PRIMARY CARCINOMA OF THE BRONCHUS: PROGNOSIS FOLLOWING SURGICAL RESECTION

(A clinico-pathological study of 200 patients)

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by

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SINCE EVARTS GRAHAM in 1933 first successfully performed pneumonectomy for primary carcinoma of lung more and more patients with this disease are being treated by surgery. Surgical treatment is the only present hope of cure; but, following surgery, many questions arise that as yet remain unanswered.

The purpose of this lecture is to discuss some of these problems. The questions include:—

(1) The anatomical sites of the intra-pulmonary lymph nodes;
(2) The usual path of lymphatic spread of carcinoma of lung from the various lobes towards the hilum;
(3) The nature and extent of pulmonary lymph node invasion at the time of operation;
(4) The behaviour of the various histological types of carcinoma of lung with reference to the pulmonary lymph nodes; and
(5) The relationship of invasion by neoplasm of the lymph nodes of the operation specimen to prognosis.

One also asks:—

(6) Is there any relationship between site of growth and survival time, and type of growth and survival time;
(7) Can deep X-ray therapy to the mediastinum after pneumonectomy materially affect survival time;
(8) What is the relationship between symptomless carcinoma of lung first detected by mass radiography, extent of lymph node invasion at the time of operation, and survival time;
(9) Is there any relationship between neoplastic invasion of the bronchus at the line of bronchial section and the subsequent development of post-operative bronchial fistulae;
(10) What are the more usual causes of post-operative death; and
(11) Is the maxim "Surgery of carcinoma is surgery of the lymphatic system" as true for lung as elsewhere?

Between the years 1933 and April, 1951, 1,800 patients with primary carcinoma of the lung have been investigated by the North Regional Chest Surgery Centre, now at Shotley Bridge Hospital, Newcastle-upon-Tyne. Of these 1,800 patients 45 per cent. have had an operation. In

26 per cent., as the growth was irremovable, thorocotomy alone was performed ; the remaining 19 per cent. of the total were resected. This lecture concerns that 19 per cent. of patients.

There were 94 per cent. males and 6 per cent. females, and their ages ranged from 32 to 69 years.

The majority of these operation specimens of lung have been preserved, for immediately after operation they had been fully inflated with 10 per cent. formalin solution and stored away. During the past three years 200 have been dissected, and 992 lymph nodes examined—i.e., an average of five lymph nodes per specimen. The specimens and slides of this material are still available.

At the time of dissection the site of each lymph node was charted on a drawing of each lung. If it was later found to be invaded by growth, the node was completed in black ink. Each of the nodes dissected was sectioned, and histologically examined by Dr. Dawson and her staff of the Research Laboratory of the Royal College of Physicians of Edinburgh. The primary growth and a circle of bronchus at the line of section were also histologically examined. It was not possible to cut serial sections of the lymph nodes ; but further sections were made when microscopic findings differed from what was suspected by macroscopic examination.

HISTOLOGICAL TYPES OF CARCINOMA OF LUNG

These carcinomas were divided into three main histological patterns :—

(*a*) The epidermoid or squamous celled carcinoma,
(*b*) The adenocarcinoma, and
(*c*) The undifferentiated carcinoma, including oat, round and small-cell types.

It is recognised that these divisions are purely arbitrary, that there is a wide range of differentiation possible in one type of carcinoma, and that great pleomorphism is often present in one tumour, so that, whereas a tumour may be predominantly epidermoid, it may also have areas of acinar structure, and areas where the cells are small and undifferentiated. It is nevertheless felt that these three groups show the essential histological features, and that greater sub-division is neither indicated nor necessary.

INDICATIONS FOR RESECTION

Mason (1949) has stated the indications for resection used in the North Regional Chest Surgery Centre.

Exploratory thorocotomy is recommended in all cases without obvious contra-indications such as clinical or radiological evidence of dissemination of growth, bad general condition of the patient, bronchoscopic evidence of distortion and widening of the bifurcation of the trachea, and extension of the growth too close to the bifurcation of trachea or into the mediastinal viscera. Advanced age, poor cardio-respiratory reserve, emphysema, and arteriosclerosis, especially coronary insufficiency, have been shown to be contra-indications.

Although as yet no growth has been operable in the presence of recurrent nerve palsy, diaphragmatic palsy does not conclusively indicate malignant invasion of the phrenic nerve, which may be injured by pressure alone or by associated inflammation. Empyema is certainly not a contra-indication, and habitual and complete investigation of all cases of empyema, including bronchoscopy and bronchography during convalescence, has occasionally yielded an operable growth. Barium examination of the oesophagus has long been standard practice, for patients have never proved operable where the oesophagus has been found to be distorted.

All operations were performed with careful hilar dissection technique, removing all surrounding lymph nodes, and the pericardium if invaded. More recently, extensive mediastinal block dissections of lymph nodes and pericardium have been the rule.

WHAT ARE THE USUAL SITES OF INTRA-PULMONARY LYMPH NODES?

These will be indicated in relation to the normal anatomy of the bronchial tree.

It is stressed that lymph vessels from each lung not only converge on the bifurcation of the trachea, but also communicate with the posterior mediastinal lymphatic vessels along the path of the inferior pulmonary veins and through the lymph vessels running in the pulmonary ligaments.

The path to the mediastinum is therefore broad.

The Lymph Nodes of the Right Lung (Fig. 1a)

Ninety-three specimens of right lung were dissected, and a total of 486 lymph nodes from right lungs examined. (Table I.)

These nodes were found in 16 different sites. They included a group removed in the block dissection of the mediastinum.

The commonest site for lymph nodes in the right lung was lying between the upper and middle lobe bronchi.

The second commonest site was found to be along the medial surface of the right main bronchus.

Nodes were also found lying above, medial to, and behind the *right upper lobe bronchus.*

The middle lobe bronchus was surrounded with nodes lying both medial and lateral to it, and in the angle between it and the lower lobe bronchus.

In the lower lobe, nodes were dissected from above the apical bronchus, medial to it, and between it and the posterior basal bronchus.

In relation to the *basal bronchi*, nodes lay medially and laterally; and finally also along the line of the *pulmonary ligament.*

The Lymph Nodes of the Left Lung (Fig. 1b)

From 100 lungs, 495 lymph nodes were removed. They occurred in 17 sites, including also a group removed in the block dissection of the mediastinum. (Table II.)

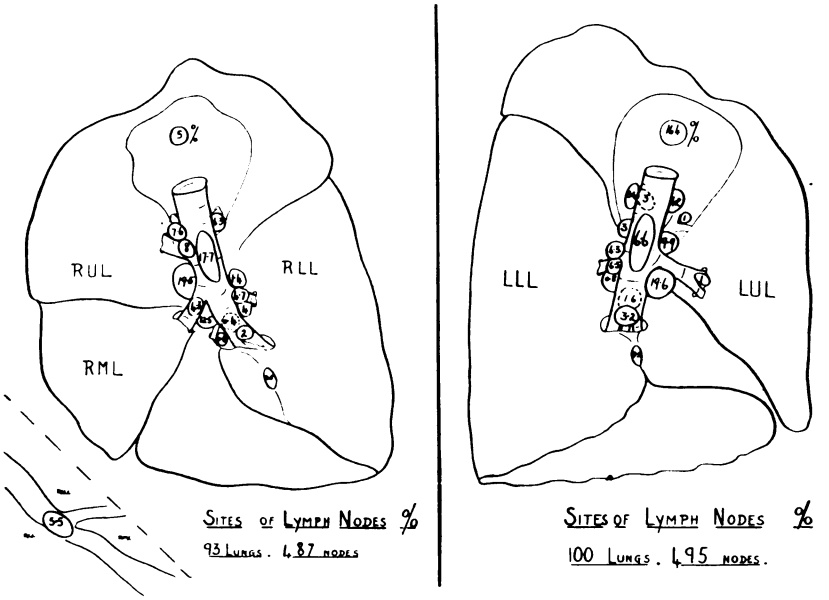

Fig. 1. Diagram of medial surfaces of right and left lungs showing sites of lymph nodes per cent.

The commonest site within the left lung was at the division between the upper and lower lobes, which region appeared to be the " lymphatic sump " within the left lung.

Around the *left main bronchus* was a collar of nodes lying in front, behind, medially and laterally to it.

A similar collar of nodes lay around the *left upper lobe bronchus*, being situated above, behind, medial and lateral to it, and at the carina dividing the apical and anterior bronchi of the left upper lobe.

The nodes of the *left lower lobe* mirrored those of the right lower lobe.

Small and less constant nodes lay in the angles of sub-division of the segmental bronchi within both lungs.

Besides 193 specimens of lung, seven lobectomy specimens for carcinoma were dissected. The sites of lymph nodes in these specimens followed the pattern established in dissection of whole lungs.

THE USUAL PATH OF LYMPHATIC SPREAD OF CARCINOMA OF LUNG FROM THE VARIOUS LOBES TOWARDS THE HILUM : AND THE NATURE AND EXTENT OF PULMONARY LYMPH NODE INVASION AT THE TIME OF OPERATION

On this anatomical pattern of the usual sites of lymph nodes around the bronchial tree I now wish to show the usual path of lymphatic node

TABLE I

TABLE OF DISTRIBUTION OF LYMPH NODES IN RIGHT LUNG
TOTAL: 486 Nodes. 93 Lungs

	No.	Per-centage	No. Invaded
1. On medial surface of main bronchus	86	17·7	24
2. Removed in mediastinal strip with specimen	25	5	2
3. Lying above upper lobe bronchus	37	7·6	4
4. Lying posterior to upper lobe bronchus	21	4·3	3
5. Lying medial to upper lobe bronchus	39	8	5
6. Lying between upper and middle lobe bronchus	95	19·5	24
7. Lying lateral to mid-lobe bronchus and pulmonary artery	27	5·5	4
8. Lying medial to mid-lobe bronchus and pulmonary artery	21	4·3	5
9. Lying below mid-lobe bronchus and pulmonary artery	60	12·5	15
10. Above apical bronchus to lower lobe	7	1·4	—
11. Medial to apical bronchus to lower lobe	23	4·7	9
12. Below apical bronchus to lower lobe	20	4	5
13. Medial to lower lobe bronchi	9	2	—
14. Lateral to lower lobe bronchi	2	0·4	—
15. Between anterior and mid-basals	3	0·6	—
16. In pulmonary ligament	11	2·5	1
Total	486	100%	101

Percentage of total nodes invaded=20 per cent.

TABLE II

TABLE OF DISTRIBUTION OF LYMPH NODES IN LEFT LUNG
TOTAL: 495 Nodes. 100 Lungs

1. Removed in mediastinal strip	81	16·4	12
2. Lying medial to left main bronchus	33	6·6	2
3. Anterior to left main bronchus	21	4·2	2
4. Posterior to left main bronchus	17	3·4	2
5. Lateral to left main bronchus	13	3	2
6. Above upper lobe bronchus	49	9·9	11
7. Posterior to upper lobe bronchus	14	3	1
8. Medial to upper lobe bronchus	29	6	1
9. Lateral to upper lobe bronchus	6	1	1
10. In sub-carina between apico-posterior and anterior bronchus	6	1	—
11. Between upper and lower lobe	97	19·6	33
12. Above apical bronchus lower lobe	22	4·3	5
13. Medial to apical bronchus lower lobe	32	6·5	3
14. Below apical bronchus lower lobe	4	0·8	—
15. Medial surface of basal bronchus	16	3·2	2
16. Lateral surface of basal bronchus	8	1·6	—
17. Pulmonary ligament	47	9·5	2
Total	495	100%	79

Percentage of total nodes of left lungs invaded=16 per cent.

invasion from primary growths in the various lobes of each lung towards the hilum, and the extent of pulmonary lymph node invasion at the time of operation.

Forty-six per cent. of the right lungs and 50 per cent. of the left lungs had one or more nodes invaded by neoplasm at the time of pneumonectomy.

Right Lung (Table III)

With *right upper lobe* growths the collar of nodes around the right upper lobe bronchus was readily affected. Equally important were those nodes

TABLE III

RIGHT LUNG

TABLE OF SITES OF INVADED NODES IN RELATION TO THE LOBES

Site of Node	R.U.L.	R.M.	R.M. & L.	R.L.L.	Total
Mediastinal strip	2	—	—	—	2
Medial to main bronchus	2	—	2	20	24
Above upper lobe bronchus	4	—	—	—	4
Medial to upper lobe bronchus	2	—	—	3	5
Behind upper lobe bronchus	2	—	—	1	3
Between upper and middle lobes	5	2	1	16	24
Medial to middle lobe bronchus	—	—	—	5	5
Lateral to middle lobe bronchus	—	—	—	4	4
Below middle lobe bronchus	—	—	1	14	15
Medial to apical bronchus of lower lobe	—	—	—	9	9
Below apical bronchus of lower lobe	—	—	—	5	5
In pulmonary ligament	—	—	—	1	1
Total	17	2	4	78	101

lying in the angle between the upper and middle lobe bronchi, and also along the medial surface of the right main bronchus. The line of invasion did not extend below the level of the middle lobe bronchus. (Fig. 2*b*.)

Where the primary growth was in the *right middle lobe* alone, just those nodes lying between the upper and middle lobe bronchi were found to be invaded. (Fig. 2*a*.)

Where the primary growth occurred *in both middle and lower lobes*, neoplastic cells were arrested in nodes between these two lobes, as well as in the groups lying between the upper and middle lobe bronchi, and along the medial surface of the right main bronchus. (Fig. 2*c*.)

Primary growths of the *right lower lobe* affected a much wider lymphatic field, nodes in at least 10 of the possible 16 sites being invaded.

The collars of nodes arranged around the basal bronchi and the apical bronchus of the lower lobe, that is the regional lymph nodes of these lung segments, were frequently invaded.

Medially spreading growth invaded those nodes lying in the pulmonary ligament and around the inferior pulmonary vein.

Upward spreading emboli, draining towards the hilum of the lung, were arrested in nodes surrounding both the middle and upper lobe bronchi, and above all in that right lymphatic sump between the upper and middle lobe bronchi, and along the medial side of the main bronchus.

There was one important difference between the percentage invasion of lymph nodes per lobe of the right lung. Whereas in the upper and middle lobe growths no more than 13 per cent. of resected nodes were invaded by growth, in *right lower lobe growths* as much as 26·3 per cent. of nodes were invaded at the time of operation.

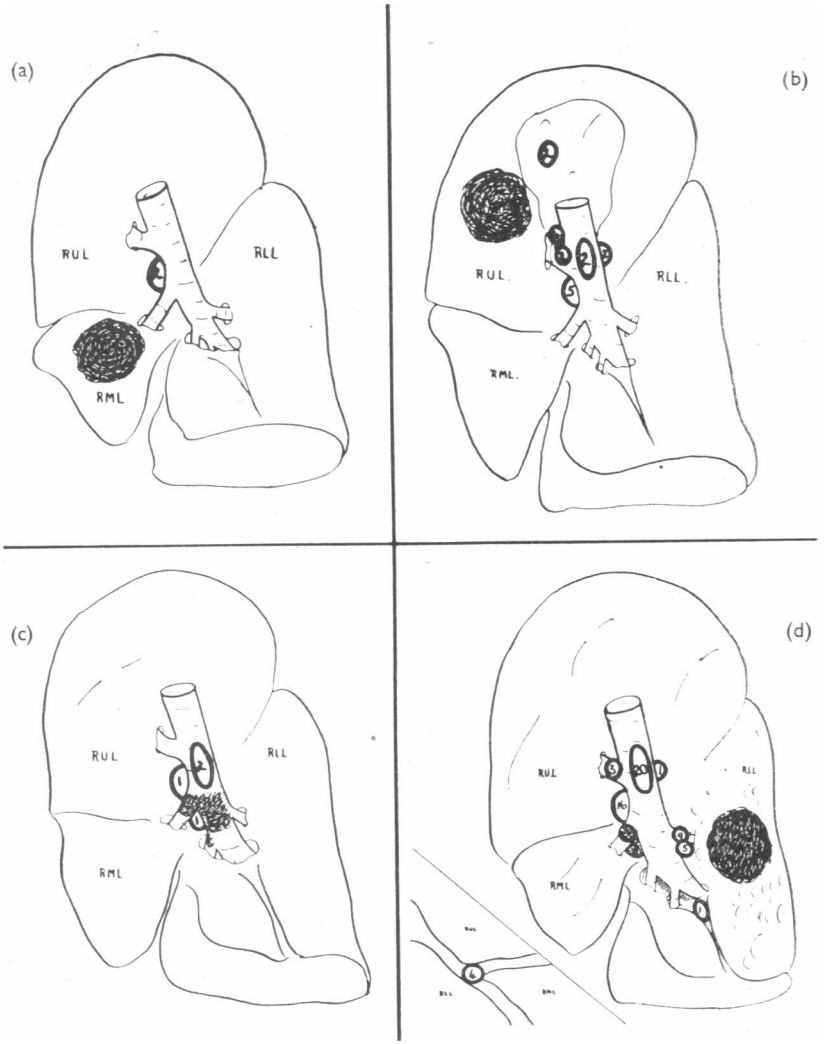

Fig. 2. The nature and extent of lymph node invasion at the time of resection. (The figures are the total number of nodes invaded.) (See Table III.)

(*a*) Middle lobe growths treated by pneumonectomy. 4 cases. 16 nodes dissected. Site of 2 invaded nodes. Invasion rate, 12 per cent.

(*b*) Right upper lobe growths treated by pneumonectomy. 26 cases. 132 nodes dissected. Site of 17 invaded nodes. Invasion rate, 13 per cent.

(*c*) Growths involving right, middle and lower lobes treated by pneumonectomy. 8 cases. 42 nodes dissected. Site of 4 invaded nodes. Invasion rate, 9·5 per cent.

(*d*) Right lower lobe growths treated by pneumonectomy. 55 cases. 297 nodes dissected. Site of 79 invaded nodes. Invasion rate, 26·3 per cent.

Left Lung (Table IV)

With *left upper lobe growths* invaded nodes were resected from the mediastinum, from around the left main bronchus, and around the left upper lobe bronchus. The nodes lying between the upper and lower lobe bronchi were also invaded, and even lower groups in relation to the apical and basal bronchi of the *left lower lobe.* (Fig. 3*a*.)

With *left lower lobe growths* the area of lymph node invasion was as extensive as with right lower lobe growths, 11 of the possible 17 sites being affected. The groups included nodes around the lower lobe bronchi, in the pulmonary ligament, between the upper and lower lobe bronchi, as well as around the upper lobe bronchus, the left main bronchus and in the mediastinal strip. (Fig. 3*b*.)

In neither of the lobes of the left lung was lymphatic invasion per lobe ever so high as the 26·5 per cent. of the right lower lobe. On this left side it averaged 16 per cent.

Conclusions

From a study of these charts it is concluded :—

1. That the regional nodes of each lobe lie around the base of the segmental bronchi.

2. That in the right lung neoplastic invasion *does appear to* progress from one lymph node barrier to the next, and that the most frequently invaded groups are :

(*a*) those lying between the right upper and middle lobes, and

(*b*) medial to the right main bronchus.

3. That in the left lung the progress of spread is similar, the most frequently invaded groups of nodes being those lying :

(*a*) between the left upper and left lower lobes, and

(*b*) medial to the left main bronchus.

TABLE IV

LEFT LUNG

TABLE OF SITES OF INVADED NODES IN RELATION TO THE NODES

Site of Node	L.U.L.	L.L.L.	Total
Mediastinal strip	5	7	12
Medial to main bronchus	—	2	2
Anterior to main bronchus	2	—	2
Posterior to main bronchus	2	—	2
Lateral to main bronchus	1	1	2
Above upper lobe bronchus	7	4	11
Medial to upper lobe bronchus	1	1	2
Lateral to upper lobe bronchus	—	1	1
Posterior to upper lobe bronchus	—	—	—
Between upper and lower lobe bronchi	15	18	33
Above apical bronchus of lower lobe	3	2	5
Medial to apical bronchus of lower lobe	—	3	3
Medial surface of basal bronchus	1	1	2
In pulmonary ligament	—	2	2
Total	37	42	79

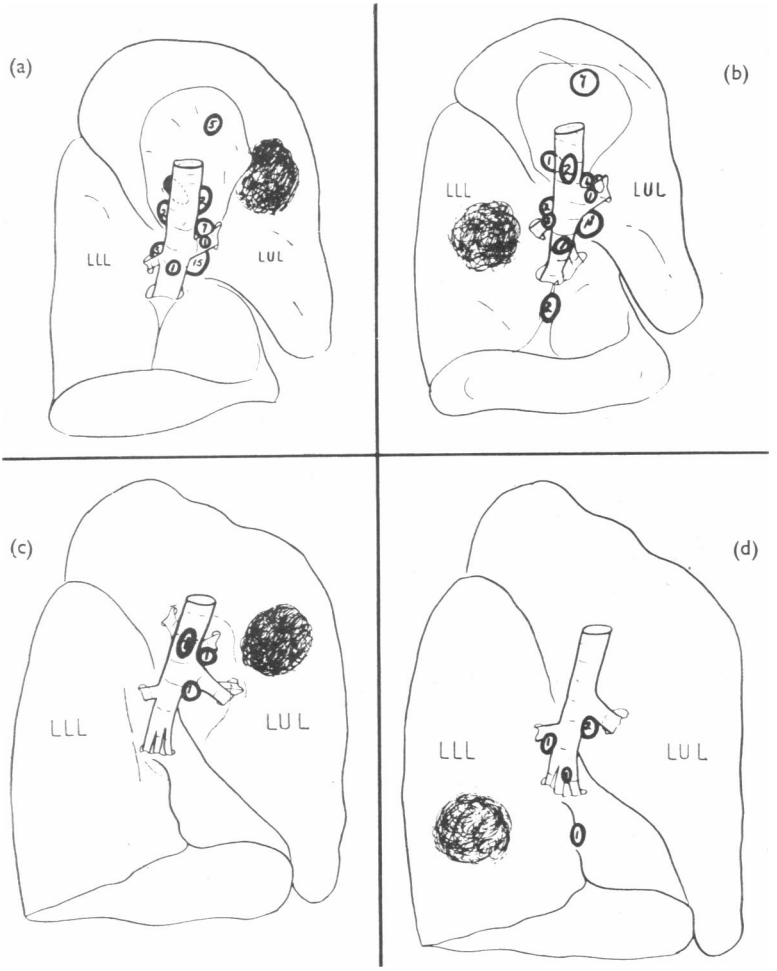

Fig. 3. The nature and extent of lymph node invasion at the time of resection—continued. (See Table IV.)

(*a*) Left upper lobe growths treated by pneumonectomy. 39 cases. 246 nodes dissected. Site of 37 invaded nodes. Invasion rate, 15 per cent.

(*b*) Left lower lobe growths treated by pneumonectomy. 61 cases. 249 nodes dissected. Site of 42 invaded nodes. Invasion rate, 17 per cent.

(*c*) Left upper lobe growths treated by lobectomy. 3 cases. 3 nodes invaded in 2 specimens.

(*d*) Left lower lobe growths treated by lobectomy. 3 cases. 5 nodes invaded in 2 specimens.

This is not surprising, for these are the sites where intra-pulmonary nodes were most commonly found.

4. Further, these findings emphasise the importance of that region between the *upper* and *middle* lobes on the right side, and between the *upper* and *lower* lobes on the left side, and show why lobectomy, even as a palliative procedure for carcinoma of lung, is frequently not technically possible.

Lobectomy

The extent of pulmonary lymph node invasion at the time of lobectomy for carcinoma bore a close relation to the findings established for pneumonectomy.

Seven lobectomies were performed, one right lower lobe, three left upper lobes, and three left lower lobes. (Fig. 3*c* and *d*.)

The figure shows :—

(1) The sites of the eight invaded nodes, all in the left lung, and

(2) That lobectomy was performed where nodal invasion was present.

It is noteworthy that all but two who had lobectomy died within a year of operation. The two survivals, both recent operations, each had a lower lobectomy for epidermoid growth ; one of these was found to have one lymph node invaded.

IS THERE ANY VARIATION IN BEHAVIOUR OF THE HISTOLOGICAL TYPES OF CARCINOMA OF LUNG IN THE PULMONARY LYMPH NODES?

In this series of 200 resections there were :—

68 per cent. *epidermoid growths*,
27·5 per cent. *undifferentiated*, and
4·5 per cent. *adenocarcinoma*.

By way of contrast, the total lymph node invasion rate from these three cell types showed a remarkably different pattern. In the average of right and left lungs, *whereas only* 42·5 *per cent. of the epidermoid growths* had extended into the lymph nodes at the time of resection of the lung, as *high as* 70 *per cent. of the undifferentiated growths* HAD INVADED THE LYMPH NODES. Adenocarcinomas only invaded the lymph node once. (Fig. 4*a*).

Right Lung

The distribution of neoplasm within the lobes of the *right lung* was as follows :—

R.U.L. 29 per cent.
R.M.L. 4 per cent.
R.M.& L. 8 per cent.
R.L.L. 59 per cent.

In all but the middle lobe did epidermoid growths predominate.

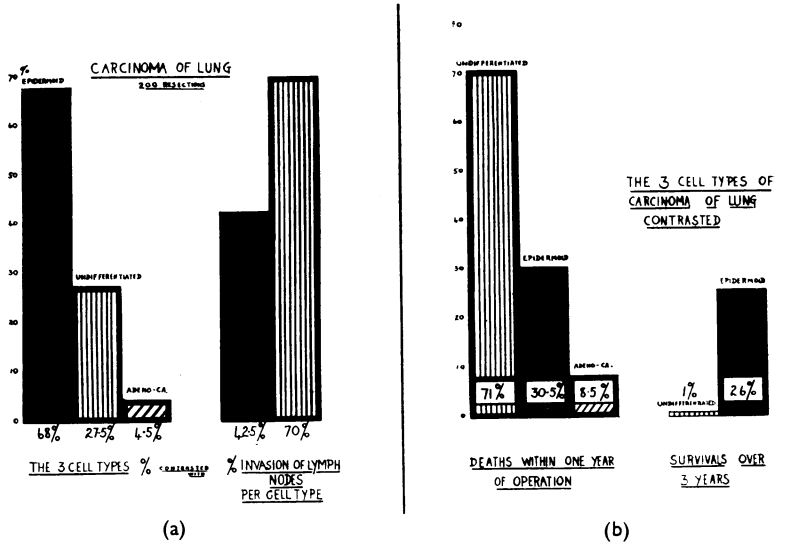

Fig. 4

(*a*) The relative frequency of the three cell types of primary carcinoma of lung contrasted with percentage invasion of lymph nodes per cell type.
(*b*) The survival time of the three cell types of carcinoma of lung contrasted.

Not only did carcinoma occur most commonly in the lower lobes (59 per cent.), but also from lower lobe growths intra-pulmonary lymph nodes were most commonly invaded. I found that, of the *group of right lungs with invaded lymph nodes*, over three-quarters came from right lower lobe neoplasms.

Left Lung

In the left lungs (106 specimens—100 lungs and 6 lobectomies) there was almost equal distribution between upper and lower lobes, there being :

49 per cent. in the upper lobe,
1 per cent. at the hilum and involving both upper and lower lobe,
50 per cent. in the lower lobe.

Summarising therefore, whereas *epidermoid growths* are by far the commonest, comprising 68 per cent. of this series of primary cancer of lung, they were *only* associated with a 42·5 *per cent. invasion rate of the lymph nodes* in all the resected specimens. On the other hand *undifferentiated growths*, which constituted only 27·5 per cent. of this series, were associated with a 70 *per cent. lymph node invasion rate.* It is therefore suggested that, apart from any other characteristic of the undifferentiated type of growth, this greater proportion of invaded nodes is one of the factors in the worse prognosis for the undifferentiated cell type of lung cancer.

CAN A KNOWLEDGE OF THE EXTENT OF INVASION OF THE LYMPH NODES OF THE OPERATION SPECIMEN REASONABLY BE USED IN ASSESSING PROGNOSIS ?

There were available for dissection 72 specimens from patients who had had pneumonectomy for primary carcinoma of the lung more than three years ago (before April, 1948) and who had survived operation. (Several long term survivals have not been included, as their specimens were no longer available.) As they have not lived long enough yet after operation, the 128 resections performed since April, 1948 have not been included in this section. These will be reviewed again in 10 years time, when a truer estimate can be made.

From a study of the earlier group, however, it is possible to get a clear idea of the extent of spread of the growth via the lymphatic system at the time of resection, and thereafter to co-relate that knowledge with survival time in an attempt to assess prognosis following successful surgery. Such knowledge has already proved its worth in determining prognosis after resection of the rectum for primary carcinoma.

In this group of 72 patients with lung resection it is emphasised that all growths had been proven histologically by bronchoscopic biopsy before resection, and/or examination of the specimen after resection. In determining the exact date and mode of death, however, as most died at home, such data had to be obtained from the family physician, for in an area as extensive as the four counties comprising the North Medical Region, namely Northumberland, Durham, Westmorland and Cumberland, besides northern-most Yorkshire, it was not possible to arrange re-admission of the patients in the terminal phase of their illness.

Of the 59 patients in this group who have died since operation, the reported causes of death were as follows :—

Death from :—	
Metastases	50
Broncho-pleural fistula	1
Pleural sepsis	1
Broncho-pneumonia	5
Heart failure after Thorocoplasty	1
Cerebral vascular Thrombosis	1
	59
Alive	13
Total	72

When deaths from metastases *alone* are considered and graphed over a four-year period, it is seen that the heaviest toll was taken in the first year, when 62 per cent. occurred. It was only after three years that there was a fall, and by then the possible number of survivals had also fallen. This chart suggests that, as with carcinomas elsewhere, one cannot expect to claim lung " cancer cures " until three years—the natural span of most cancers—have elapsed. (Fig. 5*a*.)

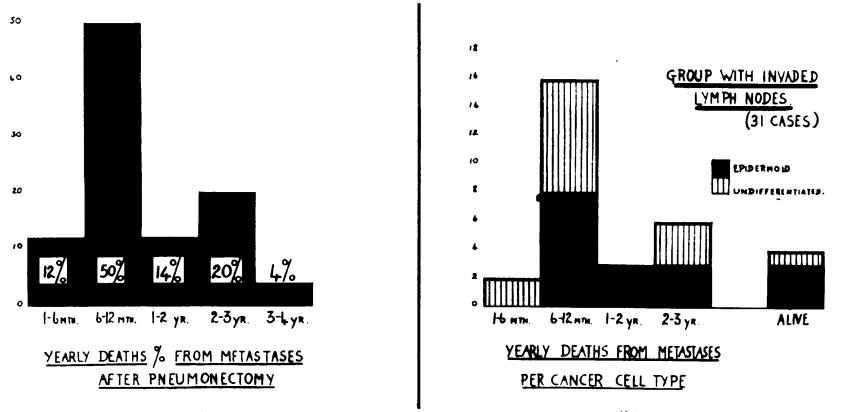

Fig. 5

(*a*) Yearly deaths per cent. from metastases after pneumonectomy for primary carcinoma of lung.

(*b*) Yearly number of deaths from metastases per cancer cell type in group with invaded lymph nodes.

What is the Behaviour of the Three Histological Types of Carcinoma of the Lung in these 72 Patients ?

Like the larger series :—

66 per cent. were epidermoid growths	(47)
29 per cent. undifferentiated	(21)
5 per cent. adenocarcinomas	(4)

In their behaviour there was also a distinct difference.

Of the undifferentiated group, 71 per cent. were dead from metastases within one year of operation—and only one patient survived beyond three years.

On the other hand, only 30·5 *per cent.* of the *epidermoid growths* were dead one year after operation, while 26 per cent. survived a period ranging from nine to three years. (Fig. 4*b*.)

The four adenocarcinomas lived 3, 6½, 30 and 48 months respectively.

The great variability in the behaviour of epidermoid growths following surgery is therefore obvious.

Is there any Clear Relation between Lymph Node Invasion and Long Term Survival ?

Metastases caused the death of 70 per cent. of this group who had operation three or more years ago. Of these patients dying from metastases, three-fifths (31 cases) had invaded lymph nodes in their specimens when resected, and two-fifths no invasion.

Of the group *with invaded lymph nodes*, more than half, 54·5 per cent., were dead one year after operation, 85 per cent. at the end of three years.

To-day, only 11 per cent. (four cases) of this group *with invaded lymph nodes* are alive.

In three of these patients only one node was invaded, and in the fourth—two nodes

Turning now to the group *with no nodes invaded*, as many as 43 per cent. of the patients died from metastases within a year of operation, and 66 per cent. at the end of three years. Thirty-three per cent. survived longer.

It is concluded that there is a small difference between the presence or absence of lymph node invasion and long term survival. In both a high percentage die early ; but, as mortality in the group with invaded nodes is higher than in the group without invasion, invasion of lymph nodes must be associated with a worse prognosis.

Before leaving this important question of prognosis following pneumonectomy, however, several further questions remain to be asked.

Does Type of Growth Affect Survival Time of Patients with Lymph Nodes Invaded on the Operation Specimen ?

There was a small difference between type of growth with invaded lymph nodes, and survival time.

As the figure of yearly number of deaths from metastases per cancer cell type shows (Fig. 5*b*), the undifferentiated growths, true to their nature, took their toll earlier than the epidermoid growths ; but by the time three years had elapsed, this early lead was lost.

Does the Number of Nodes Invaded per Specimen Significantly Affect Prognosis ?

Of the group with invaded lymph nodes, just over a half had only one node invaded (51·5 per cent.), and just under a half (48·5 per cent.), two or more nodes invaded.

As by the end of three years 85 per cent. of this total group with invaded lymph nodes was dead, divided into 45 per cent. with one node invaded and 40 per cent. with several nodes invaded, no claim can be made that the number of nodes invaded per specimen is a guide to prognosis.

Does the Position of the Invaded Node Bear any Relation to Prognosis ?

In other words, can carcinoma of lung be divided into three grades according to distance spread via the lymphatic system, and can that be used as a basis for assessing prognosis ?

It is suggested that three gradings :—

(*a*) No lymph node invasion,

(*b*) Local intra-pulmonary lymph node invasion, and

(*c*) Mediastinal lymph node invasion

might form the basis of such a division of carcinoma of the lung similar to the grading used for rectal carcinomas, and suggested for gastric carcinomas treated by total gastrectomy. (Allison and Borrie, 1949.)

Anatomical difficulties immediately present themselves. Most lymph nodes have been seen to lie along the medial surface of the bronchi, where they are in fact in direct contact with the posterior mediastinum. Spread of neoplasm medially into the mediastinum is not only possible, but, as has been seen in those patients who had thoracotomy alone, it frequently occurs.

Therefore, although one may attempt to assess prognosis according to site of lymph nodes invaded in an upward direction towards the lung hilum, unless one considers the possibility of medial spread as well, such a basis for prognosis is worthless.

The truth is that the regional lymph nodes for the lobes of the lung lie so near the lobes they drain, and themselves drain into such a wide network of nodes, that, once a neoplasm has invaded them, the prognosis following surgery cannot easily be predicted from studying those lymph nodes.

What Happens if Mediastinal Lymph Nodes are Invaded ?

At the time of pneumonectomy, 20 of the 200 patients in the whole series had invaded nodes which were removed from the mediastinum during the dissection and mobilising of the hilar structures. Sixteen of these 20 patients died from metastases within 15 months of operation.

What Happens where no Lymph Nodes are Invaded ?

Twenty of the patients who died within 15 months of operation from metastases had no lymph node invasion at all.

Further dissection of these specimens showed that the growths had either penetrated deeply into the walls of the veins around which they grew, or had even fungated into the lumen of the veins.

Clearly, blood-stream invasion occurs much earlier and more easily in lung cancers than is usually appreciated. By their nature these growths are invasive. They grow in constantly moving tissue surrounded by a vast network of capillaries. Can it be doubted that such factors affect ease of blood-stream spread ?

Is there any Relationship between Site of Primary Growth and Survival Time ?

In this smaller series of 72 patients there was the same preponderance of growths in the lower lobes as was seen in the total group of 200 patients.

In these long term cases, though numbers are small, the interesting finding was that 8 of the 13 patients alive after operation over three years ago had growths *in the upper lobe*, four on the right side and four on the left.

This finding may be of some significance for earlier it was demonstrated that, whereas around the right lower lobe bronchi 26 per cent. lymph nodes were invaded, only 12 per cent. were invaded with upper lobe growths.

Conclusions

From a study of lymph node invasion in relation to prognosis in the earlier resections, it is therefore concluded :

(1) That having survived operation by the end of 3 years a total of 82 per cent. of patients are dead, and 70 per cent. of the total are dead from metastases.

(2) That there is a distinct difference between the behaviour of the undifferentiated and epidermoid cell carcinoma, 71 per cent. of the former, and 30·5 per cent. of the latter being dead from metastases one year after operation. Few if any undifferentiated growths survive 3 years. On the other hand 26 per cent. of epidermoid growths may survive beyond 3 years.

(3) That, as 85 per cent. of cases with lymph nodes invaded, and 66 per cent. of cases with no lymph nodes invaded were dead 3 years after operation, there is, as yet, no clear relation between presence or absence of lymph node invasion, and long term survival, except that invasion of lymph nodes adversely affects prognosis and usually means death within 3 years of operation.

(4) That there was no significant prognostic factor *between type of growth invading lymph nodes*, and survival time.

(5) That the number of nodes invaded per specimen was no clear guide to prognosis.

(6) That it is not possible to divide carcinomas of lung into 3 grades according to site of invaded nodes as a basis of prognosis, for too high a proportion of patients with no nodes invaded died early from blood-borne metastases to allow of such a claim.

(7) That invasion of mediastinal nodes was usually associated with death within 15 months of resection.

(8) That upper lobe growths had a small if not significantly more favourable prognosis.

There remain a series of individual problems included in this investigation, yet to be mentioned.

DOES DEEP X-RAY THERAPY TO THE MEDIASTINUM AFTER PNEUMONECTOMY MATERIALLY AFFECT SURVIVAL TIME?

The aim of deep X-ray therapy to the mediastinum after pneumonectomy has been to treat any possible remaining deposits of metastatic tumour.

Of the total of 200 patients, 55 or just over a quarter had such treatment in doses ranging up to 5,000 roentgens, and given over a period of 4-6 weeks. There were 28 undifferentiated growths and 27 epidermoid cell growths.

This group may be divided into four sections :—

(1) Epidermoid—without lymph node invasion .. 25·5 per cent.
(2) Epidermoid—with lymph node invasion .. .. 23·5 per cent.
(3) Undifferentiated—without lymph node invasion .. 5·5 per cent.
(4) Undifferentiated—with lymph node invasion .. 45·5 per cent.

The high proportion of lymph nodes invaded by the undifferentiated growths is striking. It follows the rule that undifferentiated growths readily invade the lymph nodes.

The survival time of the *undifferentiated growths* in no way differed from the overall pattern—there being only two patients alive—16 and 11 months after operation respectively. The remaining 26 patients had all died within one year of operation, deep X-ray therapy having had no favourable effect on the course of their disease.

Of the epidermoid growths with invaded nodes there were two long survivals—one 5⅓ and the other 6 years from operation. One other is alive—but just 13 months from operation. The remaining 10 are all dead, nine having lived less than 18 months and the tenth 29 months.

Time may yet show more promising results amongst the 14 *epidermoid growths without lymph node invasion.* In this group there were two long term survivals, of 5 and 5½ years. Five of the remaining 12 are alive up to 13 months from operation. The final seven all died from metastases, death occurring between 12 and 36 months after operation.

Conclusions

Regarding these four long term survivals, as there are nine patients who survived just as long *without* deep X-ray therapy, as this noticeable difference in behaviour between undifferentiated and epidermoid growths has been shown to occur irrespective of deep X-ray therapy, and, as deep X-ray therapy did not significantly lengthen survival time per cell type of growth, it is concluded that such therapy has little effect on survival time.

Its great value has been found in easing certain symptoms in those *not* suitable for surgery :—

(*a*) by causing necrosis in a tumour and thereby unblocking a blocked bronchus to allow reaeration of a collapsed lung,

(*b*) by relieving pain from metastatic deposits in bone, and

(*c*) by relieving the suffocating distress of superior mediastinal obstruction. Even superior mediastinal obstruction, due to local recurrence after pneumonectomy, has been relieved by deep X-ray therapy.

(Pre-operative deep X-ray therapy has not yet been given in this unit.)

SYMPTOMLESS CARCINOMA OF LUNG DETECTED BY MASS RADIOGRAPHY, EXTENT OF LYMPHATIC SPREAD AT OPERATION, AND SURVIVAL TIME

Eight of the 200 patients were symptomless. Their carcinomas were first detected when mass radiography revealed an unsuspected shadow in the lung fields.

The growths were situated :—

Right middle lobe	.. 1	Left upper lobe	.. 3
Right lower lobe	.. 2	Left lower lobe	.. 2

In only two patients were biopsies positive. In the remaining six resection was performed for a symptomless round shadow, which, in the absence of any other cause, was believed to be primary carcinoma. Six patients had pneumonectomy, and two lobectomy.

Subsequent examination of the specimen showed that in three of the eight cases, hilar lymph nodes were invaded. Two of these patients are dead seven and eight months after operation, and the third is alive 18 months from operation. (Fig. 6*a*.)

The final outcome is not surprising, for, where several lymph nodes are invaded at the time of resection, death is likely within a year of operation. On the other hand, it is again emphasised that, with one node invaded, or none, no assurance for the future can be given.

Three patients had no lymph node involvement, yet lived but a short time after operation, dying from metastases, three, nine and 19½ months respectively. (Fig. 6*b*.)

Two others—one a lobectomy, and one a pneumonectomy—are still alive, both 16 months after operation. Neither had lymph node invasion.

In thinking about this group, it does seem remarkable that such *peripheral* neoplasms, first detected as a round shadow on an X-ray film, can have spread into the lymph nodes so soon. And yet, the fact that such *does* happen, only emphasises the more that situation of primary growth in the lung alone confers *no* immunity and *no* security against early lymph node invasion, and that, because these peripheral growths do not readily cause the blocked bronchus syndrome of *cough, spitting of blood*, lobar infection, pleurisy and pain, they are often far *advanced* when first detected.

Again, early death from distant metastases, without lymph node invasion in this group of peripheral neoplasms only emphasises the more the importance of early blood-stream spread, and of the unpredictable nature of primary lung cancer following surgery.

THE RELATIONSHIP BETWEEN NEOPLASTIC INVASION OF THE BRONCHUS AT THE LINE OF TRANS-SECTION, AND THE DEVELOPMENT OF POST-OPERATIVE BRONCHIAL FISTULAE

From all specimens a complete circle of bronchus was cut to include the edge of the bronchus at its line of trans-section. This piece of bronchus was then examined microscopically to determine if there was any invasion by neoplasm.

In one lobectomy and seven pneumonectomy specimens, microscopic evidence of invasion of this line by growth was obtained.

Three of the growths were epidermoid in nature, and five undifferentiated cell.

Their situation was as follows :—One in the right lobe, one in the right lower lobe, one in the left upper lobe and five in the left lower lobe.

All these patients are dead. Three succumbed to the effects of operation, and five survived from three to 18 months to die from metastases.

Examination of a further series of 11 lungs from patients known to have developed bronchial fistulæ after pneumonectomy before 1948 showed no microscopic invasion of the bronchus by growth at the line of transsection. It is therefore concluded that in this series there was no relationship between invasion of the bronchus by growth at that point and fistula formation.

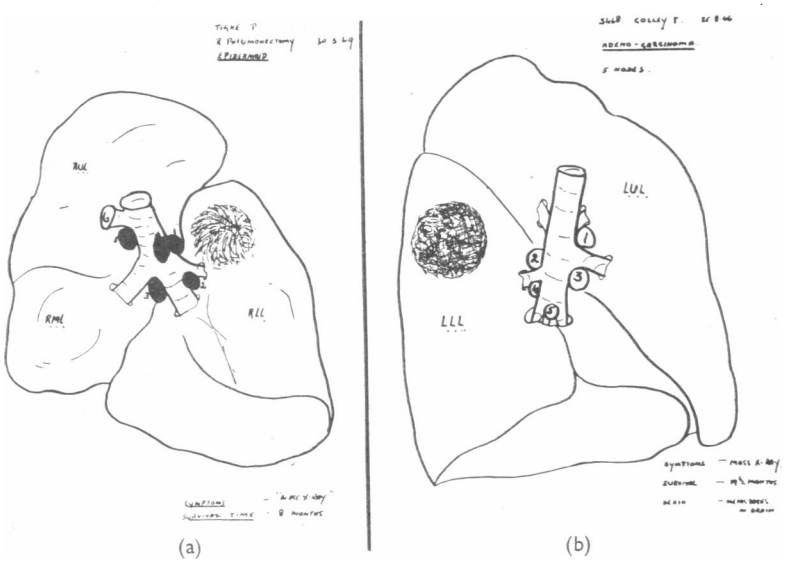

Fig. 6

(*a*) Symptomless round shadow in apical segment of right lower lobe first detected by mass radiography. Five lymph nodes were invaded. Death occurred from metastases 8 months after pneumonectomy.

(*b*) Similar lesion to (*a*). No lymph nodes were invaded. Death occurred from metastases 19½ months after pneumonectomy.

THE CAUSES OF POST-OPERATIVE DEATHS

There were 28 post-operative deaths in a consecutive series of 128 resections for carcinoma of lung performed after April 1948, an operative mortality of 22 per cent. Necropsy was performed in 24 of these 28 patients.

The causes of death were :—

(A) **Operative**

Hæmorrhage R. Pulmonary Artery	1
Hæmorrhage L. Upper Lobe Vein	1
Anoxia	1

(B) **Post-Operative**

(1) (*a*) Pyothorax without bronchial fistula	5	
(*b*) Following total thoracoplasty for pyothorax ..	2	
	—	7
(2) Massive pulmonary embolus		6
(3) Bronchial fistula		3
(4) Cardiac failure		3
(5) Pneumonia in remaining lung		3
(6) Hemiplegia (cerebral vascular catastrophy)		2
(7) Hæmorrhage intercostal vessel		1
		28

(a) Operative Deaths

One patient died following haemorrhage from the pulmonary artery, another after haemorrhage from the upper pulmonary vein, and a third of cerebral anoxia.

(b) Post-Operative Deaths

The commonest cause of post-operative death was *pyothorax without bronchial fistula* or its sequel—a total thoracoplasty, the two combined accounting for seven of the 28 deaths, i.e., 25 per cent. of the group.

The next most common cause of post-operative death was *massive pulmonary embolus,* of which there were six cases *all proven by necropsy,* i.e., 21 per cent. of the group.

Since this investigation was completed two further such deaths have occurred in the clinic.

It is emphasised that chest surgery is by no means immune from this complication.

One asks," Did the emboli arise on the stump of the divided pulmonary artery ? " In none was this proven to be so, and in all, the parent thrombus was shown to be in the veins of the legs.

The emboli occurred without any warning in five patients on the 3rd, in two on the 9th, in one on the 12th and in one on the 39th day after operation. The last, with warning femoral thrombosis, had received anti-coagulant therapy, but this failed to prevent the fatal embolus occurring on the 61st post-operative day.

Concerning the group of cases who had necropsy, a further question arises. *Did any of the patients who had resection, and who later died, have any evidence of distant metastases found at necropsy*—metastases which were not detected in the pre-operative assessment of the patient ? Four of the 28 patients, *or* 14 *per cent.* had such undetected microscopic metastases.

Clinic No.	Symptoms	Type of Neoplasm	Survival	Cause of Death	Findings
4901	18 mths.	Epidermoid	1 day	Heart failure ? Air Embolus	L. suprarenal metastases
5793	6 mths.	Epidermoid	Immed. post op.	Anoxia	Ditto.
6505	6 mths.	Epidermoid	39 days	Pulmonary Embolism	Suprarenal liver and pleura
6199	9 mths.	Epidermoid	44 days	Pyothorax	Suprarenal

Their pre-operative symptoms ranged from six to 18 months.

All four had epidermoid cell growths and all four had unsuspected *suprarenal gland metastases.* As yet metastases in this organ cannot be detected pre-operatively by any known method, but the fact that they can be present though undetected, when surgery is performed, and without there being any regional lymph node invasion by neoplasm, makes one realise the more, that lymphatic spread is only half the story and that some methods must be devised to detect visceral blood-stream metastases if one ever wishes to be assured before operation that there is certain prospect of removing all neoplastic tissue.

I have left to the last the question, " *Is the maxim ' surgery of carcinoma is surgery of the lymphatic system ' as true for lung as elsewhere ?* "

It has been seen that an appreciable number of patients with no lymph node invasion at operation die within a year from widespread metastases.

This was further borne out in the group with peripheral round shadows, and also in that last group described dying a few weeks after operation and on whom necropsy revealed unsuspected suprarenal metastases.

Invasion of the veins of the lung was also found in specimens of patients dying from widespread metastases but with no pulmonary lymph node invasion.

In the face of this evidence, it is difficult to accept that surgery of primary carcinoma of lung is surgery of the pulmonary lymphatic system, and that alone.

I have come to the present conclusions :—

(1) That surgery in the treatment of primary carcinoma of lung, successfully commenced in 1933, is still in its earlier years. Surgical technique is now standardised ; but time must elapse before final evaluation of results can be made.

(2) That resection for lung cancer, though possible in only 19 per cent. of these 1,800 patients, should be continued with increased intensity.

(3) That " cures " can be obtained ; but that extent of lymph node invasion in the operation specimen cannot yet be taken as a certain criterion for assessing prognosis except to say that :—

(*a*) 20 per cent. of resections are likely to be alive 3 years or more after operation ;

(*b*) few with several lymph nodes invaded survive long beyond a year ;

(*c*) where one node only is invaded, *or none*, and the growth is epidermoid in type, early deaths or late survivals may be found—a problem answered only by time.

(4) That the lymphatic system offers an important path for dissemination of growth ; and, therefore, until more is known about the nature of carcinoma of lung at the time when it can be resected, thorough mediastinal block dissection, as advocated by Brock (1948), is worthwhile. But lymphatic spread is not the only spread.

(5) That due regard must also be paid to the important early blood-stream spread ; and, therefore, when resecting lungs for carcinoma, there appears to be every good reason for ligating the pulmonary veins before the pulmonary artery, as advocated by Allison and Aylwin (1951) of Leeds, in order to prevent further spread from operative handling.

(6) That, in the present state of our knowledge, even when surgery is possible, the chance of a cure is still unpredictable. Every patient presenting with primary carcinoma of lung must therefore continue to be viewed as an individual problem, and treated accordingly.

If investigation shows that surgery is indicated and possible, then the operation most suited to the particular needs of that patient at that time should be done, be it radical or palliative to relieve symptoms ; careful follow-up of all patients should be rigorously pursued, and further impartial surveys of this vast field of surgery be regularly made in true Hunterian spirit.

I wish to express my thanks to Dr. E. K. Dawson, Dr. T. W. Lees, and Dr. J. D. McGregor, of the Research Laboratory of the Royal College of Physicians of Edinburgh for all their help in examining the microscopic sections, and to Mr. George A. Mason, Consultant-in-Charge, Northern Regional Chest Surgery Centre, Shotley Bridge Hospital, Newcastle-upon-Tyne, for the use of his material.

REFERENCES

ALLISON, P. R., and BORRIE, J. (1949) *Brit. J. Surg.* **37**, 1.
AYLWIN, J. A. (1951) *Thorax* **6**, 250.
BROCK, R. C. (1948) *Brit. Med. J.* **2**, 737.
GRAHAM, E. A., and SINGER, J. J. (1933) *J.A.M.A.* **101**, 1371.
MASON, G. A. (1949) *Lancet* **2**, 587.

COURT OF EXAMINERS

NOTICE IS HEREBY given that at the meeting of the Council to be held on 3rd April, 1952, a proposal will be put forward for the election of a temporary member of the Court of Examiners.

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Lincoln's Inn Fields, London, W.C.2.

KENNEDY CASSELS,
Secretary.