1-1-1943

Bronchogenic carcinoma

Richard Leroy Lawton
University of Nebraska Medical Center

BRONCHOGENIC CARCINOMA

[1]Richard L. Lawton

Senior Thesis Presented to the
College of Medicine, University of Nebraska,
Omaha, 1943.

INDEX

INTRODUCTION

Cancer of the lung is recognized today as one of the major (probably second to cancer of the gastro-intestinal tract) malignant diseases with which the clinicion, pathologist, roentgenologist, and surgeon must deal with.

When one reviews the literature he is impressed with the ultimate prognosis of these cases. The verage duratin is about ten months. When we view the result of therapy we are likely to think in terms of therapeutic nihilism, however, nihilistic tendencies have no place in medicine. We are dealing with an older age group, and although therapy is at present sound (total pneumonectomy), the diagnosis has come too late. We can remedy this by greater acuity and diagnosis, but we can only approach the minimum incidence by getting at the source, either diagnostically, or prophylactically.

The literature on the subject is comparatively recent, but nonetheless voluminous, particularly the statistical and etiological papers. Experimentation has not been slighted, and although no definite conclusions have been drawn from this work, some hypotheses of value have been forthcoming.

The ultimate goal of all work whether pathological, clinical, or experimental, is to attempt to eradicate,

or reduce the disease in question to a minimum. It is recognized today that no specific form of prophylaxis can as yet be instituted, and, that the greatest amount of hope for a person with cancer of the lung lies in an early diagnosis. With this in mind, the paper has been written, stressing clinical considerations in the hope that taken as a whole they might in some way help in making an early diagnosis of cancer of the lung.

HISTORY

There seems to be no doubt in the minds of most historical observers, that cancer of the lung existed many years before it was recorded. It is difficult ofttimes to glean from ancient records the history of some specific disease, because we are acutely aware of the pleomorphism of most disease entities. This statement is even more apropos when it concerns disease of organs not exposed to the human gaze. The symptology of cancer of the lung was probably noted, but not as such, quite as early. There are besides other intrathoracic growths, a number of inflammatory reactions which will give rise to the same symptomatology.

There is no unanimity of opinion amongst various authors, as to whom the honor of first describing cancer of the lung should be ascribed. Simon gives instances of the description of intrathoracic growths by various authors starting with Agricola (1521) to Küchenmeister (1869), but does not attribute to any of them the honor of first describing the disease adequately. Both Simon, and Davidson are in accord in giving the honor to Morgagni, who first described a case in 1761 in which a diagnosis of ulcus cancrosum of the lung was made at autopsy. Ewing accords the honor to Boyle who reported a case in 1810, of concommitant cancer and tuberculosis. Due to the

coexistance of these two diseases in this instance some confusion arose as to which was which. It appears that Laennec, of auscultation fame, did much to clear up this discussion. It appears that Bell in 1846 was the first to clinically diagnose a case of cancer of the lung.

In more recent times some of the progress in diagnosing and recording cases goes to Stokes (1842), and Graves (1848) and Ebermon (1857), Bennett (1872), and more recently Adler (1912), whose monograph on the subject is highly respected.

One of the first recorded cases of broncho-genic carcinoma in America was by George W. Covey, M.D., of Lincoln, Nebraska. This case was reported in the Nebraska State Medical Journal in 1916. This author at this time remarks on the infrequency of the disease, and quotes Wolf who found an incidence of .2 per cent in 20,160 autopsies.

Recently numerous articles have appeared, and some of these will be used in the paragraphs that follow.

INCIDENCE

No paper on carcinoma of the lung would be complete without some space devoted to the statistical aspects of this subject. In recent years every article written, it seems, has some mention of the great statistical question--is cancer of the lung increasing relatively or absolutely? No one to date has stated categorically that the increase is or is not relative or absolute. Thousands of cases have been studied, from various aspects, but the statistics won't give the answer. The reason why statisticians have failed is because there are too many variables to consider. There is no doubt that the diagnostician of today with all his accoutrements, is more likely to make a clinical diagnosis today than were his ancestors of several centuries past. It is also true that a minimum of mis-diagnoses emanate from the necropsy room than formerly. In this respect it must be stated that many mediastinal tumors were probably, in days gone by, confused with cancer of the lung. Such a state of affairs would tend to lower the incidence of cancer of the lung proper.

Recently, also, there has been a decided increase in the number of autopsies done which confirm or disprove clinical diagnoses which in the past had to be considered final.

Regardless of the statistical controversy, medical men are aware of the higher recognized incidence today, compared

with former years. Barron from the University of Minnesota surveyed 4,362 autopsies in the years 1899-1921. He grouped these into three periods:

YEARS	NECROPSIES	CARCINOMA OF LUNG	PER CENT OF TOTAL
1899-1911	1,333	0	0.0
1912-1918	2,026	4	0.2
1919-1921	1,003	9	0.9

Most authors agree with the above. Rosahn of Boston City Hospital studied 3,004 autopsies from the years 1910 to 1921 out of which primary cancer of the lung showed an incidence of 0.7 per cent of all autopsies, or 6.7 per cent of all carcinomas. In the period of 1925-1928 he found an increase of 20 per cent for all carcinomas, and an 81 per cent increase for cancer of the lung. On this basis the above author postulated an increase (absolute) in cancer of the lung. This might be a legitimate conclusion if we consider our diagnostic ability in other fields to keep pace with that in thoracic work.

There are some variations in different parts of the country as noted by Hoffman in his studies.

LOCALITY	PERIOD	MORTALITY RATE PER 100,000
ALBANY	1919-1923	2.5
NEW ORLEANS	1919-1923	2.8 white
NEW ORLEANS	1919-1923	0.6 colored
SAN FRANCISCO	1920-1924	4.7
BOSTON	1920-1924	3.9

LOCALITY	PERIOD	MORTALITY RATE PER 100,000
CHICAGO	1924	2.8
CHICAGO	1925	2.0
BUFFALO	1922-1926	3.2
PROVIDENCE OF ALBERTA	1921-1925	1.3
BRITISH COLUMBIA	1920-1924	2.1
WINNIPEG	1920-1924	3.3

It is difficult to evaluate statistics such as the above because there are a great many factors that must be considered.

Eggers in 1928 made a study of the relationship of the degenerative diseases to malignant diseases and could find no increase in malignancies. In this study, race, age, and sex were considered, and it is concluded that the increased incidence of malignancies is due to the fact that today more people are reaching the cancer age.

Madge Macklin states that persons of cancer age have fewer diseases to die of and hence die in increased numbers from those present. No one knows the number of cancers of the lung that were in the past mis-diagnosed, but we do know that diagnosed cancer of the lung is increasing at a greater rate than that of other diagnosed cancers.

The increase of the reported numbers of cancer of the lung is ubiquitous. Most of the literature on the subject has emanated from the United States, England, and Germany.

Duguid reports a number of cases which were studied in

the Manchester Royal Infirmary.

PERIOD	POST MORTEMS	CASES	PERCENTAGE
-----1886	2,107	5	0.24
1886-1890	1,014	16	1.58
1891-1895	1,175	15	1.28
1896-1900	991	12	1.21
1901-1905	1,083	26	2.40
1906-1910	898	12	1.34
1911-1915	1,141	27	2.37
1916-1920	910	22	2.42
1921-1925	1,126	29	2.57
1926-----	335	11	

Oscar Harmos says that less than two decades ago malignant tumors of the lung comprised less than 1 per cent of total malignancies, and now the percentage has increased between 7 and 10 per cent. In a series of 15 post-mortem malignancies studied by this author 33 per cent were found to be pulmonary malignancies.

In 1938 carcinoma of the lung was third in frequency of all cancers being exceeded only by cancer of the stomach, and intestine. Shapiro in a study of 1100 medical patients found that 9 had primary carcinoma of the bronchi, 0.8 per cent of the entire group. Of 67,000 general admissions in 1935, 104 had primary pulmonary cancer.

Menne and Anderson found in their investigation that particularly during the past 25 years there has been a

decided increase of reported cases of bronchogenic carcinoma all over the world. They are of the opinion that the increase is more apparent than real, and that in past years there was confusion concerning the differential diagnosis of cancer of the lung from mediastinal tumors, lymphosarcoma, and Hodgkins disease.

There seems to be a lack of comprehension of the terms used in the incidence controversy e.g. if some author states that the increase is more apparent than real this does not constitute a denial of an absolute increase, but merely indicates that the increase is due mostly to a relative state existing between diagnosis and statistics.

Menne and Anderson sent out a questionaire to physicians in the Pacific North West, and they revealed that from 1920-1940, 33,945 post-mortems were made, and 517 instances of bronchogenic carcinoma recorded. This incidence of pulmonary cancer is about 1.52 per cent of total autopsies. The above number of cases studied become more significant if the 20-year period be divided into 4 year intervals. When this is done, the authors found that:

From	1920-1925	3	lung cancers
	1926-1930	63	lung cancers
	1931-1935	201	lung cancers
	1936-1940	407	lung cancers.

In some instances the number of cases of bronchogenic carcinoma does not parallel the number of autopsies. We

cannot infer from the above table that there has been an absolute increase, but regardless of this, the incidence is high enough to make cancer of the lung a major diagnostic problem.

ETIOLOGY

No one knows the etiology of cancer of the lung, but it would seem, in the light of present day knowledge of things that we are getting closer to the answer. Scientists of all types have been seeking for the elan vital for centuries but have not really approached their goal, except in a manner philosophical. I am of the opinion, that should the cause of tumor growth be found, that we shall be very close, maybe too close, to the spring of life.

It is interesting to note the progress that has been made in all fields of scientific research, particularly those pertaining to medicine. The metabolism of the cell is being studied in all details, and by methods most ingenious. It would be most unfair to view all the research with a nihilistic attitude, although it is sometimes difficult to do otherwise. Since the sine quo none of all medical research should be toward alleviating human suffering, and of this we have ample proof, it becomes easier to reconcile ourselves to the seeming impasse. If we would never find the cause of cancer, but could detect it early, and treat adequately, certainly the medical goal is reached. The same holds true for the realm of prophylaxis.

Many theories have been propounded to treat with the etiology of cancer, but none have proven entirely adequate. Most authors agree that the basic cause of cancer lies in the micro-metabolism of the cell. Physiologic chemists are aware that tumor cells do not metabolize the same as do normal cells, but just where the difference lies is not known. Myerhof in a discussion of tumor

metabolism, points out that certain enzymes seem to be at fault, particularly some of the cytochromes. It seems that in tumor tissue there is a relative lack of cytochrome. Quite apropos to the topic at hand, this author points out that pulmonary tissue under normal conditions contains a minimum of cytochrome.

The above statement could be used to make some interesting speculations, especially in the light of opinions of some men, viz. Bela Holpert says: "Cancer of the lung is becoming the second, if not the first, most common malignant neoplasm". With a constitutional lack of cytochrome in the lung, plus the increase in irritating substances inhaled, we could prove then that the increase in cancer of the lung is absolute.

The above postulation is far from the realm of truth, no doubt, but it indicates somewhat the multiplicity of hypotheses that one can make.

I believe that there is concert of opinion amongst investigators in that the production of rapid proliferation of cells is not the result of one single force. We are inclined to look at the situation from a nature-nurture standpoint; a person with a natural predisposition, reacting to environmental stimuli of less potency than the possessor of no natural susceptibility.

In the next few paragraphs we will study a few of the factors possibly influencing the development of cancer of the lung.

HEREDITY: In a certain number of cases, by no means even approaching the majority, there is found a history of cancer in parents, or ancestors. We cannot say that the finding of this minority with a positive ancestry is grounds for insisting that cancer formation is due to recessive mutable gene, but on the other hand we would be foolish to ignore the possibility. Weller definitely associates the chronic irritative factor with a constitutional predisposition.

TRAUMA: That trauma has anything to do with the development of cancer is a very difficult thing to prove. In order that certain requirements be fulfilled before a tumor is labeled the result of trauma, Ewing set down definite rules:

1) sufficient severity
2) previous integrity of wounded part
3) relation of injured area to tumor growth
4) a type of tumor that could result from trauma
5) proper interval between injury and development of tumor.

Wells and Cannon report a case in which trauma played a paramount part, but they realize that it cannot absolutely be proven.

TUBERCULOSIS: There have been many cases on record stating the presence of a tuberculosis with a bronchogenic carcinoma. No one to date has proven any etiologic significance of this fact. Nelson reports 2 cases in men, one 59, one 60, who had the disease coexisting. This author states that opinion concerning

the place of pulmonary tuberculoses in etiology of bronchogenic carcinoma of the lungs is highly debatable. Most men find that cancer of the lung is not as frequent in tubercular patients as in a control group; e.g. Carlson and Bell studied 11,195 autopsies and found active tuberculosis much less in patients with cancer of the lung than those without.

INFLUENZA: Many authors put influenza as a main etiologic factor in the causation of cancer of the lung. Winternitz, Wason, and McNamara found evidence of metaplasia of the bronchial epithelium in patients dying of influenza, and suggested that this disease might be a pre-cancerous change.

SCHNEEBERG CANCERS: One of the greatest stimuli to the study of bronchogenic carcinoma has come from the Schneeberg Mining District in Saxony. It had been noted at an early date that miners in this locality were prone to develop cancer of the lung. Some of the earliest literature on the subject emanated from here. Indeed, so prevalent is the disease that a special research committee, the Committee on Cancer Research in Saxony, has been organized. In 1926 this committee studied 154 cases; in a four-year period 21 of this number passed on and of this lot 13 were found to have bronchogenic carcinoma, better than 50 per cent of all deaths. A control group showed

not a single case. A similar situation obtains at Joachimsthal in Bohemia.

A number of other factors have been incriminated, most acting however in the role of chronic instants. Excluding the localities mentioned above no definite correlation between occupation and cancer incidence has been established. Brockbank studied about 900 cases and found that they were relegated to various occupations as follows:

LABORERS	170
DUSTY OCCUPATION	137
HOUSEWORK	120
CLERKS	52
MANUAL LABORERS	48
CARPENTERS	28
BUILDERS	22
METAL WORKERS	18
VANMEN	16
CIGAR MANUFACTURERS	15
BUTCHERS	13
TRAVELERS	12
CHAUFFEURS	10
BAKERS, CHEMISTS	8
GARDENERS	7
DOCTORS	3
BAILIFF	1
JANITOR	1
GOLD BEATER	1

It seems from the foregoing that there is a decreased incidence in those doing manual labor in contrast to those possessing occupations of a more sedentary nature. We must realize the fallacy present in obtaining an accurate story as to the occupation of a person, or if we assume occupation to play a significant role in the etiology, which, of the usual numerous occupations was the one responsible for causing the pulmonary pathology.

Tobacco smoke has been incriminated at various times as a causative factor. Menne and Anderson found that in 1880, 582,717,995 cigarettes were smoked, and that in 1939, nearly 2000 times this number were smoked, or 169,847,245,964. Further studies show that habitual smoking produces inflammation of the mouth, pharynx, larynx, and bronchial mucosa. The smoker consumes about 1 kilo of tobacco a month and from this about 70 c.c. of tar may be obtained. There are numer us nocuous substances in tobacco smoke e.g. formaldehyde, arsenic, methylamine, hydrogen sulphide et al. It would be interesting to correlate the number of cancers of the lung today, with the number of women smokers.

MOTOR EXHAUST FUMES: The recognition of the increased incidence of cancer of the lung, and the increase in number, and knowledge of the carcinogenic properties (experimental) of gas fumes of automobiles, has led to an indictment of said fumes as a causative, or the causative factor in the production of bronchogenic carcinoma. However no definite proof exists that will substantiate

the above assertion.

PNEUMOCONIOSIS: J. Henry Dibble studied a number of cases of silicosis and said, "A group of cases of pulmonary cancer exists in which the organs contain an excess of silica and show histological evidence of silicotic fibrosis. The conclusion is, we think, that the role of silicosis is aetiological.

J. Argyll Campbell did some interesting experiments with mice, using various lung irritants among which were: 1) Silicon dioxide, 2) Aluminen trioxide, 3) Iron oxide, 4) Czechoslovak dust, 5) Dust. He found that any combination, or any single one of the above would cause an increase in lung cancers compared with the controls. He concludes that heredity, plus carcinogenic agents, plus age are definite factors in the production of cancer. Pneumoconiosis falls into a group of diseases whose causes are basically irritative, or more specific, chronically irritative. Chronic irritation causes scarring of the bronchial mucosa. When the mucosa is injured regeneration of the epithelium is started from the basal layer, and if the irritation is constant a protoplasia, or metaplasia will result (Tuttle and Womack). Condon did some interesting work in this connection, noting metaplastic changes in injured bronchial epithelium of the cat. He could produce by direct injury a protoplasia of the normal ciliated columnar epithelium t the more resistant, easier proliferating stratified squamous epithelium. He produced the same

condition by using vitamine A deficient diets. An irritant plus vitamine A deficiency accentuated the growth of a stratified squamous epithelium. Colchicine, a drug which arrests mitosis in the metaphase, was used to ascertain the rate of mitosis, and it was found that the normal mucous membrane regenerate slowly, but a metaplastic type possesses a higher mitotic rate.

CONCLUSIONS: Not any one of the above mentioned agents can be said to be responsible for the cause of cancer of the lung. We can, however, infer that under the proper conditions, i.e. hereditary background, environmental, and hygienic standing of a person, any one of the factors listed, mostly as chronic irritants, is capable of being the immediate cause of bronchogenic carcinoma.

If we are to understand the pathology of primary tumors of the lung we should have some idea of the structure of this organ. In reference to bronchogenic carcinoma we are interested primarily in the histology of the eipthelium lining the air passages, particularly the main bronchi and its primary subdivision.

The primary bronchi and its subdivision are lined with a ciliated pseudo-stratified columnar epithelium in which are to be found goblet cells. These cells appear to be differentiated from ciliated cells. The epithelium lies on a basement membrane and on this membrane lie the basal cells from which the other cells are said to originate. (Maximow and Bloom). Some authors call these reserve cells. Ordinarily not many mitoses are seen in the basal cell layer, but if an injury has been sustained by the bronchial mucous membrane mitotic figures can be seen. As we progress distally toward the respiratory bronchioles the epithelium becomes less cellular, goblet cells decrease as well as ciliated cells, and the cells adjacent to the lumen assumes first a cuboidal then a flat appearance (squamous), (Gazayerli). It is said by some authors that no eipthelium can be demonstrated lining the alveoli. Others contend that there is present a flat ill-defined type. From an embryo-logical point of view we would postulate the presence of an alveolar eipthelium, but histologists, that is most histologists, fail to demonstrate its presence with histological techniques. The study of

the pathology of tumors of the lung tends to refute the presence of an epithelium lining the alveoli, because of the lack of tumors apparently rising from this tissue, howev er, some men claim that there are such entities as alveolar carcinomas. Gazayerli in a study of 95 cases claimed to have found 2 cases not presenting characteristic appearance of bronchogenic tumors. He represented these cells as "cubical", and columnar cells around the alveoli, replacing the pavement epithelium, and most cells having primitive but definite cilia. It seems that the changes here described could be explained on a basis of metaplasia of bronchiolar epithelium. It is probable that the so-called alveolar tumors were called such because of their peripheral location. The possibility of these tumors being metastatic from an insignificant hilar neoplasm must be considered.

The blood supply to the lung is copious and lends easily to rapid dissemination of tumor particles. The lymphatics all have a tendency to drain to the hilus of the lung. There are two main groups, the sub-pleural, and the parenchynal group. There are two main groups, the sub-pleural, and the parenchynal group. There are many valves in these lymphatics, but where cancer growth and dissemination is concerned these valves are of little importance, (Ochsner and De Bakey). The lymph drainage from the upper lobes of the lung is to the hilar nodes primarily and also the tracheo-bronchial nodes. This fact is of some importance

from a diagnostic point of view, because bronchoscopically some deviation of the carina or tracheo might be noted if the tracheo-bronchial glands were involved due to a primary lesion in one of the upper lobes.

There are a number of conditions obtaining in a diseased lung which tend to modify the pathological picture, 1) the status quo of the lung structure, bacterial flora, and site of growth. The pathological changes in the lung, in toto, are due to the sequellae incident upon the alteration of structure and function of the pulmonary tissues.

Menne and Anderson have designed a type of classification based on the location of the tumor mass, i.e. either central, or peripheral. This classification is allowed by most pathologists with few variations, and seems to fit very nicely into the histo-pathologic, clinico-pathologic, roentgeno-pathologic, therapeutic, and prognostic classification. The growths in the primary, and secondary bronchi produce an obstructing pathological lesion, those in the parenchyma or peripherally produce not as much subsequent changes in lung tissue except the presence of tumor, but clinically are notorious because of early and rapid dissemination systemically.

The main pathologic classification may be written as follows: A) the hilar nodular type under which you would possibly obtain such changes as 1) hyperplasia, hypertrophy, and metaplasia (histologic changes); 2) partial or complete occlusion (pathologic, clinical); 3) extension through

bronchial wall with subsequent fibrous reaction; 4) lymphatic extension; 5) hilar node involvement; 6) limited, slow but massive extension throughout the lung. B) the diffuse necrotic type where the initiation of the pathological process is in the smaller bronchioles. With this type of lesion you expect early systemic involvement due to lymphatic invasion and such is the case. 1) a hypertrophy and hyperplasia of eipthelium (reserve cell type) 2) early extension into peri-bronchial lymphatico with circulatory and lymphatic stasis; 3) engorgement and thrombosis of blood vessels; 4) secondary lobular pneumonia infection; 5) diffuse carcinosis; 6) coagulation necrosis with miliary abscess formation; 7) bronchietosis limited to terminal bronchi; 8) regional hilar involvement occuring with more or less frequency. (Menne and Anderson).

Neuhof and Rabin have divided cancer of the lung into two main groups; 1) circumscribed; 2) non-circumscribed. They claim that 29 per cent are circumscribed and delimited, and that 71 per cent were non-circumscribed. The first or circumscribed group is the same as the diffuse necrotic type of Menne and Anderson. This is the parenchymal or peripheral type of lesion. The hilar nodular group of Menne and Anderson is similar to the non-circumscribed group of Rabin and Neuhof.

The protean manifestation of this disease semeiologically and symptomologically is compatible with the varied

pathologic findings. It would be well at this time to discuss some of the macroscopic findings.

In various autopsy rooms the presence of the female is quite scarce as concerns bronchogenic carcinoma, and almost a rarity is a negro, male or female. The ratio between males and females is variously stated, ranging from 1:8 to 1:4. Bela Halpert's figures agree with the latter ratio. He found that 59 occurred in men and 15 were found in women. This inequality in the ratio of males to females has given clues as to what the etiological factor, or more probably, factors might be. One author shows a close ratio between males and females. In his 22 cases 12 were males, 10 were females. (C. Kelman Robertson).

If we were to walk into an autopsy room where a person known to have died of bronchogenic carcinoma was to be autopsied we could place this person fairly well into a certain age group. There is some variation in age, in fact it varies according to some authors from 1 year to 90 years. Bela Halpert in his 74 cases found a variation of: 1) youngest 32 years; 2) oldest 83. Sixteen of these died in the fifth decade, 34 in the sixth decade and 19 in the seventh decade.

AGE INCIDENCE OF CANCER OF THE LUNG

AGE IN YEARS	MALE WHITE	MALE NEGRO	FEMALE WHITE	FEMALE NEGRO
31-40	2	0	3	0
41-50	12	2	2	0
51-60	29	1	4	0
61-70	9	0	4	0
71-80	4	0	1	0
81---	0	0	1	0
	56	3	15	0

The above table by Halpert brings out the age incidence, and also the preponderance of males to females, and the practically non-existence of cancer of the lung in negroes.

C. M. Rice in a survey of 30 proven cases from 1925-1935 found a sex incidence of 3:2, and the average age for males, 55 years, females 45 years.

After the thorax of a person had been opened what would we likely find? According to Robertson, we would find 9 pleural effusions, and one fibrinous pleurisy out of 21 cases. In 38 cases reviewed by Arkin and Wagner, 6 haemorrhagic pleural effusions were found, and one encapsulated straw colored effusion. The cause of various types of effusion is due to the pathology in the lung. Those tumors situated peripherally and sub-pleurally are more apt to be accompanied by an effusion. The nature of

the effusion will depend on proximity of blood vessels to the tumor, lymphatic stases, and the presence of organisms.

The possibility of finding cancer in the right or left lung is about equal, the greater number occuring in the right. Olin and Elliot report of 29 cases in which the right lung was involved 21 times and the left lung 18 times. Eloesser reports on 23 cases proven, and finds 16 in the left and 7 right. There is a peculiar bit of evidence, which cannot be explained adequately, brought out by C. Kelman Robertson in his series of 22 cases:

RIGHT LUNG	MALES	9	FEMALES	4
LEFT LUNG		3		6
		12		10

In most instances if a number of autopsy reports be used it will be found that the right lung is more frequently affected. This can be explained somewhat, if we postulate that one of the causes is irritation. The explanation lies in the anatomical position of the right main bronchus which makes it more prone to the onslaught of irritating materials entering the trachea.

There is not only a difference between right and left lung as concerns incidence, but also a difference between the various lobes in the lung. Rabinovitch brings this out in

his study of 40 cases.

SITES AND ORIGIN IN 40 CASES

LOCATION	RIGHT SIDE	LEFT SIDE	TOTAL
MAIN BRONCHI	7	8	15
UPPER LOBE BRONCHI	11	6	17
LOWER LOBE BRONCHI	2	3	5
MIDDLE LOBE BRONCHUS	1	0	1
MIDDLE AND UPPER	1		1
MIDDLE AND LOWER	1		
	23		40

Boyd describes 3 types of cancer of the lung grossly. 1) hilus tumors; 2) miliary; 3) diffuse. The first is the most common and comprises about 90 per cent of tumors, and the diffuse form is the rarest and simulates pneumonia.

Upon removing the lungs at autopsy, we are apt to note a number of masses situated around the hilus. These are lymph nodes. Nodes may also be found enlarged along the trachea and at the carina of the trachea. If tumor has involved one of the primary bronchi, an atelectatic state of the lung might be noted. There are cases on record where at autopsy nothing gross could be definitely detected, but on routine microscopic examination an early bronchogenic carcinoma was found. Incidentally some such tumors never give rise to symptoms referrable to the lungs during life, and death is due to some other cause.

Those tumors found on gross section to lie in a main bronchus will probably present a mulit-pathological picture. Their main effects are due to abstruction. When seen they may appear as an ulcerating mass, or a papillomatous mass protruding into the bronchus. Yet another hilar or magna bronchi type is sometimes seen, the stenosing type. The hilar tumor gives the appearance of traveling peripherally along the bronchi, exciting a more or less fibrotic reaction. (Frank).

Distal to the primary mass atelectasis may occur. This can be demonstrated radiologically and sometimes physically. The degree of atelectasis will depend upon the type of obstruction. Not all obstructing bodies in a bronchus need cause atelectasis, but may cause emphysema. This is due to the ball-valve action of a papillomatous growth. This type is rarer than the atelectatic type.

Abscess formation is likely to occur distal to the obstruction in the hilar type of cancer of the lung. Throughout the lung parenchyma, and bronchi, germs are ever present. These organisms are relatively benign when associated with a constant environment, howev er, if a portion of the lung becomes obstructed, not necessarily totally, an abscess is likely to result. This abscess may wall itself off or it might from the first, be delimited from the actual tumor growth. The reason for one of these abscesses eroding

into a bronchus and producing thereby a typical symptomatology is probably due to an initiation of a gangrenous process into the walls of the abscess cavity. Abscess occurs in a high percentage of hilar nodular carcinomas of the lung. (Joffe).

Bronchiectasis may occur distal to an obstructing lesion, however, the question arises as to which came first, bronchiectasis or tumor. In some cases no doubt this is a legitimate question, but in others the bronchiectasis is obviously the result of tumor. Bronchiectasis is said by some to be a congenital malformation, others think it is incidental to occupational irritants or such an irritant as the purulent material from a focus of infection draining into the upper reaches of the respiratory system. The epithelium of the bronchus or bronchioles, so affected by the process known as bronchiectasis show consistently a metaplasia from the pseudo-stratified columnar epithelium to the stratified squamous variety. This offers tempting food to the searchers for the etiology of bronchogenic carcinoma. (Davidson).

The tumors situated in the periphery of the lung may present pathological changes similar to those situated at the hilus, but on a lesser scale. These tumors are sometimes classed as "silent tumors," because they do not cause many symptoms until late in the disease. With these

tumors there is more apt to be pleural involvements.

HISTOLOGY: At the fore part of this pathological discussion the normal histology of the bronchi was explained. On this basis three types of tumor are generally considered to obtain: 1) cylindrical cell (adenocarcinoma); 2) squamous cell (epidermoid) and, 3) the anaplastic or small cell type occurs more often in the periphery of the lung and is the most malignant bronchogenic carcinoma. (Tuttle and Womack). The least malignant of all is the squamous cell, keratinizing or non-keratinizing, and it occurs most frequently at the hilus in the large bronchi. The cylindrical cell tumors are considered by some of intermediate malignancy.

There is by no means a clear-cut delineation between the various types, and various authors use a more complicated histological classification. Rabinovitch classifies bronchogenic carcinoma as follows:

1) squamous cell carcinoma
2) cylindric cell carcinoma
   A. adenocarcinoma
   B. undifferentiated cell carcinoma
      a. medullary carcinoma
      b. round cell carcinoma
      c. oat cell carcinoma
3) pleomorphic cell carcinoma.

We recall that there is present in the bronchial epithelium a group of cells known as basal cells, and that mitoses have been seen in these cells. Although some authors still postulate the theory of metaplasia of an existing normal epithelium to the various types of tumor cells I believe that the majority now postulate the theory of protoplasia, i.e. the indirect metaplasia of the toti-potent basal or reserve cells of the bronchial mucous membrane to the cells finally composing the tumor mass. (Tuttle and Womack, Fried).

According to Bela Halpert the epithelial lining of the respiratory tree is of entodermal origin and is capable of producing under certain environmental conditions, all the various types of cells produced by this primitive cell. These cells are known as reserve cells.

Ochsner and De Bakey classify bronchogenic carcinomas into three groups, not differing greatly from Boyd's classification:

1) reserve cell carcinoma

2) cylindrical cell carcinoma

3) squamous cell carcinoma.

Tuttle and Womack found that there was an association between degree of malignancy and prognosis. The average life expectancy for a person with a grade I cancer was 22.6 months, grade II 16 months, and grade III 12.8 months.

Arkin and Wagner believe the squamous cell cancer to have the best prognosis. These workers in their series at Woodlawn Clinic found 7 squamous cell, 1 round cell, 2 alveolar, 1 mixed, 1 adenocarcinoma, and 1 medullary type.

Gazayerli found 66 out of 95 cases to be oat cell tumors and the 28 remaining were adenocarcinoma, squamous and spheroidal carcinomas.

The oat cell tumor is highly undifferentiated and anaplastic. It is considered to arise directly from the reserve cells. There is a tendency to relegate these types of tumors into the realm of sarcomas because of their microscopic appearance and malignancy. They are malignant because of their anaplasticity and, too, because they are usually situated peripherally in the pulmonary tissue and metastasize early. The presence for the preponderance of these highly malignant tumors in the lung periphery is not known. It is this type of tumor that is more amenable to X-ray therapy than others.

Broders designed a classification of tumors on the basis of their microscopic appearance, i.e. degree of differentiation, method of infiltration, permeation of blood vessels and lymphatics, and finally a study of the individual cells for the presence, and number of mitoses size, shape, and degree of staining of the nuclei, and the

a pearance of the cytoplasm. He classifies malignancies into four categories, according to the presence or absence of the above mentioned characteristics known as Grade 1, Grade II, Grade III and Grade IV. The last being the most malignant.

It has been found that a certain amount of inference can be drawn as to prognosis and type of therapy to be administered, by the degree of malignancy of the tumor according to the Broders' system. The more malignant a lesion, the more amenable it is to roentgenologic treatment, everything else being equal. The peripheral tumors of the lung and the most highly differentiated of any found in the lung and are most malignant and most amenable to roentgen rays, or radium. These same tumors, however, are also the most accessible surgically, and thus an argument arises. The argument between the roentgenologist and surgeon cannot be too lengthy because once one of these tumors are detected, the patient has an average longevity of about one year. (Tuttle and Womack)

Oscar Berghausen states that highly undifferentiated forms of bronchogenic carcinoma simulate sarcoma. This author found the histology in 56 cases as follows:

1) squamous cell carcinoma 31
2) adenocarcinoma 13
3) reserve cell carcinoma 12

Embryologically, the various types of cells seen in the adult bronchial mucosa originate from the primitive entodermal cell. This cell is toti-potent, and from it most any of the differentiated adult cells could be formed. This type of development in an adult epithelium would coincide with Connheim's theory of the development of cancer from embryologic cell rests. Normally, basal cells, or reserve cells, develop from the primitive entodermal cell. It is claimed by some authors that through a protoplasia of the basal cell layer of the normal epithelium tumor growths may result. Protoplasia is sometimes spoken of as indirect metaplasia. Instead of the differentiated cells comprising the mucous membrane reacting to environmental changes within the lumen of the respiratory tree, the basal cells, or more undifferentiated cells, by a process of indirect division (protoplasia) form the various tumor growths known to the histologist. It is possible, by a process of metaplasia,for the ciliated columnar epithelium of the bronchial mucosa to form,under the proper conditions, a tumor growth composed of any of those cells known to the histo-pathologist.

In the chart that follows the various methods of tumor formation spoken of in the above will be presented:

PULMONARY TUMORS

Squamous-cell)	Entodermal cell	E
)		M
Adenocarcinoma)	Cell rests (Connheim's	B
)	theory)	R
Oat-cell)		Y
		O
		L
		O
Squamous-cell)		G
)		I
Adenocarcinoma)	Basal cell (Reserve cell)	C
)		A
Oat-cell)	Protoplasia	L
Sarcoma?		D
		E
		V
		E
Squamous-cell)		L
)		O
Adenocarcinoma)	Ciliated Columnar Epithelium	P
)		M
Oat-cell)	Metaplasia	E N T

PATHOLOGY

METASTASES: There are four methods by which tumor cells can be disseminated. These are: 1. Hematogenous; 2. Lymphatic; 3. Aerogenous; 4. By direct extension. We will dismiss briefly the aeorgenic mode, merely stating that there are cases on record where seeming proof existed for the postulation of such an event. Similarly, we will dismiss the infiltrative extension, noting that it is ever present where malignancies are concerned and that ofttimes this mode of spread is so extensive as to involve single lobes or even an entire lung.

We will discuss mainly the hematogenous and lymphatic metastases. The lung is a singular organ possessing a duo blood supply and an abundance of lymphatic channels. Tumor growths situated in other organs tend to be filtered out as they metastasize by the lungs. However, with malignancies located in the lungs itself, this filtering barrier is broken down, and blood vessels tend to be readily eroded and tumor cells excluded into their lumina. Because of the consistency of the veins and arteries, the first vessels to be eroded are the veins. Once this has happened, the portals are opened for a wide spread of tumor cells. The erosion of larger vessels and subsequent hemorrhage often times will lead to fatal termination or a serious degree of anaemia. Hematogenous spread once initiated

is very rapid. Boyd reports a high incidence of invasion of blood vessels in all cases of cancer of the lung. He states that in instances where there is no vascular involvement there will likely be no remote metastases.

Tumors of the lung are notorious for their ability to metastasize. All malignant pulmonary tumors do not, however, metastasize with equal rapidity. The ability of a tumor to be transported remotely is due in some respects to its location in the lung. Those located peripherally in the lung parenchyma seem to form mestatic deposits at an earlier date than those situated near the hilus. (Koletsky). The histologic differentiation of malignant tumors of the lung determine somewhat the rapidity with which they will disseminate. Those tumors of a high grade of undifferentiated type. Thus we find that the oat-cell tumor or reserve-cell, tumors which represent a high degree of malignancy and incidentally located peripherally offer a poor prognosis due to this combination of characteristics. To carry our histo-anatomico-pathologic comparison still further we will take the instance of the squamous cell carcinoma; this tumor is usually a high degree of differentiation and located at the hilus of the lung. From the two above statements as to location and malignancy of the squamous cell cancer we might infer, and likely so, that this tumor does not metastasize as readily as the more undifferentiated reserve-cell tumor, (Rabinovitch).

It is stated (Ochsner) that superficial lymphnode involvement is found in 5-20 per cent of all cases. This can ofttimes be explained by the presence of pleural adhesions, but in other cases, an orthograde, plus a retrograde type of dissemination can be found. If an enlarged axillary node is found in a proven case of cancer of the lung it could have obtained metastatic deposits by one of two ways, excluding pleural adhesions, 1) metastases to a regro-peritoneal gland--to a paravertebral gland, and by retrograde permeation to an axillary gland, or, 2) an anterior mediastinal gland may be affected, and orthograde extension to internal mammary glands, to jugulosubclavia confluence, and from there by retrograde dissemination to the supraclavicular and axillary nodes.

Miller states that the lung contains the best lymphatic supply of any tissue in the body. Rouviere has studied the lymphatic drainage of the lung and finds that the superior portion of the left upper lobe drains into the lateral tracheal chain and thence to the jugulosubclavian confluence. The inferior portion of the left upper lobe, and the entire lower lobe drain into the intertracheal bronchial nodes. The right middle and lower lobes drain into these same nodes, and thence to the right lateral tracheal nodes, to the right jugulosubclavian confluence. The upper right lobe

drains into the right lateral tracheal chain. Retro-peritoneal metastases may reach this position by extension from the lung through the lymphatico of the ligamentum latum pulmonum, to a retro-oesophageal node (supradiaphragmatic node), from here via an efferent transdiaphragmatic vessel to a juxta-aortic node.

The lymphatic dissemination tumor cells is of importance from a standpoint of diagnosis and prognosis. There is no unanimity of opinion as concerns the frequency of remote metastases from a primary malignant focus in the lung. Overholt studied 100 cases and found that 62% had clinical manifestations of metastases, and only 14% were free from extra-pulmonary involvement at the time of surgical interference. Because of early dissemination and other factors Brock in observice 106 cases found only 12.3% which he considered exploratory risks and of these only 4 were operable. Most authors are of the opinion that borderline cases should be given the benefit of an early exploration.

Many times the first evidence of a cancer of the lung is its distant metastases. Rogers reported on 50 cases and found 44% of them with symptoms referable to remote foci. Ochsner and De Bakey find that about 15% of cases can be diagnosed by biopsy of the axillary lymphnodes.

The various areas to which metastases travel in order of frequence are fairly constant. Eloesser in a study of 27

cases proven cancer of the lung found the remote metastases in the various organs as follows:

1. Supraclavicular nodes-5	5
2. Paribronchial	11
3. Mediastinal nodes	8
4. Retroperitoneal	4
5. Heart	7
6. Liver	6
7. Spleen	1
8. Kidney	5
9. Prostate	1
10. Ribs	1
11. Lungs	4
12. Pancreas	4

Cazayerli observing 95 cases found that the regional nodes were involved 84 times, abdominal glands 18, cervical glands 13, liver 35, adrenals 19, pancreas 18, kidney 16, and bones 11. Ochsner and De Bakey find regional lymphnodes involving 72% of cases, liver 33%, pleura 30%, lungs 23%, bone 21%, adrenals 20%, kidneys 17%, and brain 16%, heart and pericardium 13%. The pancreas is involved in about 7%; peritoneum, 5%;gastro-intestinal tract 4%; skin 3.6%, spleen 3½%, thyroid 2.3%, tonsil 1.8%, tongue 1.6%. It can be seen from the above that there is not tissue in the body immune from the met. deposit emanating from a primary

malignancy of the lung. Most authors find that cancer of the lung is notorious for its ability to mestatisize to the brain. Cushing found 35% of metastatic brain tumors that originated from the lung; Fried and Buckley found 15 xases out of a total of 38 with intracranial involvement. The author finds that after removal of these brain metastases that a few of the patients can look forward to a five-year period of longevity. Usually the outcome is not so successful and the removal of the brain tumor is merely a form of palliative treatment.

There has been an excellent article written on the various modes of lymphatic spread of tumor tissue. The author of this article is Handley, and this article was primarily written about breast tumors. He finds that tumor tissue is spread via the lymphatics by two main methods: 1. Permeation; 2. Transportation. Permeation, or lymphatic permeation, is "the master process of dissemination." This author contrasts infiltration and permeation. Infiltration usually precedes permeation, but once permeation has taken place spread is quicker than by infiltration because the tumor is growing into the lumen of a vessel. In this manner the smallest anastomatic plexuses may be traversed. This type of extension is called orthograde. If the lymphatic stream be blocked by fibrosis, the tumor will grow intra-luminally against the lymphatic current. This is called retrograde dissemination.

The spread of metastases by transportation is possible at any time after the lymphatic vessels have been infiltrated and permeated. This phenomenon of spread by transportation is characterized by a breaking off of particles of tumor tissues and these in turn being carried to remote positions by the lymphatic current.

The study of metastases is important from the standpoint of prognosis, diagnosis, and treatment. The chief type of dissemination seems to be lymphatic except possibly in the case of adenocarcinoma which has a tendency to invade blood vessels. All authors seem to be in agreement that the hilar squamous cell carcinoma offers the greatest possibilities of a surgical cure. King finds an average duration of life from the onset of symptoms of 9.6 months for a squamous cell carcinoma, 7.5 months for adenocarcinomas, and 5.6 months for oat-cell carcinoma. Koletsky reported on a number of cases and found that remote metastases occured most frequently or 89 per cent with the small cell carcinoma, the next greatest offender was the adeno-carcinoma, 86 per cent, and finally the squamous cell carcinoma only 35%.

The foregoing account imbues in us the necessity of an early diagnosis, if any type of curative treatment is to be initiated. The trend in this direction is total pneumonectomy, (Reinhoff).

DIAGNOSIS

At the present time the only hope for prolonging the life of an individual with cancer of the lung lies in the early detection of the lesion. The prognosis at best after symptoms have shown up is in most cases less than a year of life remaining. (King) Surgery has promise of eradicating the disease in a certain number of selected cases. Besides the danger of late diagnosis, we are here dealing with a group of patients (average age 55 years) who must, because of their age forsake their only hope, surgery. The surgeons, however, are now doing the operation of total pneumonectomy in several stages which allows a few more to obtain possible cure, but at least relief. (Overholt)

We must not think wholly in terms of roentgenology, bronchoscopy, or other accessory methods of diagnosis when dealing with the diagnosis of cancer of the lung. The real diagnostic ability of a person is proven when the history of a patient must be evaluated.

It is interesting to note the apparent increase in our diagnostic ability through the past two decades. Arkin and Wagner state that twenty years ago that 5 percent of cancer of the lung was diagnosed; today, 50 percent is diagnosed, and they believe that 90 percent of carcinoma of the lung should be detected.if proper evaluation of the patient's history be done, especially as regards a history of bronchitis, pneumonia, influenza, or pleurisy.

HISTORY: The history is the most important of the diagnostic picture, because it is usually upom this that we decide whether a person should be given the benefit of further diagnostic aids, or whether we are here dealing with some type of innocuous chest lesion. Shapiro says that a person 45 years old with a chronic or sub-acute chest complaint or complaints may have tuberculosis, bronchiectasis, abscess, or neoplasm; a patient 50 years old with the same complaints is more apt to have neoplasm than tuberculosis; a patient from 55-60 years is most likely to have a neoplasm.

In a great number of cases of cancer of the lung that present themselves before the physician, a preceeding disease of pulmonary origin will be described e.g. Stein observes that 33 percent of his patients with primary cancer of the lung gave a history of antecedent, "heavy cold", "flu", "pleurisy", "chills and fever", or as "pneumonia". Berghausen reported that many give a history of previous pulmonary e.g. pleurisy, pneumonia, influenza, chronic smoker's bronchitis, or tuberculosis.

Most people, and especially men, will not come to see a physician for such a minor complaint as cough, but however if they cough up blood they usually consult with a physician. There may be only vague chest signs, the patient hardly being aware of them, and they must be prompted to speak of them. Some people have definite pain in the thorax. Still others

will have no history revelant to the chest, but come in with joint pains, or cerebral symptoms. (Shapiro) Bailey says that in a patient of middle age or beyond who develops a rapidly infiltrating tumor of the brain, cancer of the lung must be considered in the differential diagnosis.

In contrast to those who come in with vague complaints, are those who approach you as a classical replica of the disease, that is, cough, bloody sputum, loss of weight, anorexia, shortness of breath, limp, failing vision, pain in the chest, plus the numerous systemic complaints due to widespread metastases.

SYMPTOMS AND SEMEIOLOGY: The symptoms and signs alone are never diagnostic of cancer, but can be suggestive of intrapulmonary pathology. Berghausen reports that the early symptoms are due mainly to irritation of the bronchial mucosa--cough, dyspnoea, and frequent hemoptysis. Later signs are the result of obstruction, infiltration, and degeneration.

There is no unanimity of opinion as concerns the frequency of occurrence of the various symptoms or symptom complexes. Bauer noted the following: Eleven patients presented cough, thoracic pain without hemoptysis; ten patients presented the symptom complex of cough, thoracic pain, and hemoptysis; eight patients had cough, no thoracic pain, with or without hemoptysis; six had no cough,(two with pain, one with pain and hemoptysis). The same author listed

the incidence of chief complaints as follows:

NUMBER OF PATIENTS	
10	THORACIC PAIN
10	COUGH
5	THORACIC PAIN AND COUGH

Olin and Elliot in a study of 38 cases found cough in 18, blood stain sputum 8, chest pain eight, dyspnoea 10, loss of weight 8, weakness 13, brachial neuritis 4, and sacral pain 3. With apical tumors a Horner's syndrome may be present.

Robertson found pain the chief complaint in 10 cases, 6 of these had pain of a pleuritic nature, hemoptysis an initial symptom in 5 cases, dyspnoea in 3, cough 3, difficulty in walking in one instance. The symptom triad most frequently met in the disease (carcimona of the lung) is pain, cough, and dyspnoea (Frank)

McCrae charted the symptoms and incidence of symptoms at the onset and on admission to the hospital as follows:

SYMPTOMS	PERCENT AT ONSET	PERCENT ON ADMISSION TO HOSPITAL
COUGH	60	100
PAIN	15	67.5
LOSS OF WEIGHT AND WEAKNESS	12.5	80.0
HEMOPTYSIS	7.5	57.5
DYSPNOEA	2.5	52.5
HOARSENESS	2.5	10.0

Eloesser states that if the tumor growth is located peripherally in the lung only one out of every three will have complaints referable to the lung. This substantiates the view that parenchymal lung tumors,located in a position not adjacent to vital structure has a tendency to metastasize early.

Stein finds the symptomatology in order of frequency as follows in 164 cases, cough, loss of weight, pain, dyspnoea, weakness, expectoration with or without hemoptysis, gastro-intestinal symptoms, hoarseness, night sweats, anorexia, palpitation, orthopnoea, and pain other than pleuracic.

I can find no way to explain the difference in frequency of the chief symptoms over a number of cases, except that these symptoms are not chronologically distant, and that it is within the realm of probability that they should vary slightly in frequency.

If we follow the histo-pathological concept, formulated earlier in the paper under the heading of pathology, we find that it applies quite well clinically. The histo-pathological classification has simply divided tumors into two groups anatomically; those located centrally near the hilus (hilar nodular), and those located peripherally, or the diffuse necrotic type. Those centrally located produce a varied and local symptomatology refeable to the lung and thorax. Those peripheral growths do not cause symptoms

early, but when they do it is usually the result of distant metastases.

Tumors in general are known to have deleterious systemic effects. These are usually exemplified by weakness, loss of weight, anaemia, cachexia, leucocytosis, night sweats, fever etc.. These systemic effects do not concern us greatly because they are usually late in onset and herald the beginning of the end. When a person presents these symptoms he or she has passed from the realm of possible cure to that category in which only palliative and symptomatic treatment can be used. It is with this group of patients that the roentgenologist can do much to allay distressing symptoms.

The varied symptomatology can be explained by, 1) anatomical location, 2) pathological processes present in the lung, 3) metastases, 4) physiological status. One of the chief symptoms is cough. This is produced in early cases by irritation of the bronchial mucosa. As the pathologic processes continue, the cough increases in severity, at times being almost paroxysmal. There are various types of cough that will present during the illness produced by a malignant lung tumor. The variety is most dependent upon the location of the tumor which in turn regulates the degree of occlusion of the respiratory passages. Obstructing tumors located in the larger bronchi will produce a wheezing type of cough. The quality of a cough will depend somewhat upon the degree

of moisture present in the tracheal bronchial tree. In the early stages it is the cough, chronic nature, that is ofttimes the only symptom present, and regardless of its quality or intensity it should be regarded with suspicion if it occurs in a patient who has reached the fifth decade.

Pain is many times an early sumptom of cancer of the lung. It may come on suddenly as an acute pain or gradually, reaching a climax within a period of days or weeks. Once pain has started it is usually persistant unless the patient's condition so rapidly declines that the threshold of pain is increased . The pain is usually more acute in nature when located sub-pleurally, and the distribution may be along the course of one or several intercostal nerves. A tumor located in one of the lower lobes of the lung, and in juxta-position to the central tendon of the diaphragm may produce a kind of pain referred to the tip of the shoulder. Those tumors located centrally, or hilar tumors, usually do not cause as severe pain as tumors located peripherally. This central lesion has a boring type of pain associated with it, and is not well localized.

Dyspnoea occurs with great frequency with those tumors located near the hilus of the lung. It is the result of obstruction, partial or complete, of one of the main bronchi, or main stem bronchi. Not only is air-hunger due to obstruction, but may also be the result of a collection of fluid in the

smaller respiratory bronchioles, and even in the alveoli. This symptom sometimes occurs as the result of reflex stimulation arising from the region of the tumor. We might find this condition obtaining in cases of early cancer of one of the larger bronchi, plus an acute ulcerative condition. As the disease progresses, dyspnoea is most often directly or indirectly the result of obstruction.

Most people who have had bronchogenic carcinoma for any length of time bring up a certain amount of sputum. The quality of the sputum depends on the duration, the location, and the subsequent pathologic processes which may obtain. It is assumed that the organisms responsible for certain types of sputum are ever-present in the pulmonary air passages. Early cases of carcinoma of the lung will have no sputum to speak of. Likewise those with peripherally located masses will have no expectoration early or even in that the disease. Hemoptysis will occur quite early and of some severity in a few possessing a tumor located near the hilus. Im many instances this will be the only presenting complaint. Purulent sputum is discharged late in the disease because of abscess formation with subsequent erosion into a bronchus, or extensive bronchiectasis. We may have a combination of the various types of sputa if one of the above conditions has concommitantly superimposed upon it anyone or several of the above pathological processes.

McCrae stated that cough is the most common symptom and occurs in all cases sooner or later. The onset may be insidious or abrupt. Some will give a history of an attack of influenza or pneumonia that never cleared up. The above author found cough most prominent in 60 percent of his cases. In 24 studies 17 patients presented a dry cough, 7 productive.

Edwards found pain could be the most prominent sympton in 60 percent of his cases, and pain in one case was due to spontaneous fracture of a rib actually invaded by tumor. This same author maintains that parenchymal pain of a peculiar type constant, and deep seated may occur in peripherally located tumors; hemoptysis occurs in about 40 percent; dyspnoea may occur as a result of paralysis of the phrenic nerve; and loss of weight is only a late symptom.

As can be seen, the symptomatology of cancer of the lung is indeed varied, and if we are to diagnosis this condition, the highest grade of diagnostic acumen must be called to the fore. Undoubtedly any case in which the clinician attempts to make a diagnosis on symptomatology alone, will be disproven in some instances at the autopsy table.

PHYSICAL DIAGNOSIS: We are interested primarily in detecting cancer of the lung at an early date. Today we do not rely on physical diagnosis as in the past. It does, however, have its place in the diagnosis of pulmonary disease. There are few clinicians today who possess any great skill along these lines. When a pulmonary disease such as cancer of the lung has progressed to a stage where we are able to detect it on the basis of our natural senses, it is usually too late for the therapeutist to do anything about it. At the stage when abnormal physical signs are noted the picture may simulate many other diseases in this respect. It is this pleomorphic, changeable picture that is of diagnostic importance.

With those tumors located in the hilar region of the lung very few physical signs can be detected until very late by auscultation, percussion, palpation. With an obstructive lesion in this locality, sometimes rhonchi may be heard. If complete or partial atelectasis has resulted as a result of obstruction this may be picked up by auscultatory methods. This same condition may be delimited through the medium of percussion.

The various instruments used in physical diagnosis are not of great value even with those lesions located more peripherally. There may be an area of dullness over the tumor, with a decrease in breath sounds. If abscess formation with cavitation has taken place we might obtain

by use of the stethoscope a peculiar type of sound known as cavernous breathing.

From the standpoint of inspection, many things may be detected. If we view a person who has this ailment (cancer of the lung) we might find that he is cachetic, that is he may be bed-ridden, emaciated, and possess what is known of as a Hippocratic facies. We note this condition only in the late stages of the disease. Due to systemic involvement there may be an accompanying anemia which manifests itself outwardly by a paleness of the general body skin, and mucous membranes. If there is a considerable degree of obstruction to the pulmonary respiratory tree there might be besides dyspnoea and accompanying cynosis. This cynosis would be generalized, but there is another type not generalized, but localized to the thorax, neck, head, and upper extremities. If a tumor is located in the superior lobe of the right lung, it might very well obstruct the superior vena cava thus causing cynosis. In this case the cynosis would be accompanied by an oedema limited to the same area as the cynosis.

In some cases the tumor growth may impinge on and partially obstruct the arteries. Tumors located at the apex of one or the other lung might and sometimes do put pressure on the subclavian artery which results in an inequality of volume of the radial pulses. (Anderson)

Clubbing of the fingers and toes may be noted in cases

where the pulmonary pathology has existed for some time. This clubbing probably exists on a basis of incomplete aeration of the blood. This condition is noted in other diseases where an anoxic anemia is present. Other vicible signs are present . Splinting of the chest occurs if there is any pleural irritation. Points of tenderness on the thorax are rare, and if present are probably due to infiltration of nerves by the primary growth, or to metastatic involvement. Eloesser reports three cases of thrombosis of the iliac veins due to an infiltration of the tumor at the pulmonary hilum retarding venous return.

Physical diagnosis is not so important from the standpoint of an early diagnosis in cancer of the lung, but rather in determining the extensiveness of the lesion.

SPECIAL DIAGNOSTIC AIDS: The bronchoscope is said to be the most important single diagnostic aid as concerns cancer of the lung. (Overholt) Non-circumscribed tumors located at the hilus of the lung are most amenable to bronchoscopic vision. The circumscribed lesions are usually more peripherally located and therefore are inaccessible to the bronchoscope. Neuhof and Rabin report that 75 percent of the non-circumscribed tumors can be diagnosed bronchoscopically, and 42 percent of the circumscribed can be diagnosed by the above method. Jackson is of the opinion that 75 percent of cancers of the lung can be diagnosed by bronchoscopy.

With the bronchoscope we are able in many cases to view the tumor directly. In other cases the presence of a tumor can be detected because of the effects of metastases to bronchial or tracheal nodes. Deviation of the trachea, carinal thickening or broadening is evidence of metastatic growths.(Dorsey) Biopsy of the tumor growth can be done at the same time as the growth is viewed with the bronchoscope, thus obtaining tissue for direct microscopic examination. Overholt in a study of 24 cases diagnosed 22 of them with a bronchoscope. This author states that 65 percent of all cancers of the lung originate within the primary or secondary bronchi; this accounting for the importance of bronchoscopic studies of the tracheal bronchial tree.
X-RAY: The use of x-rays in the diagnosis of cancer of the lung has assumed a position second only to the bronchoscope. The picture presented to the radiologist may be one of many, determined only by the rate of growth, location, important structures involved, degenerative changes, and concommitant disease. Therefore a pleomorphic radiological picture in a person with suggestive symptoms, who falls into the cancer age group, should probably be diagnosed as cancer of the lung. Shapiro noted roentgenographic changes in the lung occurring as rapidly as in two to four weeks.

Those tumors which have the most varied picture fall into the hilar nodular group of Menne and Anderson, and the

reason for this is due mainly to obstruction. Sometimes bronchiectasis may dominate the picture, at other times abscess formation with or without a demonstrable fluid level may be seen; there may be a massive atelectasis due to obstruction, or emphysema due to the same cause; finally the tumor mass itself may be visualized.

In the diffuse necrotic or parenchymatous form of lesion, the pleomorphic picture seen in the nodular type does not obtain. There may be, however, pleural involvement. The actual tumor mass located at the hilus will not be viewed as often at an early date as will be a tumor located peripherally. The radiographic location of the tumor agrees, on the whole, with our bronchoscopic, histologic, pathologic, and clinical classification.

Extra-pulmonary lesions may be noted, according to Robertson, in many instances. In his study of 22 cases, he found that 9 had pleural effusions, 3 atelectasis, and one a fibrinous pleurisy. Andrus found that of 64 proven cases of cancer of the lung, 58 of these showed definite x-ray evidence. Rice in 28 cases found definite x-ray findings in 7, presumptive evidence of cancer of the lung in 4, atelectasis and effusion in 16, and the plate was negative once.

The section on primary malignancies of the lung in Holmes and Ruggles' book begins with the statement that

"primary malignancy of the lung is rare". These authors describe two types roentgenologically, 1) nodular, 2) infiltrative.

The nodular type presents dense, rounded masses near the hilus, and infiltrative type shows a ragged irregular cavity. Involvement of hilar nodes may be evident, and if massive collapse of a lobe or entire lung has occurred a shift of the mediastinum to the side of the tumor will be evident. Harrison uses somewhat the same classification as that used above.

Some of the radiologic classifications become quite extensive, but probably the more simple ones will suffice in most instances. The radiologist is of real significance in the diagnosis of malignant lung tumors.

There are other accessory methods of diagnosis used in diagnosing cancer of the lung. Some claim that sputum studies are of real value. Hochberg found positive sputum in 68 percent of proven cases. This same author studied pleural effusions and found tumor cells therein in 40 percent of cases; lung puncture gave a positive diagnosis in 6 percent of cases. Exploratory thoracoscopy, and exploratory thoracotomy are procedures advocated by some men. The first of these procedures is used to localize the lesion and obtain tissue for biopsy. The latter procedure may be done as in preparation for radical surgery, to determine the presence of local metastases.

Holinger sums up the diagnostic view quite well. He says that in cases of obscure pulmonary pathology early diagnosis can be made only if routine inspection of the tracheo-bronchio tree is undertaken.

THERAPY

In the last ten years rapid strides have been made in the realm of therapy as concerns bronchogenic carcinoma. Ths surgeon particularly offers great aid, and possible cure to those who are affected with this ailment. Graham in 1933 successfully extirpated an entire lung. Since this time many techniques have been described whereby pulmonary tissue may be removed en masse. Total pneumonectomy is not the only procedure used by the surgeon, sometimes it seems that a lobectomy may be indicated.

The radiologist is of definite importance as concerns cancer of the lung. McCrae reports apparent cure in 4 cases of lung cancer. Most radiologists, however, do not report many definite cures, but rather state that their forte is palliation. Tuttle and Womack report that in 71 percent of cases having serious discomforting symptoms, radiation will give them relief. Fulton found that in 16 patients with palliative treatment a survival of 3.5 months was obtained. 5 patients who received no treatment died in 2 months. This author took a group of patients and subjected them to various dosages over different lengths of time. 7 patients who received a total of 3,000r had an average survival of 5 months. 8 patients received 6,000r over a period of 6 weeks, and the average survival of this group was 7 months. The conclusions from this work are as follows: that there should be one period of treatment, and that the

maximum dosage should be used.

Surgery offers possible cure if instituted at an early date. Overholt was successful in 80-90 percent of his lobectomies, and in 65 percent of his pneumonectomies. In 37 cases at the Lahey Clinci in the past four years, 35 cases were diagnosed clinically with histologic confirmation. Of this group 12 were rejected for operation because of poor condition or metastases, 10 were explored and found inoperable. Two lobectomies, and 10 pneumonectomies were done and of this group there were 4 survivals, one for three years and five months, and the others two years and ten months, eleven months, and three months respectively. Neuhof and Rabin found that 46 cases they inspected were clinically operable. 29 of this group were operated and 16 were found free of regional node involvement.

The criteria for surgical excision of a pulmonary neoplasm are , 1) good general condition of the patient, 2) lack of involvement of structures by metastases, 3) a pleural effusion of any significance. (Dorsey) This author maintains that less than 60 percent will be found operable. Reinhoff, Overholt, and Rumel are of the opinion that the operation of choice in any neoplastic disease of the chest is total pneumonectomy. Overholt found that a diagnosis was made in the operable stage 22 percent of 70 cases. 33 percent of these cases showed clinical metastases, 56 percent

were given an exploratory thoracostomy and about half of these were considered inoperable.

Surgery of the lung is today considered a safe and logical procedure. The necessity for the early diagnosis of cancer of the lung becomes even more urgent in view of the fact that there is a possible cure for this disease.

CONCLUSIONS

We are aware today of an increased incidence in the number of bronchogenic carcinomas. Our interest lies not so much in the discussion as to whether this increase is relative or absolute, but rather can our diagnostic and therapeutic procedures promise those possessors of this disease any hope of a cure? I am certain that medical men today are more cognizant of cancer of the lung than in the past. With this increasing interest concerning a universally fatal disease we have hope that more early diagnoses will be forthcoming, and the proper therapeutic procedure instituted with a possibility of cure.

The pathology of carcinomas of the lung, while not dogmatic as concerns the histology of the tumors, nevertheless, some unanimity, as regards their classifications, exists. It will be noted that throughout this paper there has been an attempt to classify bronchogenic carcinoma uniformly from the standpoint of anatomical location; finding the while that this simple form (1. hilar nodular type, 2. peripheral type) of classification is amenable for use in the various specialities.

The cause of cancer of the lung today, as far as we know, is based on two main factors: 1) a constitutional predisposition, or hereditary factor, 2) and the environmental factor or local factor ofttimes thought of in terms of chronic irritation.

Bibliography

I- Anderson,W.N. Physical Diagnosis, Philadelphia: Lea & Febiger I940

2- Andrus,W.De. Report of chest tumor registry,Jr. of Thor. Surg. 4:236 Jan.'35

3- Arkin,A. and Wagner,D.H. Primary cancer of the lung J.A.M.A. I06:%' I936

4- Bailey,P. Intracranial tumors, Springfield,Ill. C.C. Thomas & Co.

5- Bauer,J.T. Difficulties in early diagnosis of cancer of the lung, Delaware St. Med. J. I2:I9 Feb.'40

6- Berghausen,Oscar Clinical aspects of malignancy of the lung, Ohio state M.J. 37:757 Aug.'4I

7- Bonser,G.M. Incidence of tumors of the respiratory tract in Leeds, J. of Hygiene 23:240 I928-29

8- Boyd,W. Notes on pathology of primary cancer of the lung,Canad.M.A .J. 23:2I0,I930

9- Boyd,W. Atextbook of pathology Philadelphia: Lea and Febiger I939.

I0- Brock,D. Pulmonary newgroths,pat ology,diagnosis, and treatment, Lancet 2:II03, I938.

II- Campbell,J. Argyll, Lung tumors in mice, British M.J. I;2I7 Feb. I4, I942.

I2- Condon,W.B. Regeneration of tracheal and bronchial epithelium, J. of Thor. Surg. II;333-346 Feb. I942.

I3- Covey,G.W. A case of malignant disease of the lung Nebr. St. Med. J. I:82 I9I6

I4- Cushing, H. Intracranial Tumors, Springfield, Ill. C.C.Thomas Co.

I5- Davidson,M. Cancer of the Lung, New York; Wm. Wood & Co. I930.

Bibliography

I6- Dibble,J.H. Silicosis and cancer of the lung J. of Hyg. 38:I85 Mar.'38.

I7- Dorsey,J.M. Diagnosis and treatment of bronchogenic carcinoma, Surg. clin. of N. Am. 20: I63-I83 Feb.'40

I8- Eggers,H.E. The increased mortality rate of cancer J. Cancer Research, I2 : 9 I928.

I9- Eloesser,L. Primary tumors of the lung, Arch. of Surg. I0;445,I925.

20- Ewing,J. Neoplastic Diseases, New York City, Saunders, I940.

2I- Faget,R. Primary cancer of the lung- a study of 5 cases, Virg. Med. Monthly 65;I8-24 Jan.'38.

22- Fulton,J.S. X-ray therapy in cancer of the lung, Brit. M.J. 2:67I-73 Oct.3, I936.

23- Frank,L.W. Primary cancer of the lung, Rocky Mt. M.J. 35:468 June, '36.

24- Fried and Buckley Primary carcinoma of the lung with intracranial metastases, Arch. of Path. 9:483, Feb.'30

25- Frissel,L.E., Knox,J.C. Primary cancer of the lung Am. J. of Cancer 30:2I9, I937.

26- Gazayerli,M. Observations on primary cancer of the lung,

27- Halpert,Béla The incidence of cancer of the lung, Cancer Research, I:900 Nov.'4I.

28- Halpert, Bela I0 year survey of necropsies, J.A.M.A. II7:I090 Sept.'4I.

30- Handley,R. Cancer of the Breast New Work: Paul B. Hoeber Inc.I922.

3I- Harrington,S.W. Pneumonectomy for cancer of the lung J. of Thor. Surg. II:396,I940-4I.

Bibliography

32- Harrison,B.J. A Textbook of Roentgenology,Baltimore: Wm.Wood & Co. I936.

34- Hammond,A.E. Carcinoma of the lung,Arch of Otolaryng. 3I:780 May'40.

35- Hochberg,L.A. Accessory methods for the diagnosis of cancer of the lungs, Dis of the Chest 8:70-78 Nov.'42

36- Hochberg,L.A. Carcinoma of the lung,Arch. of Int. med. 63:80-99 Jan'39.

37- Holmes,G.W. and Ruggles,H.E. Roentgen Interpretation, Philadelphia: lea&Febiger,I926.

38- Holinger,R.H. The diagnosis of bronchogenic carcinoma bronchoscopic aspects,Ill.M.J. 72:43I Nov.'37.

39- Jackson,C. Bronchoscopy and the diagnosis of primary cancer of the lung,J.Thor. Surg.4:I64, I934.

40- Jaffe,R.H. Primary cancer of the lung,J.of Lab. & Clin. Med. 20:I227 '35.

4I- Kennaway,N.M.& E.L. Incidence of cancer of th lung, 36:236 June I936.

42- King,C.A. Primary cancer of the lung, New England M.J. 2I9:828 I938.

43- Konterwitz,H. Early diagnosis of primary neoplasms of the lung,Dis. of Chest 7:366 Nov.'4I.

44- Macklin,M.T. Has a real increase of cancer of the lung been proven? Ann. of Int. Med. I7:308 Aug.'42.

45- McCrae,T. Bronchogenic neoplasms,Arch.of Otolaryng. I2:727 Dec.'30.

46- Menne and Anderson, Bronchogenic carcinoma,J.A.M.A. II7:22I5 Dec. 27,I94I.

47- Myerhof,Otto, A Symposium on Respiratory Enzymes, Madison:The University of Wisconsin Press, I942.

Bibliography

48- Nelson, K. Pulmonary tuberculosis and cancer of the lung, Virg. Med. monthly 63:530, Dec. '36.

49- Neuhof, H. and Rabin, C.B. Cancer of the lung, J.Thor. Surg. 11:388-95, 1940-41.

50- Ochsner,A. and De Bakey,M. The Significance of Metastases in Primary Cancer of the Lung, J.Thor.Surg. 11:357-285, April, '42.

51- Olin,H.A. and Elliot, C.A., Primary bronchogenic carcinoma of the lung, Am.J. of Surg., 54:614,1940.

52- Olson,C. Primary cancer of the lung, Am.J. of Path., 11:449 1935.

53- Overholt,R.H., Curability of primary cancer of the lung, Surg.Gyn. & Ob. 70:479,1940.

54- Overholt,R.H.,Clinical studies of primary cancer of the lung, J.Lancet, 59:155, Apr.'39.

55- Overholt,R.H.,Clinical studies of primary cancer of the lung, J.A.M.A. 114:735, Mar. '40.

56- Overholt,R.H.,Primary malignancy of the lung, Surg.Clin. of Nor. Am. 17:895-904, June, '37.

57- Overholt,R.H.,Apparent cure of cancer of the lung by pneumonectomy, J.A.M.A. 113:673, Aug. 19, 1939.

58- Rabinovitch,J., Primary cancer of the lung - a histo-pathologic study, J.Thor.Surg. 9:332, Feb. '40.

59- Reinhof,W.F.,Jr., Graded Pneumonectomy in treatment of tumors of the lung, Bull. of John's Hopkins Hospital, 64: 167, 1939.

60- Rice,C.M., Primary cancer of the lung, J.Lab. and Clin. Med. 21:906-909, June, '36.

61- Robertson, C.K.,Primary new-growth of the lung, Edinburgh M.J. 69:110-117, 1942.

62- Rosahn, P.D.,Incidence of primary carcinoma of the lung, Am.J.M.Sc., 179:803-811, June, '30.

63- Shapiro,W.W.,Primary carcinoma of the lung M. Clin of North Am. 22:125-137 Jan. '38

64- Stein,J.J. Cancer of the lung, U.S. Nav.Med.Bull. 38: 329, July,'40.

65- Simon,E.J., Primary cancer of the lung. The Year Book Publishers, Inc.: Chicago, 1937.

66- Stein,J.J. Pulmonary Apex tumors, Texas St. M.J. 33: 293, Aug. '37.

67- Tuttle,W. and Womack,N.A. Bronchogenic carcinoma, J.of Thor. Surg. 4:125, 1934.

68- Winternitz, N.A., Wason,I.M., and McNamara,F.P.The Pathology of Influenza, New Haven:Yale University Press, 1920.