

# PRIMARY CARCINOMA OF THE LUNG \*

## A PATHOLOGICAL STUDY

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### INTRODUCTION

Primary carcinoma of the lung is exciting an ever increasing interest, both because of its alleged rising incidence and because of the improvement in surgical technique allowing the cure of this disease in its early stages. The purpose of this paper is to classify the pathological anatomy of 69 autopsied cases of lung carcinoma occurring at the Boston City Hospital from Jan. 1, 1900 to August 1, 1934. A classification based on the microscopic morphology has been utilized in an attempt to determine the malignant potentialities, incidence by age and sex, and peculiar characteristics of different types of these tumors. It is to be hoped that a more accurate diagnosis and prognosis may be made from histological study of biopsied or expectorated tissue from these carcinomas in the future.

In 1912 Adler<sup>1</sup> published an analysis of 374 cases which had been reported in the literature up to that time. Of recent years, and especially since 1920, the literature abounds with references and historical reviews. For an adequate discussion of the historical, anatomical, pathological and clinical aspects of this subject, the reader is referred to the works of Adler,<sup>1</sup> Pilcher and Brindley,<sup>2</sup> Barron,<sup>3</sup> Vinson,<sup>4</sup> Weller,<sup>5</sup> Brunn,<sup>6</sup> Brockbank<sup>7</sup> and, more recently, Fried,<sup>8</sup> Gillespie<sup>9</sup> and Hill.<sup>10</sup>

### CLASSIFICATION

Little or no uniformity exists in the classification of primary lung carcinoma. Thus, older authors divided their cases into tumors arising from (*a*) the epithelium lining the bronchi, (*b*) the epithelial cells forming the mucous glands, and (*c*) the epithelium said to line the pulmonary alveoli (the air sacs). More recent investigators deprecate a histogenetic classification and utilize a histological stand-

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ard. Adler, in 1912, expressed the view that most lung carcinomas were bronchiogenic in origin, and more recently Fried has thoroughly reviewed the subject and concluded that all primary lung carcinomas originate from the lining mucous membrane of the bronchi. Certainly if non-bronchiogenic carcinomas exist they are of rare occurrence. A classification based on the gross pathology seems to lend little clarification to the subject.<sup>11</sup>

For the present study the histological classification used by Weller,<sup>5</sup> Rogers,<sup>12</sup> and in part by Fried,<sup>8</sup> and other recent writers, has been utilized. The pleomorphism so frequently mentioned in relation to these tumors was occasionally found but presented no serious barrier to classification. The 69 carcinomas of this series have been divided into three large groups, namely, (a) squamous cell carcinomas, (b) adenocarcinomas, and (c) undifferentiated carcinomas. These will be discussed more fully below.

*Squamous Cell Carcinomas:* These tumors consist of the typical large cells with large clear nuclei and prominent single nucleoli, arranged in a manner suggesting the squamous epithelium seen in patches in the lining of the bronchi. Forty-two per cent (29 cases) were of this type and constituted the largest single group. Twenty-eight per cent of these tumors showed the formation of epithelial "pearls." Metastases were usually of the "squamous" type and rarely showed cornification or "pearl" formation. In 55 per cent the primary tumor was located in the left lung and in 44 per cent in the right lung. Forty-four per cent were in the upper lobes, 38 per cent in the lower lobes and 18 per cent at the hilum. The lobes were involved with the following frequency: left upper 20 per cent, left lower 24 per cent, right upper 24 per cent, and right lower 14 per cent. Thirty-one per cent of the total number presented as a mass at the hilum and 61 per cent either involved or occluded a primary or secondary bronchus.

Grossly the primary tumors were single, indurated, gray or white solid masses in 75 per cent of cases. Cavitation occurred in 17 per cent. Multiple masses in one lung were found in 8 per cent. Areas of tumor necrosis were relatively infrequent.

*Adenocarcinomas:* These tumors are very difficult to classify. Among them are tumors which undoubtedly in the past have been classified as "alveolar cell" carcinomas because their histological structure resembles that of fetal lungs. They comprise 24 per cent

(17 cases) of the entire series. Composed for the most part of cuboidal or cylindrical cells arranged in acinar formation, their chief distinguishing feature appears to be the secretion of mucus and their resemblance to bronchial mucous glands. Fifty-three per cent showed definite secretory function and 47 per cent were functionless. These will be referred to henceforth as mucinous and non-mucinous adenocarcinomas.

The non-mucinous type occurred in 8 cases, 4 of which showed a papillary adenomatous arrangement, and in three of these latter tumors ciliated columnar cells were found resembling very closely the columnar cells lining the bronchial tree. The possibility of these cells being remnants of normal bronchi was considered, but the presence of ciliated cells in the metastases of two of these tumors and the similarity of the cells to adjacent, non-ciliated tumor cells tend to eliminate this possibility. The four remaining adenocarcinomas showed no distinguishing histological feature, except a slight tendency to assume a "squamous-like" structure where the alveoli were compressed. However, they were not true acanthomas. The resemblance of these tumors to fetal lungs is suggested but not striking, and in view of the cilia found in tumors not unlike these it is believed that they are less well differentiated bronchiogenic carcinomas.

The primary tumors in the non-mucinous adenocarcinomas occurred equally in the right and left lungs. Thirty-seven per cent occurred in the upper lobes, 37 per cent at the hilum, only 12 per cent were in the left lower lobe and none were in the right lower lobe. Twenty-five per cent were in the right upper lobe and 12 per cent in the left upper lobe. In 12 per cent, diffuse multiple masses involved the whole of the right lung. Primary bronchi were involved or occluded in 37 per cent of cases and were negative or not described in the postmortem descriptions of 63 per cent.

The mucinous type of adenocarcinoma has been described at length in the past and has been called variously carcinoma myxomatodes (Willert<sup>13</sup>), colloid carcinoma and gelatinous carcinoma. Their striking resemblance to bronchial mucous glands and the presence of a mucoïd secretion within the alveoli serves to mark them as a characteristic lung carcinoma. They are composed of cuboidal and cylindrical cells and careful search will nearly always reveal scattered cells in secretory phases. Their structure is most frequently

that of a malignant adenoma, although true adenocarcinomas are not rare. Their metastases in the majority of instances show mucinous secretion. However, non-secreting metastases occur.

Mucinous adenocarcinomas occurred in 9 cases and in 44 per cent the primary tumors were located in the left lung and in 55 per cent, in the right lung. Fifty-five per cent occurred in the upper lobes, distributed as follows: left upper lobe 33 per cent, right upper lobe 22 per cent. Eleven per cent each occurred in the left lower, right middle and right lower lobes. In 11 per cent the tumor encircled the lower end of the trachea and right bronchus. In 55 per cent a large bronchus was involved or occluded, while in 45 per cent the bronchi were negative or not described.

In gross the adenocarcinomas appeared most frequently as gray, firm, scirrhous tumors with scattered areas of softer, yellowish tissue frequently showing grossly visible mucus. Necrosis was uncommon but when present occurred in the papillomatous carcinomas. In 94 per cent the primary tumors were a single mass occupying a lobe, the hilum or both.

*Undifferentiated Carcinomas:* This type is composed of the "small cell" tumors which in the past have frequently been called sarcomas. Barnard,<sup>14</sup> Maxwell,<sup>15</sup> and more recently Karsner and Saphir,<sup>16</sup> have shown that these tumors are in reality carcinomas. Karsner and Saphir conclude that they are carcinomas because of their cellular arrangement, absence of reticulum, vascularization, connective tissue relations, gross characteristics resembling obvious carcinomas and distribution of metastases. Barnard describes the microscopic picture as follows. "The cells are in the main oval and when cut transversely, round and have little cytoplasm. The nuclei are oval and the majority have a distinct chromatin net with chromatin nodes, but in others the whole nucleus is so deeply stained that the nuclear structure is obscured." These tumors have been called "oat cell," "oat seed cell," small cell, spindle cell and round cell tumors in the literature.

Thirty-three per cent of the carcinomas in this series were of this undifferentiated, small cell type. Fifty-six per cent occurred in the left lung and 43 per cent in the right. Only 43 per cent of these primary tumors could be localized by lobes and they were distributed as follows: left lower and left upper lobes 13 per cent each, right upper lobe 9 per cent, and right middle and lower lobes 4 per cent

each. In 9 per cent the entire left lung was infiltrated and in 4 per cent the entire right lung. In 22 per cent the primary tumor was at the hilum of the right lung and in 24 per cent at the hilum of the left lung. The primary tumor exhibited a mass at the hilum in 65 per cent of the cases. A secondary or primary bronchus was involved or occluded in 100 per cent. Complete occlusion occurred in 30 per cent. The primary bronchi were involved in over twice as many cases as in either of the other two types.

In gross these tumors varied from a soft, pink, sarcoma-like mass to hemorrhagic, necrotic and sometimes caseous masses. Hemorrhage and necrosis were prominent and infiltration of the tumors extended along the bronchial tree.

### *Summary of Classification*

A brief description of the histological classification has been given.

Fifty-three and six-tenths per cent of all tumors occurred in the left lung and 46.4 per cent in the right lung. The primary tumors were distributed by lobes as follows: left upper lobe 18.8 per cent, left lower lobe 17.3 per cent, right upper lobe 18.8 per cent, right middle lobe 2.9 per cent, and right lower lobe 8.6 per cent. In 35.1 per cent the primary tumors were located at the hilum and in 4.3 per cent the entire lung was infiltrated from the hilum. The upper lobes and the hilum were the seat of the primary tumor in about an equal number of cases and together constituted the primary location in 72.7 per cent. The infrequency with which the right lower and middle lobes were involved is striking.

Either primary or secondary bronchi were involved or occluded in 68 per cent. In the remaining 32 per cent the bronchi were either negative or not described in relation to the primary tumor mass.

In gross the adenocarcinomas were indistinguishable from the squamous cell tumors unless mucoid secretion was visible. These tumors were usually single, indurated, gray or white masses, situated within the parenchyma of the lung, and involved the larger bronchi in less than one-half of the cases and the hilum in less than one-third. The undifferentiated tumors were soft, hemorrhagic, showed extensive areas of necrosis and, in the great majority of cases, infiltrated along the bronchial tree from a primary site at the hilum.

## INCIDENCE

*General Incidence:* Discussions of the increase in lung carcinoma are so voluminous and numerous that the subject cannot be done full justice here. That more lung carcinomas are being observed, both at autopsy and clinically, is undisputed. However, whether this is an absolute or a relative increase is undecided. Rosahn<sup>17</sup> summarized most of the available autopsy statistics in 1930 and found that lung carcinomas increased 102 per cent in the period from 1920-1928, as compared to the period from 1910-1919, while during these same periods carcinoma in general increased only 30 per cent. He cites this as proof of an absolute increase. Derischanoff<sup>18</sup> found both a relative and an absolute increase and Dissmann<sup>19</sup> believed there was an absolute increase in about the same periods. Sitsen<sup>20</sup> found no increase at Innsbruck. Lipschitz<sup>21</sup> in an analysis of postmortem statistics found an increase in lung carcinoma at Dresden and Zwickau and practically no increase at Copenhagen and Turin, and pointed out that these last two cities are much greater industrial centers than the first two. He believed the incidence of lung carcinoma to be closely related to the residence, vocation and environment of the population. These are only a few of the conflicting reports, and in conclusion it may be said that only when extensive international autopsy statistics, including both urban and rural populations, are available will the question be settled.

The incidence by 5 year periods is given in Table I. Rosahn<sup>17</sup> assembled these statistics at the Boston City Hospital from 1910-1928. Two lung carcinomas occurring between the years 1920 and 1924 have been added and Table I includes the entire period from 1900 to August 1, 1934.

Rosahn found that in the period 1925-1928 the percentage relation of all cases of carcinoma to total autopsies increased 20 per cent, while the percentage relation of primary lung carcinomas to all carcinomas rose 49 per cent, and concluded that this indicated an absolute increase in incidence. The figures previous to 1924 include so few primary lung carcinomas that they are worthy of consideration only in the aggregate. During this 25 year period the per cent of carcinomas occurring at autopsy rose from 6.12 per cent to 10.34 per cent (an increase of 68 per cent) and averaged 7.75 per cent. During this same period lung carcinoma increased in the per cent of

all autopsies but remained fairly constant at an average of 5.71 per cent of all carcinomas. Using these average figures for a basis, in the next 5 years the per cent of carcinoma rose from 7.75 per cent to 11.87 per cent (an increase of 53 per cent) while the per cent of lung carcinoma to all carcinomas increased from 5.71 per cent to 7.68 per cent (an increase of 34 per cent) or an actual decrease in incidence among all cases of carcinoma autopsied. In the subsequent period up to August 1, 1934, the number of cases of carcinoma autopsied decreased slightly from 11.87 per cent to 11.12 per cent (a decrease of 7 per cent) and the per cent of carcinoma of the lung

TABLE I

*Incidence of Primary Carcinoma of the Lung at the Boston City Hospital*

Year	No. of adult autopsies	Carcinomas		Primary lung carcinomas		
		Total	Autopsies	Total	Autopsies	All carcinomas
			<i>per cent</i>		<i>per cent</i>	<i>per cent</i>
1900-04 . . . .	931	57	6.12	2	0.21	3.50
1905-09 . . . .	865	52	6.01	4	0.46	7.69
1910-14 . . . .	438	34	7.76	2	0.45	5.88
1915-19 . . . .	526	45	8.55	2	0.38	4.44
1920-24 . . . .	957	99	10.34	7	0.73	7.07
1925-29 . . . .	1,532	182	11.87	14	0.91	7.68
1930-34* . . . .	2,624	293	11.16	38	1.44	12.96
Total . . . .	7,873	762	9.67	69	0.87	9.05

\* To August 1, 1934

in relation to all carcinomas increased from 7.68 per cent to 12.96 per cent (an increase of 68 per cent). Thus, using comparable periods, there is an absolute increase only in the period from 1930 to August 1, 1934. When traced through single years, this rise has been fairly gradual while the per cent of autopsies revealing carcinoma has remained practically constant. The percentage relation of all cases of lung carcinoma to all carcinomas from 1929 to August 1, 1934 is as follows: 1929, 7.5 per cent; 1930, 10.5 per cent; 1931, 12.7 per cent; 1932, 14.2 per cent; 1933, 10.8 per cent; 1934, 19.1 per cent.

An explanation of this abrupt increase is difficult. However, the tremendous expansion of this hospital in recent years and the increased interest in pulmonary surgery has possibly allowed many

patients to remain in the hospital until autopsied, whereas formerly they were sent to institutions or homes for the care of incurables. No single carcinogenic factor was found at autopsy to explain this rise.

*Incidence by Sex:* Of the 69 cases examined, 79.7 per cent occurred in males and 20.3 per cent occurred in females, or in the ratio of 1 female to 4.5 males. This is in agreement with most of the statistics consulted. However, of the ten lung carcinomas occurring previous to 1920, five were in males and five in females, or in the ratio of 1:1. From 1920 to August 1, 1934, nine carcinomas

TABLE II

*Distribution by Age of Primary Carcinoma of the Lung*

Age incidence	Squamous cell carcinoma	Adenocarcinoma	Undifferentiated carcinoma	All tumors
<i>years</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
20-29 .....	0	12	0	2.9
30-39 .....	10	6	9	8.7
40-49 .....	13	23	17	17.3
50-59 .....	34	23	48	36.2
60-69 .....	20	23	17	20.3
70-79 .....	20	6	4	11.5
80-89 .....	0	6	4	2.9
	<i>yrs.</i>	<i>yrs.</i>	<i>yrs.</i>	<i>yrs.</i>
Youngest .....	36	29	31	29
Oldest .....	79	89	80	89
Average .....	57	53.1	53.8	53.7

occurred in females and fifty in males, or in the ratio of 1:5.5. European investigators have noted this increasing predominance of lung carcinoma in the male and have attempted to explain it on the greater exposure of males to war gasses, and industrial smoke and dust hazards, which probably exerted their irritating influences previous to 1920. It will be interesting to note if the influx of women into industry since the war will result in an increased incidence of lung carcinoma in the female.

*Incidence by Age:* Brunn<sup>6</sup> found that 62 per cent of 576 cases of lung carcinoma occurred in patients between 40 and 60 years of age. Weller<sup>5</sup> found the most frequent age was in the 6th and 7th decades, although rarer cases occurred at the extremes of life. Adler<sup>1</sup> noted



that the 6th decade was the most common period in which patients died of lung carcinoma. In general, the age incidence of carcinoma of the lung coincides with that of all carcinoma.

In Table II the age incidence is given by decades. Thirty-six and two-tenths per cent of all lung carcinomas occurred in the 6th decade and 73.8 per cent occurred in the 5th, 6th and 7th decades. Squamous cell and undifferentiated carcinomas occurred in these same periods. However, adenocarcinomas tended to be slightly more diffusely distributed.

Both the oldest and youngest cases occurred in the adenocarcinomatous group. Ewing<sup>22</sup> mentions an adenocarcinoma occurring in a girl aged 18. Pekelis<sup>23</sup> observed 5 cases occurring between the ages of 37-38 and 4 of these were of the adenocarcinomatous type. It would seem that lung carcinoma occurring in the younger age groups is more likely to be of the adenocarcinomatous variety.

#### METASTASIS

Weller<sup>5</sup> states that carcinoma of the lung rarely fails to produce metastases. According to Klotz,<sup>24</sup> Adler,<sup>1</sup> Rogers<sup>12</sup> and Brunn,<sup>6</sup> metastases occur most commonly in the regional nodes and involve the liver, skeleton, brain, kidneys, adrenals and pancreas in approximately the order named. Metastases have been recorded in practically every portion of the body. No authors have tabulated metastases of a large series of cases according to the histological structure of the tumors. Also, direct extensions are mentioned so casually that it is doubtful if these have been carefully separated from metastases.

In the present series the body was examined in 67 cases and percentages of somatic metastases have been calculated on this basis in Table III. In 22 cases the head was examined and the intracranial metastases are discussed in a separate table. The tumors have been divided into the three groups mentioned previously and further subdivision is made where it is significant.

*Squamous Cell Carcinomas:* Twenty-seven cases in this group were examined and of this number 11 per cent failed to metastasize and 18 per cent produced secondary tumors only in the regional nodes.

A separate tabulation of primary tumors with and without cornification was made. Metastases occurred in twenty-one locations from tumors showing cornification and in twenty-four locations from those without cornification. Correlation by per cent of organs involved revealed no significant differences between these groups and it is suggested that these types have approximately the same metastatic potentialities. The presence of epithelial "pearls" and cornification possibly signifies a longer duration of the primary tumor.

Considering the entire group, metastases were most frequently found in the regional nodes. The liver, adrenals, kidneys, pleura, mesenteric nodes, heart and opposite lung were involved in that order of frequency. Rarer metastases occurred as tabulated in Table III.

*Adenocarcinomas:* Seventeen cases in this group were examined for metastases. Twelve per cent showed no metastases, 6 per cent metastasized only to the regional nodes and 88 per cent metastasized to twenty-two locations.

A tabulation of these tumors based on the presence of mucus revealed that all mucinous carcinomas showed metastases and in no instance were they confined to the regional nodes, while of the non-mucinous carcinomas only 75 per cent metastasized and in 12 per cent only the regional nodes were involved. The liver was involved in 44 per cent of the mucinous type and in only 12 per cent of the non-mucinous. The vertebrae were involved with the same relative frequency. It is concluded that non-mucinous carcinomas are less prone to metastasize than those with mucous secretion.

The adenocarcinomas exhibited a slightly less vigorous tendency to metastasize than the squamous cell tumors. Metastases occurred most frequently in the regional nodes, vertebrae, adrenals and mesenteric nodes in that order. Rarer metastases have been tabulated. The frequency with which bone is involved will be discussed under skeletal metastases.

*Undifferentiated Carcinomas:* Twenty-three cases in this group were examined and 96 per cent of these tumors showed metastases to thirty-five locations and 4 per cent showed involvement of the regional nodes alone.

These tumors exhibited the most vigorous metastatic powers of any group and spread widely outside of the thorax. Metastases

TABLE III

*Distribution of Metastases in Primary Carcinoma of the Lung*

Location	Squamous cell carcinoma	Adeno-carcinoma	Undifferentiated carcinoma	All tumors
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Peribronchial nodes	59	52	69	61.1
Liver	33	29	43	35.8
Tracheal nodes	18	23	24	25.3
Adrenals	33	17	21	25.3
Vertebrae	7	29	28	20.8
Kidneys	30	6	16	19.6
Retroperitoneal nodes	7	6	39	17.9
Mesenteric nodes	22	17	21	17.9
Cervical nodes	11	12	16	13.4
Opposite lung	14	12	4	10.4
Mediastinal nodes	0	0	16	10.4
Stomach	11	6	8	9.1
Heart	18	0	4	9.1
Pancreas	0	6	21	9.1
Iliac nodes	11	0	8	7.4
Ribs	11	12	0	7.4
Left pleura	14	0	0	5.9
Right pleura	11	6	0	5.9
Axillary nodes	0	6	12	5.9
Skin	4	6	8	5.9
Ileum	7	0	4	4.4
Spleen	4	0	8	4.4
Terminal phalanges	0	0	8	2.9
Spinal meninges	0	0	8	2.9
Uterus	4	6	0	2.9
Cecum	0	0	8	2.9
Esophagus	0	6	4	2.9
Femur	0	6	4	2.9
Diaphragm	7	0	0	2.9
Clavicle	0	6	0	1.5
Peritoneum	0	0	4	1.5
Jejunum	0	0	4	1.5
Tibia	0	0	4	1.5
Ilium	0	0	4	1.5
Appendix	0	0	4	1.5
Inguinal nodes	4	0	0	1.5
Gall-bladder	0	0	4	1.5
Psoas muscle	4	0	0	1.5
Testes	4	0	0	1.5
Ureter	4	0	0	1.5
Ovary	0	6	0	1.5
Broad ligament	0	6	0	1.5
Inferior vena cava	4	0	0	1.5
Pericardium	0	0	4	1.5
Radius	0	0	4	1.5

have been tabulated in Table III and it is of special interest to note that in 8 per cent there were extradural metastases in the spinal canal with compression of the cord. In an additional 8 per cent the terminal phalanges were involved. These odd metastases indicate the tendencies of this group to grow into blood vessels and produce secondary tumors which closely resemble sarcomas when biopsied.

*Skeletal Metastases:* Secondary tumors occurred in bone in 28.3 per cent of cases. Of these tumors involving bone, 31 per cent were adenocarcinomas, 42 per cent undifferentiated and 26 per cent squamous cell carcinomas. Fifty-five per cent of all mucinous adeno-

TABLE IV  
*Intracranial Metastases of Primary Carcinoma of the Lung*

	Squamous cell carcinoma	Adeno- carcinoma	Undiffer- tiated carcinoma	Total
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Cerebrum .....	22	33	28	22.7
Cerebellum .....	22	0	28	18.1
Dura .....	11	0	0	4.5
Pons .....	11	0	0	4.5
Pituitary .....	11	0	0	4.5

carcinomas metastasized to bone and only 12 per cent of the non-mucinous type. The relatively high frequency with which adenocarcinomas, and especially the mucinous type, involve bone is striking.

In all, 19 cases showed metastases with involvement of the vertebrae in 56 per cent, ribs in 21 per cent, skull, femur, terminal phalanges in 8 per cent each, and ilium, tibia and clavicle in 4 per cent each.

Routine examination of the lumbar spine and ribs was made in the majority of instances. However, other portions of the skeleton were not examined unless superficial examination aroused suspicion. Of necessity, these figures are incomplete.

*Intracranial Metastases:* The intracranial contents were examined in 22 cases and metastases were found in 36.3 per cent. Metastases were found with the following frequency: 44 per cent of 9 squamous cell carcinomas, 33 per cent of 6 adenocarcinomas, and 28 per cent of 7 undifferentiated carcinomas.

Table IV demonstrates that the cerebrum and cerebellum are the most frequent sites of metastases. The frequency with which secondary growths from primary lung carcinoma occur in the cranial cavity has been stressed repeatedly. Fried<sup>8</sup> found that 31 per cent of 47 cases metastasized intracranially and in many instances they were operated upon for primary intracranial tumors, and he emphasized the importance of eliminating the possibility of metastatic tumor of the lungs in all cases of suspected intracranial newgrowths.

#### *Summary of Metastases*

Somatic metastases occurred in 92 per cent of 67 primary lung carcinomas examined and involved forty-five locations. The regional nodes, liver, adrenals, vertebrae, kidneys, retroperitoneal nodes, mesenteric nodes and cervical nodes, opposite lung, mediastinal nodes and stomach are the sites most frequently involved and the frequency is in the order named. Rarer metastases were numerous and widespread, as has been enumerated.

Skeletal metastases occurred in 28.3 per cent.

Cerebral metastases occurred in 36.3 per cent of 22 cases examined.

The undifferentiated, small cell type showed the most vigorous tendency to metastasize and the squamous cell, mucinous and non-mucinous adenocarcinomas follow in the order named.

From a study of metastatic lesions it seems evident that these tumors metastasize most frequently by the lymph channels, and commonly by the blood stream. No positive proof of metastasis by the air passages was found.

#### EXTENSIONS

Direct tumor extension involving vital structures is frequently mentioned in the literature. The heart and pericardium have been mentioned as direct sites of extension. A few instances of direct proliferation to the superior vena cava or to the regional nerves with resulting pain or dysphagia have been noted. For the most part, however, it is difficult to separate metastases from extensions in the larger series in which anatomical studies have been made. In the present series a careful attempt has been made to separate these two manifestations of malignancy and they will be discussed below according to the types of tumors.

*Squamous Cell Carcinomas:* In 27 cases examined 55 per cent of primary tumors showed direct regional extension. In 14 per cent there were extensions without metastases. Cornifying primary tumors extended in 50 per cent and non-cornifying in 57 per cent. Structures involved were the mediastinum, pericardium, heart, aorta, right pleura, left pleura, esophagus, diaphragm and ribs. In 1 case the superior vena cava was invaded with thrombosis of that vessel. In another case the primary tumor directly proliferated

TABLE V  
*Distribution of Extensions in Primary Carcinoma of the Lung*

Location	Squamous cell carcinoma	Adeno-carcinoma	Undifferentiated carcinoma	All tumors
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Mediastinum .....	33	17	52	35.8
Pericardium .....	30	11	39	28.3
Aorta .....	18	6	23	17.7
Left pleura .....	11	0	34	16.4
Heart .....	18	0	17	13.4
Right pleura .....	14	11	8	11.9
Esophagus .....	11	0	17	10.4
Ribs .....	7	17	4	8.9
Diaphragm .....	11	6	8	8.9
Superior vena cava .....	4	11	4	7.4
Cervical region .....	4	6	0	2.9
Liver .....	4	0	0	1.5
Adrenal .....	4	0	0	1.5
Opposite lung .....	0	0	4	1.5
Skin .....	4	0	0	1.5
Spinal meninges .....	0	0	4	1.5
Clavicle .....	0	0	4	1.5

through the diaphragm and involved the liver and right adrenal. In another case the cervical region and skin were directly invaded.

*Adenocarcinomas:* In 17 cases examined 46 per cent extended from the primary site. In no instances were extensions present without metastases. Fifty-five per cent of the mucinous type extended locally and 37 per cent of the non-mucinous. Structures involved were the mediastinum, ribs, right pleura, superior vena cava, left pleura, diaphragm and cervical region. In 2 cases there was thrombosis of the superior vena cava as a result of tumor extension.

*Undifferentiated Carcinomas:* Of the 23 cases examined in this group 65 per cent involved the mediastinum or thoracic structures.

In 4 per cent there was extension without metastases. Extensions have been tabulated in Table V. Of special interest is one tumor which extended posteriorly between the ribs and compressed the spinal cord at the level of the fifth thoracic vertebra. In another instance the superior vena was thrombosed as a result of tumor extension.

#### *Summary of Extensions*

Of 67 cases examined 56.7 per cent showed extensions. In 6 per cent there were extensions without metastases. Sixty-five per cent of undifferentiated carcinomas, 55 per cent of squamous cell tumors and 46 per cent of all adenocarcinomas, extended locally. Only 37 per cent of non-mucinous adenocarcinomas extended locally. The percentage with which various structures were involved has been tabulated. Thrombosis of the superior vena cava occurred in 4 cases and in 2 cases the tumors extended to the cervical region and in 1 case the spinal canal was invaded with compression of the spinal cord.

Undifferentiated carcinomas exhibited the most marked tendency to extend locally and squamous cell, mucinous and non-mucinous carcinoma follow in the order named.

#### ASSOCIATED PATHOLOGICAL FINDINGS

Evidence of associated pulmonary inflammatory conditions were found in 58.8 per cent of cases. Either an active or organizing bronchopneumonia was present in 27.8 per cent; bronchiectasis, usually with small bronchiectatic abscesses, was found in 17.6 per cent. Four and four-tenths per cent showed lobar pneumonia, and fibrinous pleuritis and pneumoconiosis were present in 1.5 per cent each.

Complete atelectasis of a lobe or a lung occurred in 20.5 per cent and pulmonary infarction in 4.4 per cent. These conditions may be interpreted as the result of the mechanical occlusion of a bronchus or ramification of the pulmonary artery by direct tumor proliferation.

Chronic inflammatory disease of the lungs has frequently been accused of producing a predisposition to pulmonary cancer. It is believed that the repeated destruction of the epithelial cells lining

the bronchi leads ultimately to metaplasia and the production of atypical cells and these are thought to be pre-malignant. However, the great frequency with which the primary tumors are located at the hilum or in the upper lobes (72.7 per cent), and the frequency with which bronchiectasis, pulmonary abscesses and chronic pneumonia involve the lower lobes appears to preclude the presumption that these latter processes are sources of chronic irritation and the underlying cause of lung carcinoma in a significant number of cases. In fact, the right lower lobe, considered the most frequent location of bronchiectasis and pulmonary abscesses, was the primary site of lung carcinoma in only 8.6 per cent of cases and one of the least frequently involved lobes. In the majority of instances where bronchiectasis or chronic pneumonia was found, they occurred distal to the tumor mass and the natural assumption was that they were secondary manifestations of the tumor resulting from blockage of lymphatics and bronchi.

Active tuberculosis was present in only 1.6 per cent and healed parenchymal tuberculosis in 5.9 per cent. Thus, the total of 7.4 per cent is slightly less than that reported by Kikuth (quoted from Weller <sup>5</sup>) of 8.7 per cent, and is roughly in accord with the known incidence of tuberculosis in unselected cases. "Kikuth felt that tuberculosis plays a small rôle, if any, in determining a malignant pulmonary condition, occupying in this respect exactly the same position as a considerable number of other chronic inflammatory diseases."

Schmorl felt that the inhalation of dust and the presence of pneumoconiosis was of significance, especially in the production of lung carcinoma in the Schneeberg miners. Certainly, the frequency with which these conditions are associated at Schneeberg is more than coincidental and eventually a specific etiological factor may explain these cases. However, the relative infrequency with which these two conditions are associated elsewhere and in other mines lends doubt to the theory that the mechanical irritation is an etiological factor and it would seem more likely that the answer rests in some specific quality of the Schneeberg ore. In the present series of cases pneumoconiosis was found in only 2.9 per cent of instances, or in 2 cases, and in both of these the fibrosis was only of moderate degree. It would appear that pneumoconiosis is of insignificant importance in the production of lung carcinoma in general.



Associated extrapulmonary pathological findings were distributed as follows: pyelonephritis 13.4 per cent, cholecystitis and endocarditis 4.4 per cent each, pericarditis, acute pancreatitis and alcoholic cirrhosis 2.9 per cent each, mitral stenosis, chronic glomerular nephritis, peptic ulcer, diverticulitis, peritonitis and esophageal obstruction in 1.5 per cent each. These findings are not inconsistent with postmortem findings in unselected cases of an older age group predominantly male.

### PLEURAL CAVITIES

Pleural effusion may result either from the inflammatory processes commonly associated with primary lung carcinoma or as a result of tumor implants on the pleural surfaces. The pleural cavities were involved by tumor in 39.3 per cent of cases, either by extension or metastasis. In 11 per cent there was fluid in both pleural cavities and in 32 per cent fluid was present only on the same side as the primary lung carcinoma. In 6 per cent fluid was present on the opposite side and in 50 per cent no fluid was present. Most frequently the fluid was described as serosanguineous; however, in many instances it was clear, colorless or yellow fluid. In 2.9 per cent of cases it was seropurulent and a definite fibrinous pleuritis was present, and in 1.5 per cent frank empyema existed as a result of a bronchial fistula. These latter conditions were found on the same side as the primary tumor.

Fibrous adhesions, evidence of healed pleuritis, occurred on both sides in 38 per cent; on the same side as the primary tumor only, in 54 per cent; and on the opposite side only, in 1.5 per cent. The pleural cavities were negative in 10 per cent of cases.

Adenocarcinomas showed a slightly greater tendency to involve the pleura with the accumulation of fluid and the production of adhesions than either of the other two types described.

### SUMMARY AND CONCLUSIONS

1. Sixty-nine cases of primary carcinoma of the lung, verified at autopsy, have been presented and divided into three groups, namely: (a) squamous cell carcinoma, (b) adenocarcinoma, (c) undifferentiated carcinoma.

2. Squamous cell carcinomas constituted the largest single group and 42 per cent of the entire series. The left lung and upper lobes were the most common site of the primary tumor, and 61 per cent involved a bronchus. Cavitation in the primary tumor occurred in 17 per cent. Metastases and extensions were not so widespread as in the undifferentiated group, but were more extensive than in the adenocarcinoma.

3. Adenocarcinomas constituted 24 per cent of the series and were composed of 53 per cent mucinous carcinoma and 47 per cent non-mucinous carcinoma. These tumors probably all originated from the epithelium lining the bronchi or from the peribronchial mucous glands. The mucinous type frequently metastasized and occasionally extended, but appeared less malignant than the non-mucinous group. They involved bone more frequently than any other type.

Non-mucinous carcinomas were the least malignant and were occasionally confined to a lobe or a lung. They frequently involved the pleura.

4. Undifferentiated carcinomas constituted 33 per cent of this series. Primary tumors occurred slightly more frequently in the left lung, always involved a bronchus and occasionally infiltrated an entire lung. This group showed the most vigorous tendency to metastasize widely and to extend locally.

5. All lung carcinomas in this series occurred most frequently in the left lung, in the upper lobes and at the hilum. Primary tumors were a single mass in 95.7 per cent of the cases and usually involved or occluded a bronchus. These carcinomas metastasized widely and primary tumors were very prone to extend regionally. Skeletal and intracranial metastases were common.

6. An absolute increase in the general incidence of lung carcinoma occurred at the Boston City Hospital in the period 1930 to August 1, 1934, and is possibly explainable as a selective phenomenon.

7. Males were affected predominantly and in the ratio of 1 female to 4.5 males. The incidence in males has increased in the past 15 years.

8. The majority of cases occurred in the 6th and 7th decades. Adenocarcinomas tended to occur more frequently at the extremes of life.

9. Associated pulmonary inflammatory conditions occurred in 58.8 per cent of the cases.

10. The incidence of pulmonary tuberculosis and pneumoconiosis in this series was consistent with the incidence in unselected cases.

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#### REFERENCES

1. Adler, I. Primary Malignant Growths of the Lungs and Bronchi. Longmans, Green and Company, New York, 1912.
2. Pilcher, J. F., and Brindley, P. Primary carcinoma of the lungs; report of 10 cases. *Texas State J. Med.*, 1933, **29**, 247-253.
3. Barron, M. Carcinoma of the lung: A study of its incidence, pathology and relative importance; with a report of thirteen cases at necropsy. *Arch. Surg.*, 1922, **4**, 624-660.
4. Vinson, Porter P. Primary carcinoma of the bronchus: report of 71 cases in which the diagnosis was made by bronchoscopic examination. *Minnesota Med.*, 1932, **15**, 15-17.
5. Weller, C. V. The pathology of primary carcinoma of the lung. *Arch. Path.*, 1929, **7**, 478-519.
6. Brunn, H. Primary carcinoma of the lung: report of two operative cases. *Arch. Surg.*, 1926, **12**, 406-439.
7. Brockbank, W. The occupational incidence of primary lung cancer. *Quart. J. Med.*, 1932, N.S. **1**, 31-40.
8. Fried, B. M. Primary carcinoma of the lung. *Medicine*, 1931, **10**, 373-508.
9. Gillespie, M. Primary intrathoracic growths: clinical and pathological study of cases occurring in Victoria Infirmary, Glasgow. *Glasgow M. J.*, 1932, **117**, 296; 1932, **118**, 26.
10. Hill, R. M. Primary cancer of the lung: its incidence and pathology. *Edinburgh M. J.*, 1934, **41**, 320-333.
11. Menne, F. R., Bisailon, M., and Robertson, T. D. Bronchogenic carcinoma. *Northwest Med.*, 1931, **30**, 155-174.
12. Rogers, W. L. Primary cancer of the lung. *Arch. Int. Med.*, 1932, **49**, 1058-1077.
13. Willert, Franz. Beitrag zur Kasuistik des primären Lungencarcinoms. C. J. Becker, Würzburg, 1905. (Quoted by Ewing.)
14. Barnard, W. G. The nature of the "oat-celled sarcoma" of the mediastinum. *J. Path. & Bact.*, 1926, **29**, 241-244.
15. Maxwell, J. Primary malignant intrathoracic tumours. *J. Path. & Bact.*, 1930, **33**, 233-249.

16. Karsner, H. T., and Saphir, O. Small cell carcinomas of the lung. *Am. J. Path.*, 1930, **6**, 553-562.
17. Rosahn, P. D. The incidence of primary carcinoma of the lung. *Am. J. M. Sc.*, 1930, **179**, 803-811.
18. Derischanoff, S. Zur Statistik und Genese des Lungenkrebses. *Ztschr. f. Krebsforsch.*, 1932, **35**, 481-491.
19. Dissmann, E. Über die Häufigkeit des Bronchial- und Lungenkrebses in den Jahren 1925-1931. *Ztschr. f. Krebsforsch.*, 1932, **36**, 563-571.
20. Sitsen, A. E. Über die Häufigkeit des Lungenkrebses. *Ztschr. f. Krebsforsch.*, 1932, **36**, 313-318.
21. Lipschitz, M. Bemerkungen über die Zunahme der Lungenkrebses. *Ztschr. f. Krebsforsch.*, 1931, **34**, 376-381.
22. Ewing, J. Neoplastic Diseases. W. B. Saunders Company, Philadelphia, 1931.
23. Pekelis, E. Contributo allo studio anatomo-patologico dei carcinomi primitivi del polmone. *Tumori*, 1931, **17**, 33-81.
24. Klotz, O. An address on cancer of the lung with a report upon twenty-four cases. *Canad. M. A. J.*, 1927, **17**, 989-996.
25. Schmorl, G. Ueber den Schneeberger Lungenkrebs. *Verhandl. d. deutsch. path. Gesellsch.*, 1923, **19**, 192. (Quoted by Weller.)