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## Primary carcinoma of the lung

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PRIMARY CARCINOMA OF THE LUNG

SENIOR THESIS ---- APRIL 1933

Everett J. Garrison.

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## PRIMARY CARCINOMA OF THE LUNGS

Professional interest in a particular subject is quite accurately reflected by the current medical literature which appears during the period under consideration. Primary carcinoma of the lungs received very little attention during the last century. Adler (2) in his monograph written in 1911 states that , "On one point, however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lung are among the rarest forms of disease". Most textbooks still class the disease as very rare and Ewing (26) as late as 1922 in his book on neoplastic diseases speaks of it as a "rare condition". During the present century and particularly since 1920 there has been a marked increase in the number of articles on the subject which are appearing in current periodicals of the medical profession. This indicates an active interest on the part of clinicians, pathologists and roentgenologists who are coming in contact with the condition. The number of cases reported by many authors also suggests that the disease is not so rare as it has been considered. It is the purpose of this discussion to partially review and summarize the available literature and present the clinical manifestations of the disease.

The history of primary malignant disease of the lungs is comparatively short. Many authors credit Morgagni, 1761, as being the first to observe and record a case of primary cancer of the lung. His case was

accidentally discovered at autopsy and he applied the term "ulcus cancrosum" to the condition. Weller (99) believes this case to have been doubtful and is inclined to give the credit to Bayle (1810) , who recorded three cases one of which was probably primary carcinoma of the lung. Bayle used the term "phthisie cancreuse" to describe his cases. Stokes (1837) , Graves (1848) , Werner (1891) , Kurt Wolf (1895) and Passler (1896) are responsible for recording observations and contributing to the literature on the subject during the nineteenth century. Probably the most significant contribution on the subject up to the present time is the monograph written by Adler (2) in 1911. He discusses the clinical and pathological features obtained from his collection of 374 cases of primary carcinoma of the lung taken from the literature which had appeared before that time.

#### INCIDENCE

The frequency of primary carcinoma of the lung is the subject of much discussion, a considerable collection of statistics , and a mild controversy. All authors admit that the condition is more often observed and recorded and that it has become comparatively common. The difference of opinion arises over the explanation of this relative increase some authors maintaining that it is real and absolute and others , that the increase is only apparent.

Adler recognized that a decided increase was evident but was convinced that it was only apparent. He attributed

it to increased attention to this type of tumor and to the greater care and more extensive microscopic investigation with which autopsies were being performed. Weller (99) and Fried (33) in the United States and Boyd (13) in Canada also conclude that the increase is only apparent. They explain it upon the basis of better diagnosis, both clinical and pathological, increased attention to this condition, and the increased span of life which permits more people to reach the cancer age. Maxwell and Nicholson (67) London also attribute the apparent increase to improved diagnosis. Bonser (12) in Leeds concludes there has been no increase in intrathoracic cancer during the past thirty years (1891-1926) but her early figures show a much higher frequency than those of most authors. Homann (43) from his observations in Magdeburg believes there is no appreciable increase in the proportion of lung cancer to total cancer and attributes the increase reported elsewhere to improved diagnosis. Von Zalka (97) in Budapest observed only slight variations in frequency from 1904 to 1924 but records a sharp rise during the period 1924-1927.

Many writers (notably Manges, Rosahn, and Moses in the United States ; Duguid, Simpson and Parish in England Benda and Wahl, Brandt, VonZalka , Lindberg and Pekelis in continental Europe ) are convinced that the increase is real and absolute. Figures of incidence show marked variations depending upon the country in which they were obtained and to some extent upon the individual collector. The American figures are not convincing due to the wide variation and to the lack of statistics for the early

years of this century. Rosahn (82) for the period 1910-1918 gives the proportion of primary cancer of the lung to all cancer as 4.39% and from 1919 to 1928 as 6.98% while the proportion of primary carcinoma of the lung to all autopsies for the same periods is 0.44% and 0.89% respectively. They were obtained from a total of 3004 autopsies at the Boston City Hospital. The figures of McRae, Funk and Jackson (68) from 621 autopsies at Jefferson Hospital, Philadelphia, during 1924-1927, .66% of all autopsies and 7.54% of all cancer, compare favourably with those of Rosahn. Contrasted with these are the high figures of Moise (71), 1.38% of all autopsies and 17% of all cancer. His figures are obtained from a comparatively small group of autopsies (375 consecutive) prior to 1921 and consequently gives them less value. Much lower figures are those of Fried (31) whose statistics from 1400 autopsies prior to 1925 give the proportion of primary carcinoma of the lungs to all cancer as .63%. Ewing (26) in 1922 places this type of malignancy at about 1% of all malignancies while Grove and Kramer (40) from 3659 autopsies at the Cook County Hospital conclude that it is from 1% to 2% of all cancer.

British figures also show an increase in incidence during the last decade. Simpson from the records of the London Hospital on combined clinical and post-mortem observations shows an increase in the percentage of carcinoma of the lung to total malignant growths

(5)

from 1% in 1907 to 3.7% in 1925. Davidson (22) from the Brompton Chest Hospital gives very high figures but coming from a specialized service hospital are of no particular value for comparison. Parish (76), St. Giles Hospital, London, records an increase in the percentage of all cancer from 1.7% (1920-1924) to 2.4% (1925-1929).

Statistics from Continental Europe and particularly from Germany are even more convincing evidence of a real increase in incidence. This is best shown by the table by Huguenin taken from Davidson (22).

<u>WORKER</u>	<u>PERIOD</u>	<u>PERCENTAGE OF ALL CANCER</u>
Staehelin (Basel)	Before 1906	1.6
	1906-1914	2.9
	1914-1924	5.0
Seyfarth (Leipzig)	1900-1906	5.01
	1907-1913	6.88
	1914-1918	11.23
	1919-1923	8.75
	First Half 1924	15.5
Dora Hanf (Berlin)	1903-1906	3.3
	1922-1926	7.5
Wahl (Berlin)	1917-1922	6.0
	1922-1927	13.0
Kikuth (Hamburg)	1910-1914	5.5
	1915-1919	4.2
	1920-1924	7.7
Probst (Zurich)	1906-1910	1.13
	1911-1915	3.34
	1916-1920	6.12
	1921-1925	7.17
	1926	7.56



Zalka (Budapest)	1919-1923	2.67
	1924-1927	6.65
Berblinger (Jena)	1910-1914	2.2
	1915-1919	2.9
	1920-1924	8.3
Brandt (14) (Riga)	1901-1905	1.0
	1921-1925	10.0

(Brandt's figures are added to the table )

Statistics are very difficult to evaluate.

Correct interpretation requires intimate knowledge of the methods of collection, the amount of material observed and the standards of diagnosis upon which a case was accepted for recording. Most of the above figures were based upon necropsy records and presumably the diagnoses were verified microscopically. Practically all writers have shown an increase in the percentage of primary carcinoma of the lung of all necropsies and, of even more significance, an increase in the percentage of all cancers. Pekelis (76) of Florence is an exception to the above statement. His records for the periods 1919-1924 and 1925-1929 give .13% and .26% respectively of all autopsies but the percentage of all cancer decreases from 14.1% to 11.08% for the same periods. There are no other figures for the same periods, however, which show such a decrease and the variation may be due to local conditions.

Increased span of life and better diagnosis might account for the increased percentage of all necropsies but can hardly explain the higher proportion of carcinoma of the lung in relation to all cancer. Increased attention

to this disease might account to some extent for the change in incidence but is not sufficient to explain the marked increase in frequency which is evident. It seems reasonable to conclude that the increase is real and that it has been most marked since 1920.

#### ETIOLOGY

The immediate cause of primary carcinoma of the lung is unknown. Several theories have been advanced but as yet none has been proven. Miller and Jones (70) cite Hampeln's theory to which Heilman subscribes believing that the ciliated columnar epithelium of the bronchus is overwhelmed by the dust inhaled from the streets. This results in irritation to the basal layer of cells with the beginning of proliferation which through some unexplained change becomes malignant. This is not very widely accepted.

#### Age and Sex:

On general predisposing factors as age and sex there is fairly common agreement. Frommel (34) gives 58 years as the average age while Parish (76) places the average at 57 years. Funk (36) states that 44.2% of the cases occur between 35 and 45 years and McRae, Funk and Jackson (68) place 91% as occurring after 35 years of age. The decade of greatest incidence is quite generally accepted as between 50 and 60 years.

Sex incidence ranges from approximately equal as given by Rogers (81) to 88% males according to Parish (76).

The more commonly cited figures , however , give the proportion of males to females as 3:1 .

Heredity :

Heredity as a predisposing factor is not commonly accepted . Rogers ( 81 ) found that a history of parents dying of cancer was present in only 15% of his cases. Adler and Grove and Kramer also considered heredity of no significance. Lynch (64) in her experimental production of pulmonary tumors in different strains of mice concluded that an hereditary susceptibility was evident. Figures on the prevalence of cancer in the family histories of patients with primary carcinoma of the lung are too meager for any conclusions as to the importance of heredity in the production of this condition.

Previous Pulmonary Disease:

Menetrier (69) is quoted by Fried as stating there is "no primary lung cancer without a previous chronic inflammation". This represents an extreme view and is not generally accepted. Tuberculosis , influenza, chronic bronchitis and chronic fibroid pneumonia are all listed as possible predisposing factors in the production of primary carcinoma of the lung. Frommel (34) , Shennan (89) , Hunt (44) and Lindberg (62) all note a rather high percentage of previous lung affections in their observations. Rogers (81) found a history of previous respiratory difficulties present in 48% of his cases.

Earlier writers were inclined to stress the occurrence of lung cancer and tuberculosis and to give tuberculosis an important place in list of causative

factors. Moses believes it the chief etiological factor. Ewing and Casolo also list it as a possible factor. On the other hand Adler, Weller, Hyde and Holmes, and Grove and Kramer consider tuberculosis of no etiological importance and it occurs only coincidentally. Lindberg also believes that carcinoma of the lung shows no evidence of genetic relationship to phthisis. Very few of the recent discussions give tuberculosis a place of importance in the etiology of primary carcinoma of the lung and, although there are several instances in literature where a malignant growth has been found in lungs with tuberculous lesions, it is reasonable to conclude that this disease is coincidental and probably not a causative factor.

Statistics of incidence show a marked increase in carcinoma of the lung immediately following the influenza epidemic of 1918. Moise (71) and Lichty, Wright and Baumgartner (61) believe this increase is due to some extent to influenza. Weller (99) and Grove and Kramer (40) are also inclined to believe that the chronic post-influenzal lesions play some part in causing malignant growths of the lungs. Schuster (86) after presenting the arguments in favor of influenza as an etiological factor cites the case of Iceland which was especially hard hit by the epidemic but has had no case of pulmonary neoplasm. With the present tendency of practitioners to apply the term "Flu" to any respiratory infection even though mild it is hard to evaluate figures as to the incidence of previous influenza in the histories of patients.

Consequently a history of influenza from any patient may or may not be accurate. Proliferation and metaplasia of the cells of the bronchial mucous membrane, however, has been frequently observed following influenza and the possibility of this change being a condition which predisposes to malignant growth cannot be disregarded. So in the words of Davidson (23), "It is hardly possible to deny that a true influenza may conceivably be an exciting factor".

Occupational Factors:

That chronic irritation is an important factor in the production of carcinomatous change is almost universally accepted. This has led to investigation of the industrial hazards such as the inhalation of dust, chemical fumes and tobacco by many observers. Specific substances which have been considered in these investigations are dust from tarred roads, ores in certain mining communities, tobacco smoking, gasoline fumes and silica dust.

Klotz (54) from his investigation of conditions in northern Ontario where silica is prevalent concluded there was no indication that the lesions from silicosis were in any way responsible for carcinoma of the lung. He also states that although there is a considerable amount of pneumoconiosis present in South Africa there is no unusual incidence of pulmonary cancer. Experimental work by Smith (93) in which he exposed mice to the inhalation of tar and gas fumes showed no positive

evidence that either was a causative factor.

Investigation of his 48 cases of carcinoma of the lung failed to indicate any definite occupational factor.

Duguid (25) believed there was some suggestion that the disease was more common in transport workers but this was not substantiated by either Bonser (12) or Davidson (23).

Probably the outstanding illustration of occupational incidence of lung cancer is found in the miners of the Schneeberg and Joachimstahl districts. The conclusions of the investigators of conditions in these districts are worthy of consideration. Rostoski, Saupe and Schmorl (83) investigated the incidence of cancer of the lung in the mining and non-mining population of Schneeberg and concluded there was definite evidence of occupational influence. They found excessive pneumoconiosis in miners and believed it of primary importance although the radioactive nature of the ore dust was noted. Pirchan and Sikl (79) in Joachimstahl also found evidence of an occupational factor. Here, however, there was little evidence of pneumoconiosis and they believed the radioactive property to be the chief causative factor. Since pneumoconiosis elsewhere is not proven to be a cause of increased incidence of pulmonary cancer it seems logical to conclude that the causative occupational factor in these localities is the radioactivity of the dust from uranium mines. This seems to be the only definite evidence of occupational incidence available.

Many writers mention the high percentage of tobacco smokers in their series of cases of lung cancer and are inclined to attach some etiological significance to this fact. Although not of occupational nature this may well be considered here. When we note the high incidence of men in the total cases of lung cancer and at the same time remember that more men than women smoke we are inclined to wonder if the smoking is responsible for the high incidence in men or whether the high incidence in men results in the high percentage of smokers. Inhalation of tobacco smoke, dust of industries, dust from tarred roads, and motor car fumes must all be classed as possible but unproven etiological factors. More detailed investigations must be conducted before definite conclusions can be reached.

Trauma :

Wells and Cannon (102) have recorded a case of primary carcinoma of the lung which followed a single traumatic incident eleven months preceding the discovery of the malignancy. The tumor growth was at the site of the injury and had not been detected by x-ray examination at the time of injury. This single case does not indicate that trauma is an exciting cause. Trauma is also mentioned by other authors as a possible cause but is not proven. The relationship between primary carcinoma of the lung and any single traumatic incident is undoubtedly only incidental. The comparative rarity of lung trauma would make it of little importance even if it were definitely

shown to be a causative factor.

Summary:

1. Immediate cause of primary carcinoma of the lung is unknown.
2. Age - greatest frequency from 50 to 60 years.
3. Sex - ratio of males to females about 3:1.
4. Heredity of no known significance .
5. Chronic post-influenza lesions are probable causative factors.
6. Chronic irritation by inhalation of dust, tobacco smoke and gas fumes are possible but unproven factors.
7. No occupational incidence definitely shown except among the Schneeberg and Joachimstahl miners.

PATHOLOGY

The pathological picture of primary carcinoma of the lung varies widely both microscopically and macroscopically. Microscopic examination of more than a single part of the tumor is seldom made except with the autopsy and then the growth is well advanced. The cells have been subjected to a long series of environmental changes. Rapid proliferation, pressure from surrounding groups of tumor cells and the change in blood supply as the growth enlarges are some of the factors to which the cells must adapt themselves. As a result the cells are essentially polymorphous and not uniform in all parts of the tumor mass. The predominating cells are usually cuboidal in type. Microscopic classification is difficult due to the variety of cells found in a single tumor ; but the one used by most writers is based upon histogenesis.



Microscopic:

This classification groups them as tumors originating from (1) bronchial epithelium , (2) epithelium of bronchial mucous glands, and (3) alveolar epithelium. Different opinions as to the sites of origin appear in the literature. Genesis from the bronchial epithelium is quite universally accepted. Fried (33) believes that all primary carcinoma of the lung arise from the basal cell layer of the bronchial epithelium and advances the argument that the ciliated columnar cells and the secreting cells of the bronchial glands are fully differentiated and specialized and hence are "apotent" as to regeneration. He also cites Rose's contention that normal alveolar epithelium is of mesodermal origin to oppose the theory of origin of carcinoma cells from that source. Weller (99) also expresses the opinion that alveolar origin is not proven. Davidson (23) and several of his British colleagues are of the opinion that these malignancies originate from the bronchi. The wide range of differentiation of cells found in normal air passages, starting with the high ciliated columnar cells of the larger bronchi through cuboidal to the flat epithelium of the alveoli, make accurate cellular classification of these growths more difficult. Such a classification when made is of no real clinical value and hardly worth the effort. Since it is not the purpose of this discussion to prove or disprove any of these theories we can dismiss the subject with the recognition that it is controversial. A

A reasonable conclusion , however , is that a very high percentage of the tumors arise from the bronchi.

Macroscopic:

Consideration of the gross pathology leads to a simple classification based upon the location of the main growth , that is , parenchymal or hilar. These two classes to some extent aid in understanding the clinical picture. In advanced cases the two types are not clearly defined and the clinical manifestations are identical. Either one may involve only a limited part of one lobe, a whole lobe or in some cases the whole lung. When either type is relatively rapid in its rate of growth the center of the tumor, due to decreased blood supply, breaks down and cavitation results. Secondary infection and pleural involvement are complications which may also accompany either type. When involved the pleura shows marked thickening and pleural irritation with pain and effusion.

The parenchymal type is the less common. The growth appears as a grayish white, more or less rounded, but infiltrating mass embedded in alveolar tissue. Secondary tumors from an obscure primary growth elsewhere in the body are similar in appearance and may be mistakenly considered as primary in the lung. The parenchymal location does not necessarily mean that the tumor arises from alveolar epithelium as it may originate from the epithelium of the bronchioles. Early symptoms are very slight or absent. Rapid growth with central necrosis and secondary infection may simulate gangrene or lung abscess.

Encroachment upon larger bronchi produces bronchial irritation and the symptomatology then resembles that of the hilar form.

The characteristic site of origin of the hilar type is in the bronchial wall just distal to the bifurcation of the main bronchus. The bronchial wall is thickened and the grayish white or yellowish mass encroaches upon or may completely close the lumen. It infiltrates the surrounding lung tissue and spreads toward the periphery in finger-like projections along the branches of the smaller bronchi. The tumor by proximal extension involves the larger bronchi and may appear to come from the mediastinum. Pressure on the great vessels is produced either by extension to the mediastinum or by metastasis to the mediastinal lymph nodes. Extension to the other lung occurs frequently and involvement of the pericardium and heart has been recorded. Peripheral to the main tumor mass, when occlusion is complete, collapse occurs which may involve lobules or a whole lobe. Infection in the atelectatic area produces a picture simulating lung abscess. The symptoms in the hilar form appear earlier in the disease and are essentially those of bronchial irritation. The signs are those of bronchial occlusion.

#### METASTASIS

Metastasis from primary carcinoma of the lung varies both as to extent and the time in the progress of the disease at which it occurs. The rate of growth and clinical symptoms do not furnish any criteria upon which the

probability of metastasis can be successfully prognosticated. Microscopic details when biopsy is obtained and the roentgenological features give no additional indications. Not infrequently the primary growth produces so little disturbance or metastasis occurs so early that the symptoms which cause the patient to seek medical aid are due to secondary tumors.

Sites of metastasis are widely distributed throughout the body. The earliest and most frequently involved location is the regional lymph nodes. The groups included are the bronchial glands, those at the bifurcation of the trachea, other mediastinal glands, and the deep cervicals. The liver is also a very frequent site of secondary growths. Other organs commonly involved are the kidneys, bones, brain, adrenals, pancreas, spleen and skin. Complete lists include almost every part of the body but the above are most frequently mentioned. Involvement of the pleura may also result from metastasis since the lymph drainage of the outer third of the tissue of the lung is to the periphery. Pleural involvement is probably more common from extension than from metastasis.

#### CLINICAL FEATURES

Fried (33) presents the simplest and probably most useful clinical classification of primary carcinoma of the lung. He includes in his typical group all cases in which the initial symptoms are directly referable to the

to the respiratory system. The attention here is immediately directed to the lungs and the diagnostic problem is that of differentiating the condition from other respiratory diseases producing similar symptoms. The atypical group includes those cases in which metastases have occurred and the symptoms direct attention to the site of the development of secondary tumors. This group is distinctly in the minority but must be considered. Diagnosis in this group is reached only by a process of elimination. Cases are on record in which operation for brain tumor has been performed only to find later, usually at autopsy, the primary tumor in the lung. Symptomatology of the typical group of cases will be considered here.

Onset:

The onset is almost universally insidious. Patients seldom are able to give a definite date for the appearance of their symptoms. In occasional cases the onset resembles that of an acute respiratory infection from which the patient does not fully recover. The history is usually that of a slow and gradual development of one or more symptoms which have been for the most part mild and only slightly disturbing .

Symptoms:

Grove and Kramer (40) rank weakness as the most frequent symptom in their series of cases. This weakness is slowly progressive and seldom produces marked disability until late in the disease.

Cough is placed first in frequency of occurrence by

many writers including Weller (99) , Moses (73) and Fishberg (29). It is the result of bronchial irritation but is not characteristic of this disease. Early it is usually dry and somewhat brassy in type. A mild and persistent cough is more common than one that is paroxysmal in nature. Sooner or later becoming productive the expectorated material is at first of mucoid consistency but changes to mucopurulent as the disease becomes more advanced. The sputum often is blood-streaked but the so-called "currant jelly" sputum of earlier writers is seldom mentioned in current articles. The cough seldom becomes distressing.

Chest pain is another frequent symptom. It is ordinarily deep-seated and indefinite. Late in the disease it may become very troublesome and difficult to control. Radiation to the shoulder and arm on the same side as the lesion occasionally is noticed and differs from that of angina by being less sharp and agonizing and with no relationship to exertion.

Dyspnea on exertion not infrequently is the presenting symptom. It progressively becomes more severe but apparently is not directly proportional to the amount of lung tissue involved. A tendency for the dyspnea to be worse at times suggests that, although it may largely be due to pressure and obstruction of the air passages by the tumor itself, it may partially be caused by the temporary occlusion of the smaller bronchi by mucous secretion. Stridor from pressure of the involved glands on the bronchi occasionally occurs but is not a frequent symptom.

Marked hemorrhage from the lung seldom occurs until the disease is nearing the final stage of development. Erosion of small bloodvessels is the cause when it does occur. Slight hemoptysis, however, is not infrequent and occasionally is the presenting symptom. Hemorrhage from the lung is seldom of serious import as far as the loss of blood is concerned but does in most instances indicate that the disease is well advanced.

Loss of weight is not a constant symptom and some individuals remain well-nourished throughout the course of the disease. Some cases have shown periods of apparent remission in which a gain in weight was noted. When the disease runs a comparatively long course, however, cachexia becomes prominent during the terminal stages of development.

The temperature chart usually shows some febrile reaction which resembles that of a low grade infection. Rarely is there more than a two degree rise. A slight afternoon rise not unlike that of pulmonary tuberculosis is somewhat characteristic. The fever is probably produced by absorption of material from necrotic areas or from reaction to secondary infection.

Pleurisy is another manifestation of pulmonary carcinoma but seldom noticed until late in the disease. Actual extension of the growth or metastasis produces pleural irritation with pain and effusion. The effusion is serous at first and later becomes sanguinous. Although the presence of sanguinous pleural fluid is not pathognomonic of this condition, it may be so considered until proven otherwise. The fluid if sufficient in amount

may produce increased dyspnea and cardiac embarrassment if on the left side. Removal of the fluid by aspiration may temporarily relieve the patient and is necessary before clear flourosopic and x-ray examination is possible.

Hoarseness from pressure on the recurrent laryngeal nerve by metastatic growths in the mediastinal and deep cervical glands occasionally occurs. Other infrequent symptoms are anorexia, tenderness over the chest wall, night sweats, edema of one upper extremity and dilatation of the superficial veins of the neck and chest.

None of these symptoms is pathognomonic of this condition but the presence of one or more of them should direct attention to the respiratory system. Then with evidence of an obscure pulmonary condition primary carcinoma of the lung should always be regarded as the possible cause .

#### PHYSICAL FINDINGS

The physical signs are usually scant and not characteristic. Only Fishberg (29) considers them of early importance and he states that they "can be detected before x-ray will show the tumor". Most observers agree that the signs are chiefly those of bronchial obstruction.

Observation may direct attention to decreased expansion on the affected side. This is usually not noticeable unless there is collapse of an entire lobe or a considerable amount of pleural effusion present. An infrequent sign is the dilatation of the superficial veins of the chest and neck due to obstruction of venous return by pressure of metastatic mediastinal gland tumors on the



superior vena cava. Tactile fremitus is likely to be decreased or absent over the collapsed area. The percussion note is impaired with dullness to flatness over limited areas. Such an area may be present on only one aspect of the chest. The breath sounds also tend to be feeble or absent in areas over partially or completely collapsed lung tissue following bronchial occlusion. When a bronchus is only partially compressed increased bronchial breathing or "cornage" is present. Adler (2) and Grove and Kramer (40) are inclined to place some significance upon the presence of this sign.

If there is anything characteristic of the physical signs in this condition it is that they tend to vary from day to day being present at one examination and changed or absent at the next. This tendency to variation may be due to partial obstruction of the bronchus by the tumor itself and complete or partial occlusion depending upon the amount of mucous secretion temporarily lodged at the site of the tumor. Later in the development of the disease with cavitation, abscess formation, or pleural effusion the signs of the existing condition become constant. Early, however, before complete occlusion of any bronchus occurs physical signs may be entirely lacking.

#### Clinical Course:

The disease usually runs a comparatively short course after it is first discovered. There is no way of estimating the entire duration of the condition, however, as it is rarely diagnosed until malignant degeneration is well advanced. Fried (31) in his early

series of cases noted a duration of from three to sixteen months but in his later discussion (33) is inclined to believe that the disease runs a protracted course over several years and that actual duration cannot be estimated. Moses (73) in his case histories showed a duration of from ten days (from date of admission to the hospital) to four years ; Fishberg (29) , one to four years ; and Winternitz places his average duration as nine months. A few cases are on record in which the presence of the disease has been known for several years but such case histories are rare and exitus usually occurs within eighteen months of the discovery of the condition. Possible causes of death are asthenia or inanition, hemorrhage, thrombosis, acute intercurrent infections, pulmonary edema and asphyxia.

#### LABORATORY FINDINGS

##### X-ray:

The x-ray is unquestionably one of the most valuable aids in the investigation of pulmonary conditions. The relative importance of radiographic examination in the diagnosis of primary carcinoma of the lungs varies with different observers and is naturally placed higher by the roentgenologist than the clinician. Even though we agree with Manges (65) that "the disease has no single characteristic roentgen sign" and with Hyde and Holmes (45) that "rarely do roentgen findings present features that are pathognomonic" , the x-ray is invaluable in the

investigation of this condition.

Kirklin and Paterson (53) describe the alveolar or parenchymal type of carcinoma of the lung as most commonly consisting of an irregular rounded infiltrating nodule lying completely in the pulmonary fields and usually not involving the periphery. Kerley (51) questions the existence of an alveolar form of this cancer. He describes, however, a form consisting of rounded masses in the parenchyma which he considers is more likely to be the result of metastasis from a small hilar tumor not visualized by the x-ray. From the general acceptance of this form of tumor by other observers it probably does occur but before it is classed as primary the presence of malignancy elsewhere in the body as well as at the hilus of the lung must be excluded.

Kerley's description of the hilar form of tumor is reproduced here essentially as he presents it. The growth appears as a dense opacity at the root of the lung without collapse or consolidation of the periphery of the affected lobe. Early in the disease the mass is semi-circular in form with ill defined outer border and thick irregular lines radiating into the lung parenchyma. He also describes a lobar form separately but admits that it may develop from the hilar type, which seems more logical than the separate classification. He describes this form as consisting of two zones of increased density, the one of greater density near the root of the lung composed of the growth itself and the less dense zone toward the periphery composed of collapsed tissue due to

obstruction. He states that, "If vascular markings of the lung are invisible in the light peripheral opacity and visible in the dense opacity near the root we can diagnose carcinoma with certainty, for there is no other lobar pneumonic process which produces this dual effect".

Additional findings by x-ray films and flourosopic examination which are suggestive of pulmonary carcinoma include deviation of the mediastinal structures toward the affected side, enlarged mediastinal and bronchial glands, and paralysis of the diaphragm. The deviation of mediastinum toward the affected side is of considerable significance and frequently occurs. It is the result of the decreased pressure in that pleural cavity following atelectasis from bronchial obstruction. Enlargement of the bronchial and mediastinal glands results from metastatic involvement and while of some significance is not readily detected. Diaphragmatic paralysis when it occurs is usually unilateral and is produced by pressure from the involved glands upon the phrenic nerve or from actual involvement of the nerve by extension of the malignancy.

Stereoscopic films are of value in accurately locating the position of the tumor mass and should be a part of every roentgenological investigation in a case suspected of intrathoracic malignancy. Intratracheal injection of lipiodol in conjunction with roentgen visualization will aid in demonstrating obstruction of a

bronchus. Frequent examination will permit the determination of progression in this condition and increase the diagnostic value of the x-ray.

Sputum:

Examination of the sputum in many cases will yield no significant information. Occasionally, however, after necrosis and cavitation have occurred particles of tumor tissue may be coughed up and expectorated. Microscopic examination of these particles may demonstrate malignant cells and verify a suspected case. This means is seldom of value until late in the disease. Early the sputum is tenacious but that is of no significance.

Pleural Fluid:

Fluid aspirated from the pleural cavity after effusion should be examined microscopically. Early in the disease it is serous but later contains many red blood cells. Occasionally cancer cells have been found. Goldman (37) is inclined to place considerable importance on the cytology of the pleural fluid but reminds us that the absence of "cancer cells" does not rule out malignancy. Insertion of a large needle into the tumor mass with aspiration of small bits of the tumor tissue and verification of malignancy microscopically is reported by Sharp (88) in three of his cases. Ravdin (80) reports using the same method with enlarged metastatic glands.

Blood Findings:

The blood picture is that of a secondary anemia

which is seldom of marked severity. The presence of a leucocytosis is the result of secondary infection. It is usually a high normal white count but has been reported as high as twentyfive thousand. There is nothing in the blood findings which is characteristic of this condition.

#### Bronchoscopy:

The use of the bronchoscope during the last decade has increased tremendously . It provides a means of visualizing the bronchial mucous membrane beyond the point at which bronchiogenic carcinoma usually originated. This makes it possible to visualize the part of the tumor which encroaches upon the lumen of the bronchus and provides a means by which a small piece of tumor tissue may be removed for microscopic examination. Accurate diagnosis of its malignant or non-malignant nature can thus be verified. Bronchoscopy is limited as to its use, however , since it is impossible to reach the parenchymal type of tumor.

#### DIAGNOSIS

Primary carcinoma of the lungs has always been a difficult diagnostic problem. Figures on the percentage of correct diagnoses made during the life of the patient will illustrate this difficulty. Karsner and Saphir (49) claim to have made correct clinical diagnosis in 10 out of 25 cases; Simpson (91) during the period 1907 to 1925, 73 out of 139; Berblinger (9) 46 out of 69, Winternitz (103) 18 out of 42 ; and Junghanns (48) , 10% during the period

1908 to 1912 and 48% in 1928 and 1929. Junghanns figures for the later years show marked improvement over those of the early period but there is still considerable need for greater accuracy.

Funk (36) gives two essentials for the diagnosis of primary carcinoma of the lung. The first is to recall the possibility of bronchogenic carcinoma in any adult with an obscure pulmonary disease. Failure in this probably accounts for more missed diagnoses than any other single cause. The second essential is a complete study of the case including the clinical features and all available laboratory procedures. Davidson (22) suggests a routine scheme for complete study of a case as follows: (1) History and symptomatology, (2) Physical examination of the chest, (3) Radiographic examination by the usual methods, (4) Radiographic associated with lipiodol injections or artificial pneumothorax or both, (5) Bronchoscopy, (6) Thoracoscopy, and (7) Exploratory thoracotomy.

Artificial pneumothorax with radiographic examination will probably add little to the investigation. Thoracoscopy and thoracotomy are not practical in most instances and could be used only in selected cases. Biopsy in connection with bronchoscopy is of definite value and since bronchoscopic examination is well tolerated by almost all patients should be made a routine part of every study of a suspected case.

Early diagnosis is desirable here as in other conditions but not from the standpoint of early treatment.

Treatment is so unsatisfactory that it is not of chief importance. Early and accurate diagnosis can be of economic value to the patient, however, in that it will prevent long periods of special care in sanatoria when tuberculosis is suspected as it frequently is in these cases. Early treatment has apparently been of benefit in a very few cases of pulmonary carcinoma.

Differential Diagnosis :

Primary carcinoma of the lung is often very difficult to differentiate from other pulmonary conditions. Several of these with which it is most commonly confused with points in diagnosis are listed below. Most of these diseases should be identified if complete study of the case is made along the lines previously suggested.

Chronic pulmonary tuberculosis is one of the most confusing diseases particularly if the carcinoma is in an upper lobe. Tuberculosis is usually bilateral and calcified areas in other parts of the lung are common. The blood pressure in phthisis usually is low while it remains quite normal in carcinoma. Repeated sputum examinations should sooner or later detect the presence of acid fast bacilli in tuberculosis.

Unresolved pneumonia may be somewhat similar to carcinoma when the malignancy has obstructed a bronchus and produced collapse of a whole lobe. The history of an acute pneumonia preceding this condition is suggestive. Unresolved pneumonia runs a different course and tends to clear although this may necessitate some delay in diagnosis.



Pleurisy with effusion may be confused when there is pleural effusion with carcinoma. A history of acute illness will be present here and the pain at the onset of pleurisy is marked. Paracentesis and examination of the aspirated fluid should clear the diagnosis.

In mycoses the symptoms are more mild and the chest pain characteristic of carcinoma is very slight or absent in this disease. Sputum examination should demonstrate the presence of mycetes.

Interlobar empyema will also present a history of acute illness and the temperature course is hectic in comparison to carcinoma. Aspiration with a needle will detect the presence of the purulent material of empyema.

Bronchiectasis may be confusing but the fetid odor of the breath is suggestive. Lipiodol injection with radioscopic examination is the best means of differentiating.

Mediastinal tumors may give some difficulty as the pressure symptoms may be the same as those resulting from enlarged metastatic glands in bronchogenic carcinoma. Early the carcinoma will show as definitely separated from the mediastinum and later the infiltrative growth with the finger-like projections into the lung parenchyma should distinguish the malignancy of bronchogenic origin. Bronchoscopy is very definitely indicated for this differentiation.

Benign bronchial tumors cannot be differentiated by x-ray but bronchoscopy with biopsy should make the distinction.

Pulmonary infarct usually is marked by definite severe pain at the onset. The x-ray will show a triangular area with the apex toward the hilus. The edges of the shadow are usually quite definite without any infiltrative tendency. The course of the recovery from infarct is one of gradual improvement while with carcinoma the condition becomes progressively worse.

Lung abscess is probably the most difficult to differentiate. With necrosis and infection of the tumor area an abscess is formed and the conditions are identical as far as any clinical features are concerned. Unless the x-ray furnishes a view of tumor beyond the abscess area differentiation may be impossible.

#### TREATMENT

Prognosis in this disease is essentially bad. Treatment has been very disappointing in almost all instances. Most cases are fatal within a few months. Two cases are cited in literature in which apparent cure resulted from removal of the tumor from the bronchus by means of the bronchoscope. Jackson's patient was alive 11 years after removal and Orton's patient was well and without x-ray evidence of recurrence or metastasis 4 years after removal. This as a means of treatment is limited to pedunculated tumors which have not involved the wall of the bronchus to any extent. Pancoast, Pendergrass and Tucker (75) in two cases used the bronchoscope for the direct implantation of radon seeds in the tumor with improvement of both patients

temporarily although the time elapsed since treatment had not been sufficient to give any real indication of the efficacy of this treatment.

The most commonly used method of treatment is by deep x-ray radiation. Manges (66) gives a case in which his patient was reasonably well after 7 years and another case in which there had been no recurrence for 5 years after the first treatment and was still well one and one-half years after the second treatment. McRae, Funk and Jackson (68) also cite cases of somewhat shorter duration, the one apparently well three years after intensive roentgen therapy and another well two years under periodic x-ray treatments. Farrell (28) and Caselo (18) both remind us that no cases of cure by roentgen therapy are on record. Paterson, Laborde and Huguenin, Maxwell and Nicholson, and others advise the use of roentgen therapy for its palliative effect although it is not curative.

Dalla Torre (21) produced an artificial pneumothorax in one case and after death of the patient eighteen months later concluded there had been little influence on the growth of the tumor but that increased connective tissue had apparently limited extension to other parts of the lung. Surgical treatment with lobectomy has also been performed. The shock is terrific and usually the operator finds that the hilus is so involved or the growth has extended to another lobe so that complete removal is impossible. Lobectomy with very early diagnosis may possibly give some future hope but the

proper conditions have not as yet been combined in any case that has been operated.

We conclude that the best treatment for primary carcinoma of the lung is at present the use of deep x-ray radiation but that such therapy is only palliative and not curative.

#### SUMMARY

1. Statistics of incidence indicate there is a real increase in the frequency of primary carcinoma of the lung, that the condition is more frequent in males in the ratio of 3:1, and that the frequency is greater during the decade from 50 to 60 years of age than at any other period of life.

2. The immediate exciting cause is unknown. Irritation from previous pulmonary disease and from the inhalation of certain materials is probably an exciting factor.

3. From eighty to ninety per cent of all primary carcinomata of the lungs are of bronchogenic origin.

4. Metastases occur quite early in the disease and the most common sites in order of their frequency are regional lymph nodes, liver, bones and brain.

5. The early symptoms are due to bronchial irritation and the signs are due to bronchial obstruction.

6. Accurate diagnosis should result if the investigator is aware of the possibility of this disease and a complete study of the history, symptomatology, physical findings, radiographic and bronchoscopic

evidence is made.

7. No curative treatment is known. Deep roentgen therapy offers the best palliative effect without danger to the patient.

###

## BIBLIOGRAPHY

1. Adams, A. : Carcinoma of the Bronchus, 2:288 (Aug.) 1932
2. Adler, I.: PRIMARY MALIGNANT GROWTHS OF LUNGS AND BRONCHI, Longmans, Green & Co., N. Y. 1912.
3. Allen, C. I. and Smith, F. J.: Primary Carcinoma of the Lung, Surg., Gyn., & Obs., 55:151, (Aug) 1932.
4. Arkin, A.: Bronchus Cancer, Med.Clin. of N.Amer. 13:1255, (March) 1930.
5. Baccaredda, A.: Prim. Car. of Lungs, Boll.Soc. Med. Chir., Pavia, 44:759, 1930. (Cancer Rev., 7:43, 1932)
6. Ball, L.H.: Car. of Lung of long duration, Jour. Coll. of Surg., Australia, 3:286, 1930. (Cancer Rev., 6:511, 1931)
7. Baumgartner, E. A.: See Lichty.
8. Benda, C. and Wahl, S.: Nimmt der Lungenkrebs zu?, Zeits. f. Artzl. Fortb., 26:526, 1929, (Cancer Rev. 6:232, 1931.)
9. Berblinger, W.: Increase in Car. and Diseases of the Lung Due to Dust, Med. Klinik., 27:1337, (Sept.) 1931. (Cancer Rev., 7:102, 1932.)
10. Birnbaum, G.L. : See Coryllos.
11. Bland-Sutton, Sir John : TUMORS INNOCENT AND MALIGNANT, Hoeber, N. Y. 1922.
12. Bonser, G. M. : Incidence of Tumors of Resp. Tract in Leeds, Jour. of Hyg., 28:340 (Feb.) 1929. (Ca. Rev., 5:70 1930)
13. Boyd, W.: Notes on Prim. Car. of Lung, Canad. Med. Assoc. Jour., 23:210, (Aug.) 1930.
14. Brandt, M.: Zur Pathogenese des primaren Lungenkrebs, Deyt. Med. Woch., 53:1824, (Oct.) 1927. (Ca. Rev. 3:78, 1928.)
15. Brockbank, W.: Occ. Incidence of Prim. Car. Lungs, Quart. Jour. Med.. N.S. 1:31, (Jan.) 1932.
16. Caldbick, S. L.: Dermoid Cyst of Mediastinum, Arch. Surg., 15:660, (Oct.) 1927.
17. Cannon, P. R.: See Wells.
18. Casolo, G.: Etiol. Prim. Car. of Lung, Osp. Magg., 15:227, (Aug.) 1927. (Ca. Rev., 4:38, 1929.)
19. Cordonnier, J.: See Gray.
20. Coryllos, P. N. and Birnbaum, G. L., Obstructive Massive Atelectasis of Lungs, Arch. Surg., 16:501 (Feb.) 1928.

21. Dalla Torre, G.: Case of Car. of Lung Treated by Artificial Pneumothorax, *Riforma Med.*, 47:173, 1931. (Ca. Rev., 7:164, 1932.)
22. Davidson, M.: Intrathoracic and Pulmonary New Growths, *Lancet*, 2:1181, (Dec.) 1929.
23. Davidson, M.: CANCER OF THE LUNG AND OTHER INTRATHORACIC TUMORS, John Wright & Sons, Ltd., Bristol, 1930.
24. Delherm, and Morel-Kahn : Diag. of Tumors of Lung in Adults, *Jour. de Radiol. et d'Electrol*, 14:158, 1930. (Ca. Rev., 6:43, 1931.)
25. Duguid, J. B.: Incidence of Intrathoracic Tumors in Manchester, *Lancet*, 2:111, (July) 1927.
26. Ewing, J.: NEOPLASTIC DISEASES, 2nd ed., W.B.Saunders Co., Phila.
27. Farnias, P. L.: X-ray Study of Prim. Car. of Lung, *An. de Radiol.*, 1:47, 1929. (Ca. Rev., 6:43, 1931.)
28. Farrel, J. T.: Roent. Diag. of Intrathoracic Neoplasms, *Radiology*, 13:1, (July) 1929.
29. Fishberg, M.: Diag. of Pulmonary Neoplasms, *Arch. Int. Med.*, 37:745, (June) 1926.
30. Fremont-Smith, M., Lerman, J., & Rosahn, P.D.: Prim. Car. of Lung, *New Eng. Med.*, 203:473, (Sept.) 1930.
31. Fried, B. M.: Prim. Car. of Lungs, *Arch. Int. Med.*, 35:1 (Jan.) 1925.
32. Fried, B. M.: Prim. Car. Lungs, *Arch. Int. Med.*, 40:340, (Sept.) 1927.
33. Fried, B. M.: Prim. Car. Lungs, *Medicine*, 10:373, (Dec.) 1931.
34. Frommel, E.: Etiol. of Ca. of Lungs, *Rev. de Med.*, 44:31 1927. (Ca. Rev., 3:232, 1928.)
35. Frothingham, C.: Diff. Diag. between Pul. Tbc. and Pul. or Bron. Mal. Neoplasms, *Amer. Rev. of Tuber.*, 23:107, (Feb.) 1931.
36. Funk, E. H.: Clin. Manifestations of Prim. Bron. Car., *Jour. Amer. Med. Assoc.*, 95:1879, (Dec.) 1930,
37. Goldman, A.: Cytology of Serous Effusions, *Arch. Surg.*, 19:1672, (Dec.) 1929.
38. Goltz, E. V.: Prim. Car. Lungs and Bron., *Minn. Med.*, 13:605 (Sept.) 1930.
39. Gray, S. H. and Cordonnier, J.: Early Car. Lung, *Arch. Surg.*, 19:1618, (Dec.) 1929.
40. Grove, J. S. and Kramer, S. E.: Prim. Car. Lung, *Amer. Jour. Med. Sci.*, 171:250, (Feb.) 1926.

41. Haythorn, S. R.: On Metaplasia of Bron. Epith., Jour. Med. Res., 26:523, 1912. (Quoted by Moise)
42. Hirsch, I. S.: Roent. Diag. of Mal. Neopl. Lung, Radiology, 9:470, (Dec.) 1927.
43. Homan, E.: Lungenkrebs und Lungensarkom, Ergebn. d. inn. Med., 35:206, 1929. (Ca. Rev., 5:741, 1930.)
44. Hunt, T. C.: Pul. Neopl., Lancet, 1:759, (Apr.) 1929.
45. Hyde, T. L. and Holmes, G.W.: Roent. Aspects of Prim. Tumors of Lung, Amer. Jour. Roent., 18:235, (Sept.) 1927.
46. Jackson, C.: See McRae.
47. Jones, O. R.: See Miller.
48. Jungmanns, H. : Error in Diag, of Car, of Lungs, Munch. Med. Woch., 77:925, 1930. (Ca, Rev., 5:681, 1930.)
49. Karsner, N. T. and Saphir, O.: Small Cell Car. of Lung, Amer. Jour. of Path., 6:553, (Sept.) 1930.
50. Kerley, P.: Prim. Car. Lung with Special Reference to X-ray Diag., Cancer Review, 3:193, 1928.
51. Kerley, P.: Mal. Disease of Lung, Brit. Med. Jour., 1:416, (March) 1932.
52. Kikuth,: Ueber Lungencarcinom (Quoted by Fishberg)
53. Kirklin, B. R. and Paterson, R.: Roent. Manifestations of Prim. Car. Lungs, Amer. J. Roent., 19:20, 126, (Feb) 1928.
54. Klotz, O.: Car. of Lung, Canad. Med. Assoc. Jour., 17:989, (Sept.) 1927.
55. Kornblum, K.: Case of Prim. Car. Lung, Amer. J. Roent., 18:230, (Sept.) 1927.
56. Kramer, S. E.: See Grove.
- 57: Krampf, F.: Diag. of Lung Ca., Beitr. z. klin. Chir., 141:639, 1927. (Ca. Rev., 4:347, 1929.)
58. Laborde, S. and Huguenin, R.: Radiotherapy in Pul. Tumors, Bull. de l'Assoc. franc. pour l'Etude du Cancer, 17:74, (Feb.) 1928. (Ca. Rev., 4:123, 1929.)
59. Lehmann, K. B.: Tarred Roads from Standpoint of Hygiene, Arch. f. Hyg., 104:105, 1930. (CA. Rev., 7:103, 1932)
60. Lerman, J.: See Fremont-Smith.
61. Lichty, J. A., Wright, F. R., and Baumgartner, E. A.: Prim. Car. Lungs, Jour. A. M. A., 87:144, (July) 1926.
62. Lindberg, K.: Bron. Car. and Chronic Pneumonia, Acta Med. Scand., 34:375, 1930. (Ca. Rev., 6:322, 1931.)



63. Ludin, Max : Solitary Circumscribed Shadow in Lung Roentgenogram, Fortschr. a. d. Geb. d. Rontgenstrabbn, 34:899, 1926. (Abstracted in Amer. Jour. Roent., 18:168, (Aug.) 1927.
64. Lynch, Clara J.: Tumor Susceptibility and Heredity, Jour. Exper. Med., 46:917, (Dec.) 1927.
65. Manges, W. F.: Bron. Neopl., Arch. Otol. & Laryngol., 12:732, (Dec.) 1930.
66. Manges, W. F.: Prim. Car. Lung, Amer. J. Roent., 27:858, (June) 1932.
67. Maxwell, J. and Nicholson, W. A.: Clin. Study of Bron. Car., Quart. J. Med., 24:29, 1930. (Ca. Rev., 6:322, 1931.)
68. McRae, T., Funk, E. H., and Jackson, C.: Prim. Car. of Bronchi, Jour. A. M. A., 89:1140, (Oct.) 1927.
69. Menetrier: Traite de Med., Brouardel, Gilbert et Thionot, 1917. (Quoted by Fried)
70. Miller, J. A. and Jones, O. R.: Prim. Car. Lung, Amer. Rev. Tuber., 21:1, (Jan.) 1930.
71. Moise, T. S.: Prim. Car. Lungs, Arch. Int. Med., 28:733, (Dec.) 1921.
72. Moses, H. M.: Prim. Car. Lung, Amer. Jour. Med. Sci., 170:102, (July) 1925.
73. Moses, H. M.: Malignancy in Lung, Ann. Int. Med., 5:765, 1931.
74. Orton, H. B.: Clinic, Surg. Clinics of N. Amer., 6:1534, (Dec.) 1926.
75. Pancoast, H. K., Pendergrass, E. P., and Tucker, G.: Prim. Bronchogenic Car., Amer. J. Roent., 27:357, (March) 1932.
76. Parish, T. N.: Early Diag. of Prim. New Growths, Practitioner, 125:324, (Aug.) 1930.
77. Paterson, R.: Roent. Treatment of Prim. Car. Lung., Brit. J. Radiol., N.S. 1:96, 1928. (Ca. Rev., 3:460, 1928)
78. Pekelis, E.: Path. Anat. of Prim. Car. Lungs, Tumori, 17:31, 1931. (Ca. Rev., 7:43, 1932.)
79. Pirchan, A. and Sikl, H.: Car. Lungs in Miners of Joachimstahl, Amer. J. Cancer, 16:681, (July) 1932.
80. Ravdin, I. S.: Prim. Lung Ca., Amer. J. Surg., 6:337, (March) 1929.
81. Rogers, W. L.: Prim. Car. Lung, Arch. Int. Med., 49:1058, (June) 1932.
82. Rosahn, P. D.: Incidence of Prim. Car. Lung, Amer. J. Med. Sci., 179:803, (June) 1930.

83. Rostokki, Saupe and Schmorl : Schneeberger Lungenkrebs, Zeits. f. Krebsforsch., 25:249, 1927. (Ca. Rev., 3:10, 1928.)
84. Saphir, O.: See Karsner.
85. Schall, A. L.: Prim. Car. of Bronchi, Ann. Otol. Rhinol. Laryngol., 37:762, (Sept.) 1928.
86. Schuster, N. H.: Etiol. and Path. of Prim. Lung Tumors, Jour. Path. and Bacteriol., 32:799, (Oct.) 1929.
87. Sehrt, : Inaugural Dissertation, Leipzig, 1904. (Quoted by Fishberg)
88. Sharp, G. S.: Diag. Prim. Car. Lung by Aspiration, Amer. Jour. Ca., 15:863, (Apr.) 1931.
89. Shennan, T.: Tumors of Mediast. and Lung, Jour. Path. and Bacteriol., 31:365, 1928.
90. Sikl, H.: See Pirchan.
91. Simpson, S. L.: Prim. Car. Lung, Quart. J. Med., 22:413, 1929. (Ca. Rev., 6:213, 1931.)
92. Smith, F. J.: See Allen.
93. Smith, R. E.: Etiol. of Prim. Car. Lung, Jour. Ca. Research, 12:134, (June) 1928.
94. Staehlin, R.: Klin. Wehnschr., 4:1853, 1925. (Quoted by Fishberg.)
95. Tucker, G.: See Pancoast.
96. Von Glahn, W. C.: Neopl. of Lung, Amer. Rev. Tuberc., 21:57, (Jan.) 1930.
97. Von Zalka, E.: Zeits. f. Krebsforsch., 26:130, 1928. (Ca. Rev., 3:471, 1928.)
98. Weller, C. V.: Prim. Car. Bron., Arch. Int. Med., 11:314, 1913.
99. Weller, C. V.: Prim. Car. Lung, Arch. Path., 7:478, (Mch.) 1929.
100. Weller, C. V.: Entdifferentiation in Prim. Car. Bron. and Lungs, Jour. Ca. Res., 13:218, (Oct) 1929.
101. Wells, H. G.: Cancer Statistics, Jour. A. M. A., 88:399, 476, (Feb.) 1927.
102. Wells, H. G. and Cannon, P. R.: Prim. Car. Lung Following Trauma, Arch. Path., 9:869, (Apr.) 1930.
103. Winternitz, L.: Arch. Patol. e Clin. Med., 10:443, 1931. (Ca. Rev., 7:525, 1932.)
104. Wright, F. R.: See Lichty.