (Appendix I B, Figs. 1 and 2).

The picture becomes clearer when the 2 anatomical groups are subdivided into histological types. It is seen that some squamous carcinomas, both central and peripheral, did well (Appendix I B, Figs. 2 and 3). The oat cell carcinomas, both central and peripheral, all showed a uniformly bad prognosis (Appendix I B, Figs. 4 and 5). Some of the adenocarcinomas and the polygonal cell carcinomas also did well (Appendix I B, Figs. 6 and 7).

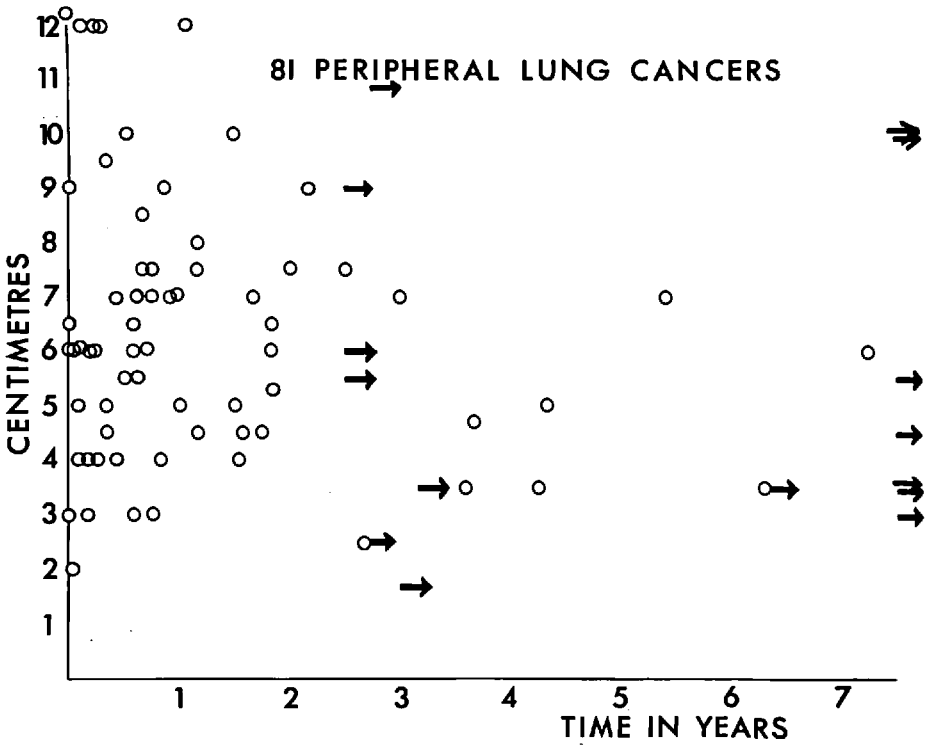
The still alive and long surviving patients were scrutinised for blood vascular invasion and glandular spread. It was found in these that lymph node metastasis was the most important

factor governing the survival of lung cancer patients undergoing surgical resection.

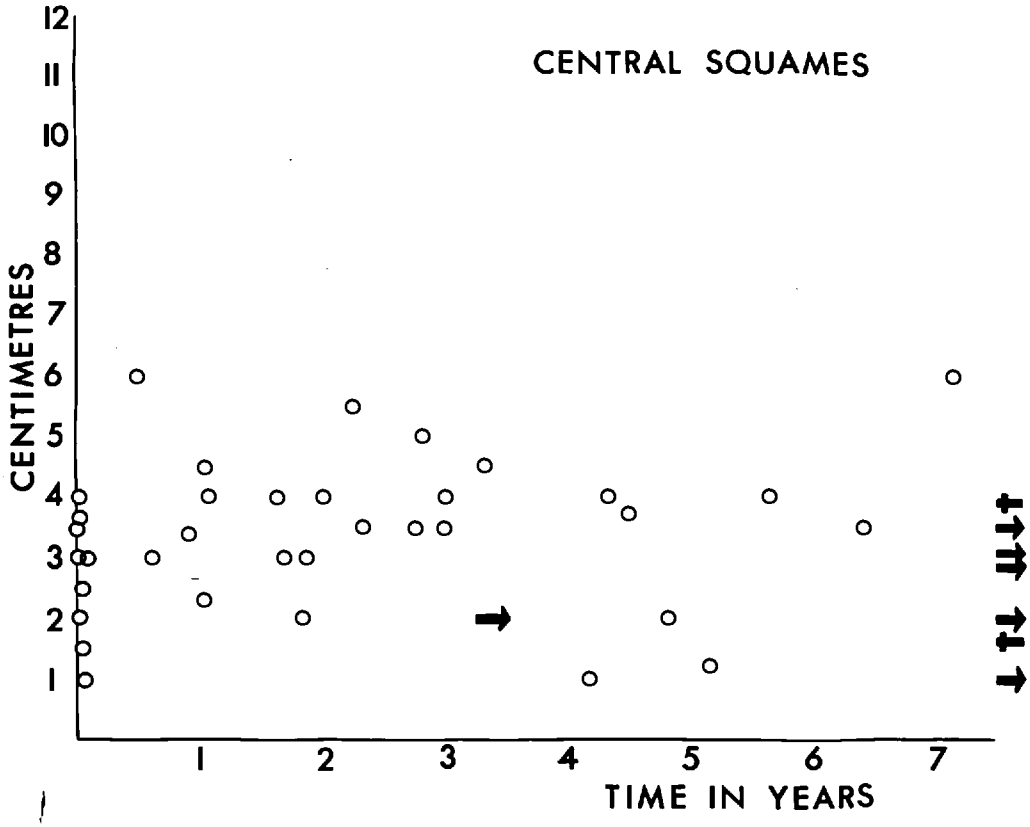
A recent growing tendency is to incriminate blood vascular dissemination solely for the poor surgical cure rate in lung cancer. Lungs, being very vascular organs, growth comes into intimate contact with numerous large and small blood vessels, particularly at the periphery, and vascular invasion is commonly seen in most tumours. Circulating tumour cells have been seen in peripheral blood by Engell (1955), Moore (1957) and others. Tumour cells have also been seen in blood draining surgical wound sites (Engell, 1955; Roberts et al., 1958).

Moore and his associates (1957) believe that the great majority of individual circulating tumour cells are destroyed. The larger tumour embolus finding a suitable soil is capable of forming a nidus of growth and is the probable reason for the widespread metastasis of lung cancer. This destruction of isolated tumour cells, as opposed to clumps or clusters, is also evident in experimental work. Watanabe (1954) found in injection experiments that metastasisability was exhibited by viable tumour cells in clumps and not by discrete single cells. Pryce and Heard (1956) inferred from their work on experimental pulmonary emboli that the metastases were probably due to large clumps and not single cells.

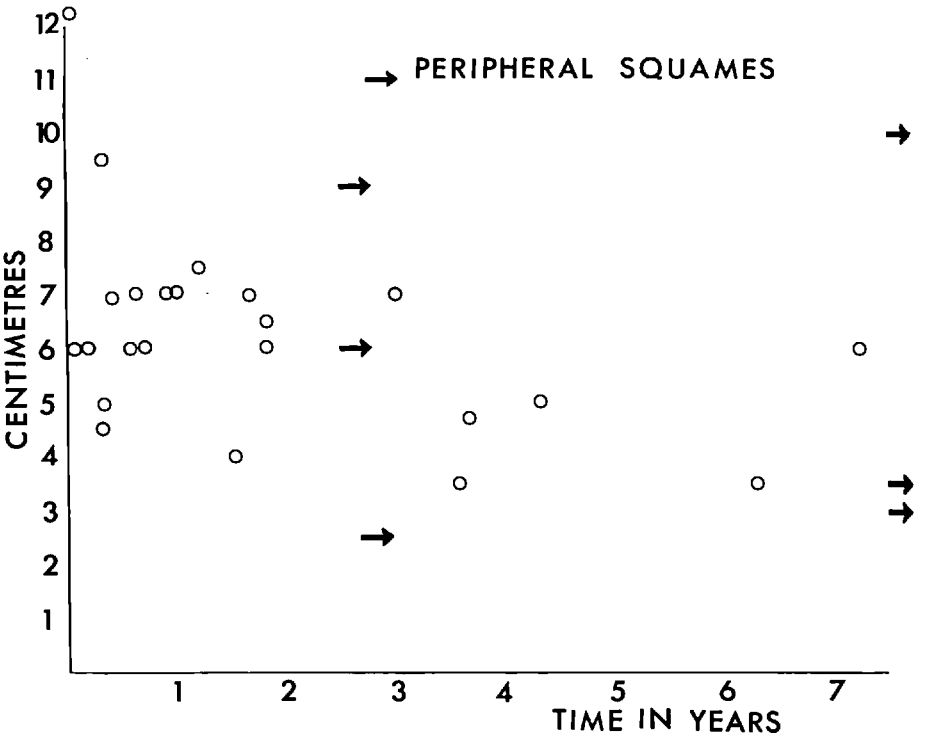
Hukill and Stern (1962) found no correlation between vascular invasion and survival in their study of survival in adenocarcinoma.



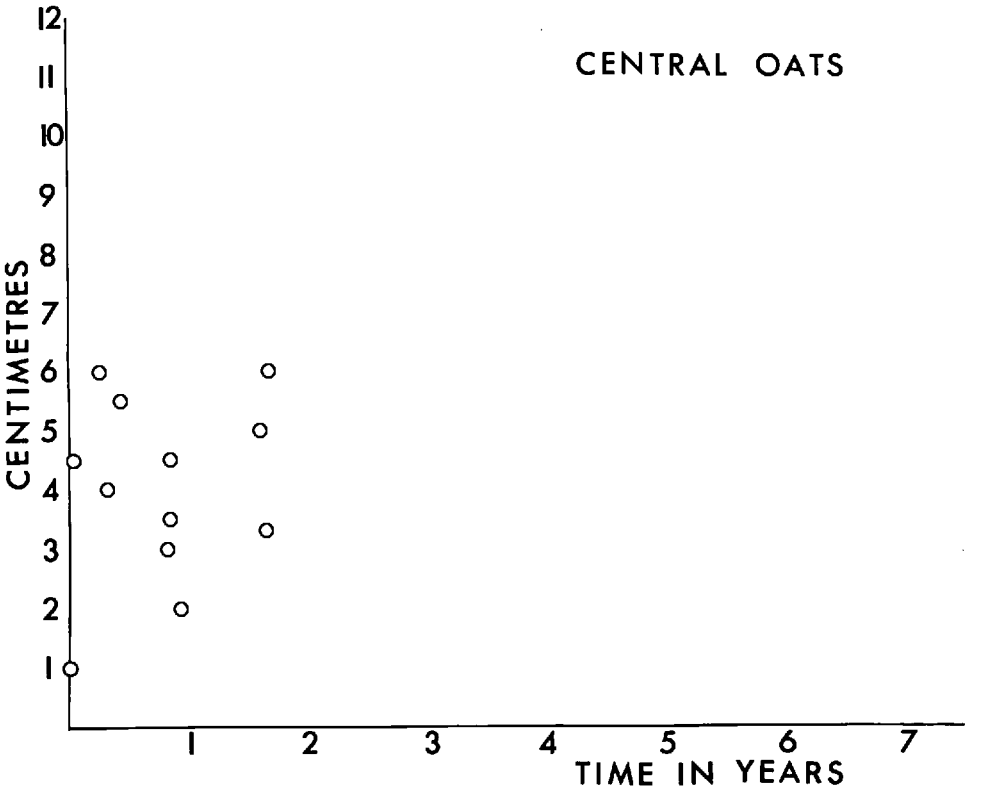
Appendix IB: Fig. 1. Post-operation survival in 81 cases of peripheral lung cancers arranged according to size.



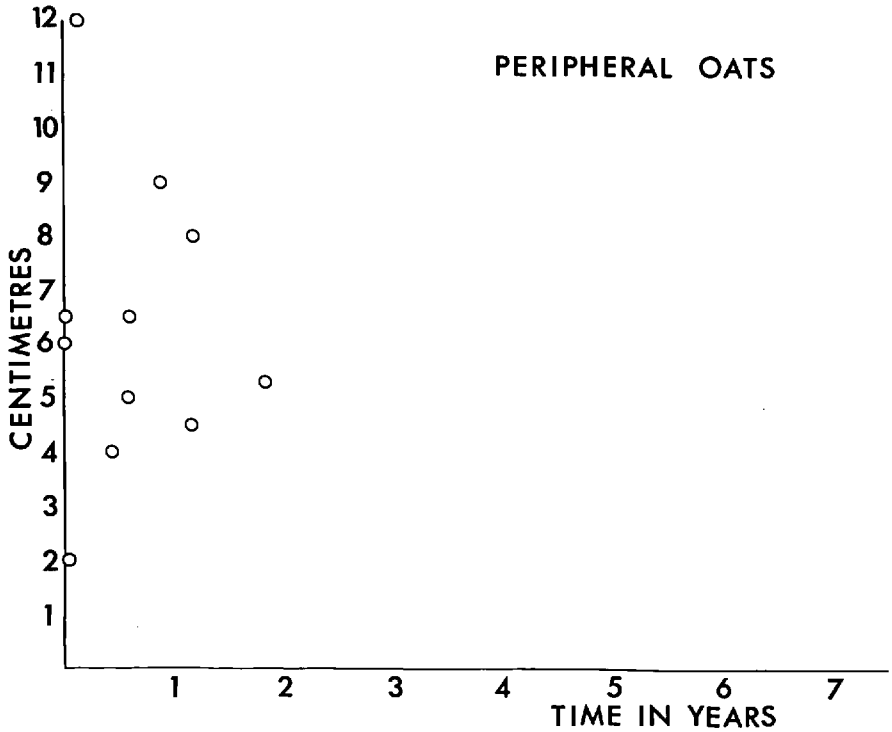
Appendix IB; Fig. 2. Post-operation survival in 43 squamous carcinomas of central type.



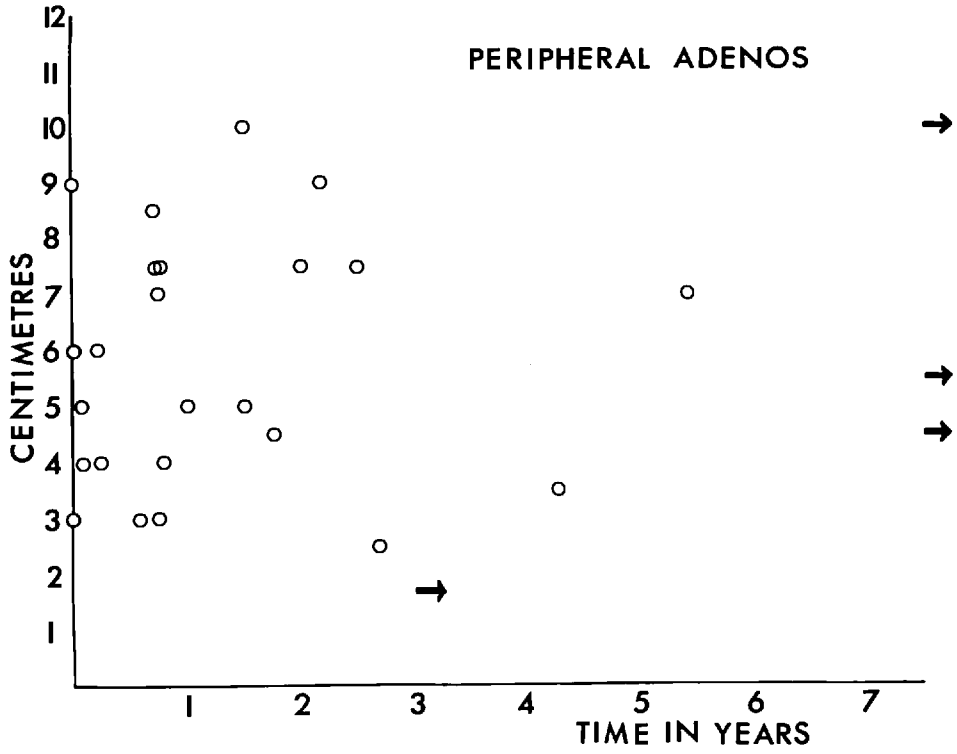
Appendix IB: Fig. 3. Post-operation survival in 30 cases of peripheral squamous carcinoma.



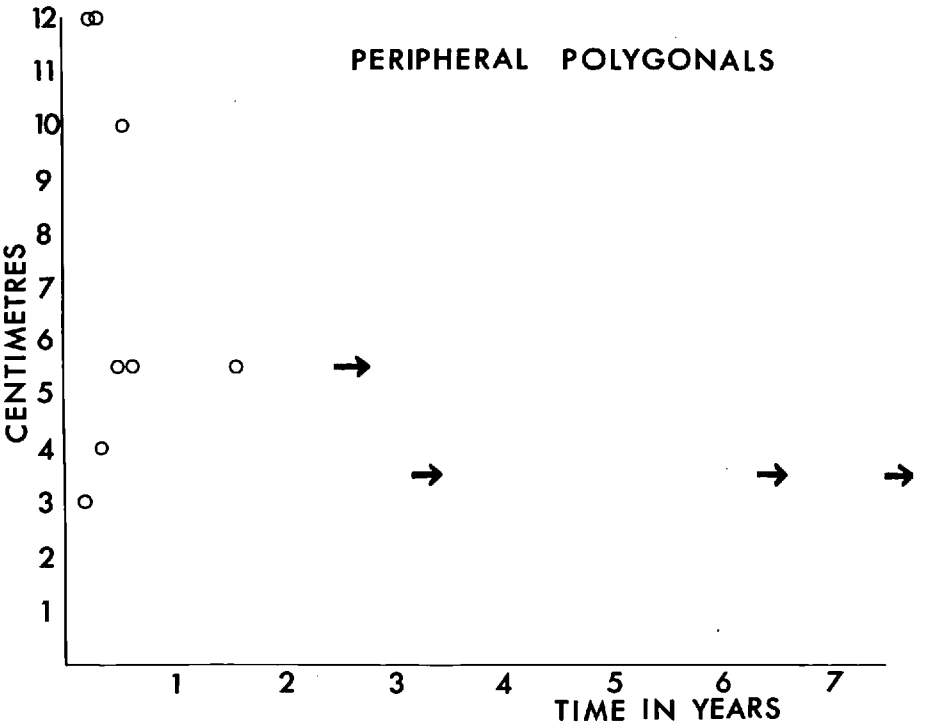
Appendix IB: Fig. 4. Post-operation survival in 12 cases of central oat cell carcinoma.



Appendix IB: Fig. 5. Post-operation survival in 11 cases of peripheral oat cell carcinoma.



Appendix IB: Fig. 6. Post-operation survival in 28 cases of peripheral adenocarcinoma.



Appendix IB: Fig. 7. Post-operation survival in 12 cases of peripheral polygonal cell carcinoma.

APPENDIX II

Presence of scars in peripheral carcinomas

It has been known for long that scars are commonly present in or in close relation to peripheral lung tumours (Friedrich, 1939; Rösale, 1943; Raeburn and Spencer, 1953; Lüders and Themel, 1954). This phenomenon has not drawn the attention it deserves, as many pathologists still hold to the theory that most of the pulmonary carcinomas arise in the major bronchi. Garland et al. (1962) say: "Based on consideration of the anatomic surface area of the different portions of the entire bronchial tree, it would be reasonable to expect a higher proportion of lesions to occur in the segmental and subsegmental bronchi than in the main or lobar bronchi ..... Needless to say, considerations other than surface areas alone are involved in the locus of origin of bronchial tumours, but presumably the larger the area at risk, the greater might be the chance of tumour arising thereon."

In Spencer's (1962) opinion most of the peripheral tumours arise in scars. He concedes the point that the appearances of a primary peripheral tumour can be simulated by a metastasis. In the present series the clinical history of each case was carefully reviewed to exclude any such possibility.

Scars were found to be of extremely common occurrence. In fact it was unusual not to find scarring in relation to these

peripheral lung tumours. In some cases cavitation and necrosis might have obscured or obliterated the scarred focus. All doubtful cases have been considered as negative.

In 99 cases (86 per cent) there was definite gross and microscopic evidence of a pre-existing scar in close relation to the tumour (Appendix IX, Figs. 1 and 2). Although Friedrich (1938) and Luders and Themal (1954) believe that most of these scars are of tuberculous aetiology there was no convincing proof of pre-existing tuberculosis at the tumour site in most of our cases.

Scars were so common because this series is very highly selected; they were seen in all types of carcinoma. If they are considered to be an important aetiological factor in the origin of peripheral tumours, as they obviously appear to be, the thesis that carcinoma of the lung is one entity is strengthened. Cancer can arise anywhere in the lung and, though different histological patterns may be used for prognostic and clinical purposes, it seems fallacious to impute different aetiological reasons for their histogenesis.

Scars	Total cases	No. with scars	Per cent
Adenocarcinoma	37	34	91
Squamous carcinoma	35	28	80
Polygonal cell carcinoma	25	21	84
Oat cell carcinoma	17	16	94



Appendix II: Fig. 1. Small peripheral tumour (adenocarcinoma) in the dorsal segment of the lower lobe showing a central scar and with the pleura puckered over the tumour. (See also Appendix II: Fig. 2).

Appendix II: Fig. 2 overleaf

Appendix II: Fig. 2. Section of tumour shown in Appendix II: Fig. 1. The pigmented scar is plainly seen. The growth reaches the adherent and retracted pleura.

Masson's trichrome stain × 10



APPENDIX III

Cavitation in peripheral lung carcinoma

It has long been observed by both pathologists and radiologists that cavitation is common in carcinomas of the lung (Atkin, 1951; Koletsky, 1958; Hauser and Walpaw, 1940). In the autopsy series studied by Atkin all the cavitating carcinomas (22 out of 93) were of the squamous cell type and, in his opinion, one could confidently predict that the cavitating bronchogenic carcinoma was almost invariably a squamous carcinoma.

Koletsky, in his study of autopsy specimens, found cavities in 52 per cent of the squamous carcinomas, 27 per cent of the adenocarcinomas and 9 per cent of the small cell carcinomas.

Our findings with surgical specimens are:

Adenocarcinoma - cavities in 4 out of 37 (10.8 per cent)

Squamous carcinoma - cavities in 16 out of 35 (45.7 per cent)

Polygonal carcinoma - cavities in 7 out of 25 (28 per cent)

Oat cell carcinoma - cavities in 1 out of 17 (5.8 per cent)

Thus, most of the cavitating tumours were of the squamous and polygonal cell types of carcinoma and the cavitating adenocarcinomas and oat cell carcinomas were unusual in this surgical series (Appendix III, Fig. 1).



Appendix III: Fig. 1. Lower lobe showing cavitating tumour (squamous carcinoma).

These cavitations are formed either by the centre of the tumour becoming anoxic because of the carcinoma outgrowing its blood supply or by vascular phenomena in and around the tumour. Thrombosed vessels invaded or occluded by tumour are often seen in the growth itself and in the periphery. These changes may, by decreasing the blood supply, produce aseptic necrosis of the tumour which is followed by sloughing away of the necrotic centre.

No correlation was observed with regard to ability to metastasise or the power of invasiveness of these cavitating growths.

ACKNOWLEDGMENTS

The present work has been made possible only with the unstinted, generous and active help of the Departments of Pathology of St. Mary's Hospital Medical School and of Harefield Hospital, Middlesex.

I am greatly indebted to Professor D.M. Pryce for encouragement, help and advice over the whole period of the investigation.

Of the many people in both laboratories who gave of their time and help Dr. E. Nassau and Dr. G.M. Hamilton are foremost.

For invaluable technical assistance I am most grateful to Mr. A. Beasley and Miss E.S. Murphy of this department, and to Mr. R.F. Cummings of Harefield Hospital. The staff of the Photographic Department of St. Mary's Hospital have always been most helpful.

I wish to express my deep gratitude for the secretarial assistance so willingly given by Miss E. Peacock and Miss J. Mahoney of this department; and to Miss W.M. Gallagher, Librarian of St. Mary's Hospital Medical School.

The expenses of the investigation were borne out of a grant from the British Empire Cancer Campaign.

Department of Pathology,
St. Mary's Hospital Medical School,
London, W.2.

August, 1962

REFERENCES

ACKERMAN, L.V. and REGATO, J.U. del (1947) Cancer: Diagnosis, Treatment and Prognosis, St. Louis.

ADLER, I. (1912) Primary Malignant Growths of Lung and Bronchi, London.

AGRICOLA, cited by WELLER, C.V. (1956) Causal Factors in Cancer of the Lung, Springfield, Ill.

ATKIN, E.E. (1931) Primary carcinoma of the bronchus, J. Path. Bact., 34, 343.

AYLWIN, J.A. (1951) Avoidable vascular spread in resection for bronchial carcinoma, Thorax, 6, 250.

BARNARD, W.G. (1926) The nature of the 'oat-celled sarcoma' of the mediastinum, J. Path. Bact., 29, 241.

BENNETT, J.R. (1872) Cancerous and Other Intrathoracic Growths, Their Natural History and Diagnosis, London.

BERG, J.W. (1956) Sinus histiocytosis: a fallacious measure of host resistance to cancer, Cancer, 9, 935.

BERG, J.W. (1959) Inflammation and prognosis in breast cancer; a search for host resistance, Cancer, 12, 714.

BIGNALL, J.R. and MOON, A.J. (1955) Survival after lung resection for bronchial carcinoma, Thorax, 10, 183.

BIGNALL, J.R. (1958) Carcinoma of the lung, Edinburgh.

BLACK, M.M., OPLER, S.R. and SPEER, F.D. (1954) Microscopic structure of gastric carcinomas and their regional lymph nodes in relation to survival, Surg. Gynec. Obstet., 98, 725.

BLACK, M.M. and SPEER, F.D. (1958) Sinus histiocytosis of lymph nodes in cancer, Surg. Gynec. Obstet., 106, 163.

BLACK, M.M. and SPEER, F.D. (1960) Lymph node reactivity in cancer patients, Surg. Gynec. Obstet., 110, 477.

BORRIE, J. (1952) Primary carcinoma of bronchus: Prognosis following surgical resection (clinico-pathological study of 200 patients), Ann. roy. Coll. Surg. Engl., 10, 165

Azzopardi, J.G. (1959) Oat cell carcinoma of the bronchus, J. Path. Bact., 78, 513.

BOUCOT, K.R., HORIE, U. and SOKOLOFF, M.J. (1959) Survival in lung cancer, New Engl. J. Med., 260, 742.

BUDINGER, J.M. (1958) Untreated bronchogenic carcinoma; a clinicopathological study of 250 autopsied cases, Cancer, 11, 106.

CAMPBELL, J.A. (1936) The effects of exhaust gases from internal combustion engines and of tobacco smoke upon mice, with special reference to incidence of tumours of the lung, Brit. J. exp. Path., 17, 146.

COCKLE, J. (1865) Intrathoracic Cancer, London.

COONS, A.H. and KAPLAN, M.H. (1950) Localization of antigen in tissue cells; improvements in method for detection of antigen by means of fluorescent antibody, J. exp. Med., 91, 1.

CHURCHILL, E.D., SWEET, R.H., SCUTTER, L. and SCANNELL, J.C. (1950) The surgical management of carcinoma of the lung. A study of the cases treated at the Massachusetts General Hospital from 1930-1950, J. thorac. Surg., 20, 349.

COMAN, D.R. (1944) Decreased mutual adhesiveness, a property of cells from squamous cell carcinomas, Cancer Res., 4, 625.

CRAWFORD, T. and WOOLF, N. (1960) Hyaline arteriosclerosis in the spleen: an immuno-histochemical study, J. Path. Bact., 79, 221.

DOLL, R. and HILL, A.B. (1950) Smoking and carcinoma of the lung, Brit. med. J., 2, 739.

DOLL, R. and HILL, A.B. (1952) A study of the aetiology of carcinoma of the lung, Brit. med. J., 2, 1271.

DOLL, R. and HILL, A.B. (1954) The mortality of doctors in relation to their smoking habits: a preliminary report, Brit. med. J., 1, 1451.

DOLL, R. and HILL, A.B. (1956) Lung cancer and other causes of death in relation to smoking: a second report on the mortality of British doctors, Brit. med. J., 2, 1071.

ENGELL, H.C. (1955) Cancer cells in the circulating blood; clinical study on occurrence of cancer cells in peripheral blood and in venous blood draining tumour area at operation, Acta chir. scand. Suppl. 201, 1.

FRIED, B.M. (1959) Tumours of the Lungs and Mediastinum, London.

FRIEDRICH, G. (1939) Periphere lungenkrebse auf dem boden pleuranaher narben, Virchows Arch. path. Anat., 304, 230.

GARLAND, L.H., BEIER, R.L., COULSON, W., HEALD, J.H. and STEIN, R.L. (1962) Apparent sites of origin of carcinomas of the lung, Radiology, 78, 1.

GIFFORD, J.H. and WADDINGTON, J.K.B. (1957) Review of 464 cases of carcinoma of lung treated by resection, Brit. med. J., 1, 1205.

GRAHAM, E.A. and SINGER, J.J. (1933) Successful removal of an entire lung for carcinoma of the bronchus, J. amer. med. Ass., 101, 1371.

HAMMOND, E.C. and HORN, D. (1954) The relationship between human smoking habits and death rates; follow-up study of 187,766 men, J. amer. med. Ass., 155, 1316.

HASSE, C.W. (1846) An Anatomical Description of the Diseases of the Organs of Circulation and Respiration, Trans. Swaine, W.E. (1856), Sydenham Society, London.

HAUSER, H. and WOLPAW, S.E. (1940) Cavitary bronchogenic carcinoma, Radiology, 34, 698.

HIRAMOTO, R., BERNECKY, J., JURANDOWSKI, J. and [illegible], D. (1960) Fibrin in human tumours, Cancer Res., 20, 592.

HUKILL, P.B. and STERN, H. (1962) Adenocarcinoma of the lung: histological factors affecting prognosis, Cancer, 15, 504.

KAAE, S. (1948) Prognostic significance of early diagnosis in breast cancer; study of early symptoms and their duration before patients come under treatment, Acta, radiol., 29, 475.

KOLETSKY, S. (1938) Primary carcinoma of the lung; a clinical and pathological study of 100 cases, Arch. intern. Med., 62, 636.

KOTIN, P. (1956) The role of atmospheric pollution in the pathogenesis of pulmonary cancer; a review, Cancer Res., 16, 375.

KREYBERG, L. (1960) Epidemiology of Cancer of the Lung: Report of a Study Group, WHO Technical Report Series no. 192, WHO, Geneva.

KREYBERG, L. and CHRISTIANSEN, T. (1953) Prognostic significance of small size in breast cancer, Brit. J. Cancer, 7, 37.

LAENNEC, R.T.H. (1819) De l'Auscultation Mediate ou Traite du Diagnostic des Maladies des Poumons et du Coeur, Fonde sur ce Nouveau Moyen d'Exploration, Paris, Trans. Forbes, J. (1821) London.

LUDERS, C.J. and THEMEL, K.G. (1954) Die narbenkrebse der lungen als beitrag zur pathogenese des peripheren lungencarcinoms, Virchows Arch. path. Anat., 325, 499.

MacCARTY, W.C. (1922) Factors which influence longevity in cancer, Ann. Surg., 76, 9.

McCUTCHEON, M., COMAN, D.R. and MOORE, F.B. (1948) Studies on invasiveness of cancer: adhesiveness of malignant cells in various human adenocarcinomas, Cancer, 1, 460.

MAYER, E. and MAIER, H.C. (1956) Pulmonary Carcinoma, New York.

MOERSCH, H.J. and McDONALD, J.R. (1953) The significance of cell types in bronchogenic carcinoma, Dis. Chest, 23, 621.

MOORE, G.E., SANDBERG, A. and SCHUBARG, J.R. (1957) Clinical observations of the occurrence and fate of tumour cells and the blood stream, Ann. Surg., 146, 580.

MOORE, G.E. (1957) The spread of cancer, Gastroenterology, 33, 313.

NOHL, H.C. (1962) The Spread of Carcinoma of the Bronchus, London.

OCHSNER, A., RAY, C.J. and ACREE, P.W. (1954) Cancer of the lung. A review of experiences with 1457 cases of bronchogenic carcinoma, Amer. Rev. Tuberc., 70, 763.

O'MEARA, R.A. (1958) Coagulative properties of cancers, Irish J. med. Sci., 394, 474.

O'MEARA, R.A. (1960) The growth-pattern of carcinomas, Arch. De Vecchi Anat. Pat., 31, 365.

ONUIGBO, W.I. (1959) Lung cancer in the nineteenth century, Med. Hist., Lond., 3, 69.

OVERHOLT, R.H. and SCHMIDT, I.C. (1949) Survival in primary carcinoma of lung, New Engl. J. Med., 240, 491.

OVERHOLT, R.H. and SCHMIDT, I.C. (1949) Silent phase of cancer of the lung, J. amer. med. Ass., 141, 817.

PRICE, D.M. and HEARD, B.E. (1956) The distribution of experimental pulmonary emboli in the rabbit, J. Path. Bact., 71, 15.

PRICE, D.M. and WALTER, J.B. (1960) The frequency of gross vascular invasion in lung cancer with special reference to arterial invasion, J. Path. Bact., 79, 141.

RAEBURN, C. and SPENCER, H. (1953) Study of origin and development of lung cancer, Thorax, 8, 1.

The REGISTRAR GENERAL'S Statistical Review of England and Wales for the Year 1960. Part I. Tables Medical, London, H.M.S.O.

RIGDON, R.H. and KIRCHOFF, H. (1961) Cancer of the lung 1930 to 1960: a review, Texas Rep. Biol. Med., 19, 465.

RIGLER, L.G., O'LOUGLIN, B.J. and TUCKER, R.C. (1953) The duration of carcinoma of the lung, Dis. Chest, 23, 50.

RIGLER, L.G. (1957) A roentgen study of the evolution of carcinoma of the lung, J. thorac. Surg., 34, 283.

ROBERTS, S. WAINE, A., McGRATH, R., McGREW, E. and COLE, W.H. (1938) The technique and results of isolation of cancer cells from the circulating blood, A.M.A. Arch. Surg., 76, 334.

ROKITANSKY, C. (1842) A Manual of Pathological Anatomy, Trans. Day, G.E. (1854) Sydenham Society, London.

ROSSLE, R. (1943) Die narbenkrebse der lungen, Schweiz. med. Wchnschr., 73, 1200.

SHENNAN, T. (1928) Tumours of mediastinum and lung, J. Path. Bact., 31, 365.

STOKES, W. (1837) ed. HUDSON, A. (1882) A Treatise on the Diagnosis and Treatment of Diseases of the Chest, New Sydenham Society, London.

SPENCER, H. (1962) Pathology of the Lung, London.

TOMLINSON, R.H. and GRAY, L.H. (1955) The histological structure of some human lung cancers and the possible implications for radiotherapy, Brit. J. Cancer, 9, 539.

WALTER, J.B. and PRICE, D.M. (1955 a) The histology of lung cancer, Thorax, 10, 107.

WALTER, J.B. and PRYCE, D.M. (1955 b) The site of origin of lung cancer and its relation to histological type, Thorax, 10, 117.

WALTER, J.B. and PRYCE, D.M. (1960) The frequency of differentiation in oat-cell carcinoma of the lung, J. Path. Bact., 80, 121.

WATANABE, S. (1954) Metastasizability of tumour cells, Cancer, 7, 215.

WELLER, C.V. (1956) Causal Factors in Cancer of the Lung, Springfield, Ill.

WILLIS, R.A. (1960) Pathology of Tumours, 3rd ed., London.

WILLIS, R.A. (1961) The incidence and histological types of pulmonary carcinoma, with comments on some fallacies and uncertainties, Med. J. Austr., 48, 433.

ZEIDMAN, I., McCUTCHEON, M. and COMAN, D.R. (1950) Factors affecting the number of tumour metastases. Experiments with a transplantable mouse tumour, Cancer Res., 10, 357.