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PRIMARY CANCER OF THE LUNG

Chairman's Address

ALTON OCHSNER, M.D.
MICHAEL DeBAKEY, M.D.
and
J. LEONARD DIXON, M.D.
New Orleans

Within the past few decades two well established and generally accepted concepts of primary cancer of the lung have been completely disproved. One is the concept that carcinoma of the lung represents the "rarest form of disease."[1] The other is the concept that pulmonary cancer is a hopeless condition. The present, completely antithetic concepts came about in the first instance through intensive and more accurate studies, which demonstrated that the lung is second in frequency only to the stomach as a primary site of malignant growth, and in the second instance through the pioneering achievement of Evarts Graham,[2] who showed fourteen years ago that resection of a primary pulmonary neoplasm is possible. This successful achievement contributed still further stimulation to studies on the incidence of the disease. In many respects these facts reflect the rapid progress which has taken place in this relatively short time in the field of thoracic surgery.

Our surgical experience with carcinoma of the lung covers a period of approximately twelve years, during which 412 patients with this disease were observed on the Tulane University School of Medicine service in Charity Hospital of Louisiana at New Orleans and in private practice at the Ochsner Clinic. Of the 412 patients, 246 underwent surgical exploration, and of the 246, 147 were subjected to primary pulmonary resection. This article is based on an analysis of the experience described, with particular emphasis on follow-up studies, which were carried out in all patients who submitted to primary resection.

INCIDENCE

In the recent literature much emphasis has been placed on the apparently increasing incidence of carcinoma of the lung. This phase of the subject has been extensively reviewed in previous publications.[3] Although some observers have expressed the opinion that this increase in incidence is actual, others believe that it is only apparent. However, the important practical consideration is that virtually all observers who have analyzed the experience in their institution over a long period of time have found a definite increase in the incidence of this disease. It now appears to be one of the most frequently encountered malignant neoplasms, being preceded only by the stomach as a primary site of cancer.

Our experience in the Charity Hospital of Louisiana at New Orleans supports these observations. During the ten year period ending Dec. 31, 1945 the annual incidence of carcinoma of the stomach, although showing transient changes, remained about the same, whereas the incidence of carcinoma of the lung revealed a steady rise. Suggestive of a racial factor is the fact that this increase in incidence occurred primarily among white patients, with little or no change among the Negro patients. This observation obtains further support from a comparison of the racial incidence of carcinoma of the lung and stomach with all admissions. Whereas the ratio of white to Negro patients is about 2 to 3 for carcinoma of the stomach and perhaps not significantly different from that for all admissions, for carcinoma of the lung this ratio is practically reversed, being 2 to 1 in favor of the white race. Although the white preponderance is even more striking among the patients in whom pneumonectomy was performed, this is readily explained by the large proportion of patients who were treated at hospitals which serve only white patients.

It has long been recognized that carcinoma of the lung is predominantly a disease of the male sex, an interesting but unexplained fact. In our series of 412 cases there were 356 (86.4 per cent) in men and 56 (13.6 per cent) in women. Of the 147 patients in whom pneumonectomy was performed, 121 (82.3 per cent) were men and 26 (17.7 per cent) were women. These figures conform closely with those obtained in a series of 8,575 collected cases in which 6,769 patients (78.9 per cent) were men and 1,806 women (21 per cent).[3a]

Carcinoma of the lung, like other carcinomas, occurs most frequently in the fifth, sixth and seventh decades of life. Approximately 90 per cent of the patients in

From the Department of Surgery, Tulane University of Louisiana School of Medicine, and the Ochsner Clinic.

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1. Adler, I.: Primary Malignant Growths of the Lung and Bronchi, New York, Longman's, Green & Co., 1912.

2. Graham, E. A., and Singer, J. J.: Successful Removal of an Entire Lung for Carcinoma of Bronchus, J. A. M. A. **101**: 371 (Oct. 28) 1933.

3. (*a*) Ochsner, A., and DeBakey, M.: Carcinoma of the Lung, Arch. Surg. **42**: 209 (Feb.) 1941. (*b*) Ochsner, A.; Dixon, J. L., and DeBakey, M.: Primary Bronchiogenic Carcinoma: An Analysis of One Hundred and Ninety Cases, Fifty-Eight of Which Were Successfully Treated by Pneumonectomy, with a Review of the Literature, Clinics **3**: 1187, 1945; (*c*) Primary Bronchiogenic Carcinoma, Dis. of Chest **11**: 97, 1945.

both our total series as well as in the cases of resection were in this age group. The youngest patient in this series was 12 years of age, and the oldest was 81.

ETIOLOGY

The apparent increase in the incidence of carcinoma of the lung stimulated much speculation concerning its cause. The numerous explanations advanced to account for this fact have been reviewed in previous publications.[3] In the analysis of this series none of these factors was found to bear a significant relation to the occurrence of the disease. Both occupation and smoking, which have been particularly emphasized by some observers as possible etiologic factors, and which we were inclined previously to consider more seriously, were found to have no special significance in his analysis. Of the 147 patients in whom pulmonary resection was performed 76 per cent were smokers and 24 per cent were nonsmokers, and the number of those who had indoor occupations was almost equal to that of those who did outdoor work.

PATHOLOGY

Most primary tumors of the lung are malignant, and with few exceptions they are bronchiogenic in origin. Recently, Ikeda [4] has called attention to the occurrence of alveolar carcinoma of the lung, which differs from most pulmonary carcinomas in that it occurs with equal frequency in both sexes and originates in the alveoli rather than in the bronchi. There is a good deal of variation in the pathologic types of bronchiogenic carcinoma. They will not be discussed here, because they will form the subject of a subsequent report. Of the 147 cases of resection, there were 141 cases of bronchiogenic carcinoma, 2 cases each of fibrosarcoma and lymphoblastoma, and 1 case each of melanoma and neurogenic sarcoma. The right lung is involved somewhat more frequently than the left in primary cancers of the lung. In a series of 4,732 cases which we [3a] previously collected from the literature, there were 2,761 (58.3 per cent) tumors involving the right lung and 1,971 (41.6 per cent) involving the left lung. In the present series of 147 cases of primary pulmonary cancer in which pulmonary resection was done, the right side was involved in 87 cases (59 per cent) and the left side in 60 (41 per cent). The upper lobes of both lungs and the lower lobe of the right lung were involved in 11.6 per cent of cases. The fact that the upper lobes in our operative series were involved so frequently is significant because of the difficulty in bronchoscopic visualization and biopsy of these lesions.

CLINICAL MANIFESTATIONS

Because of the paucity of symptoms, particularly in the earlier stages, and the usually insidious onset, it is difficult to portray a characteristic clinical picture of carcinoma of the lung. These factors undoubtedly account for the frequent delay in diagnosis. In the present series of 147 cases of resection, the commonest symptoms were cough, loss of weight, pain or discomfort in the chest, a history of a previous respiratory infection, hemoptysis and dyspnea in about that order of frequency. Not infrequently only one or two of these manifestations are present, and occasionally the patient has no symptoms, the diagnosis being made from a routine roentgenogram of the chest. Cough is particularly difficult to evaluate because it may so frequently be explained as due to smoking. For this reason it is particularly important to distinguish any change in the cough and to determine any associated thoracic symptoms of recent development. Another manifestation which deserves some consideration is a history of a previous respiratory infection. Instead of prompt and complete recovery after such an infection the symptoms persist. Too frequently the significance of this is not appreciated until several months have elapsed, and then proper studies reveal the true diagnosis.

The physical observations in carcinoma of the lung are also variable and, like the symptoms, are generally not characteristic, especially in the earlier stages. They depend on the site, size and direction of growth of the tumor. Significant manifestations are more likely to be encountered if the tumor encroaches on the lumen of larger bronchi or on the pleura. A relatively small tumor completely occluding a main stem bronchus will produce impressive physical evidence, because of the atelectasis which follows the bronchial obstruction. On the other hand, a peripherally located tumor of considerable size which does not cause obstruction to a major bronchus or encroach on the pleura may produce relatively few physical symptoms.

DIAGNOSIS

The most important factor in the diagnosis of primary pulmonary neoplasms is the consideration of its possible presence. As emphasized previously, primary carcinoma of the bronchus should be suspected in every man over 40 years of age who has unexplained thoracic discomfort, a persistent cough or hemoptysis. This is the key to increasing the incidence of early diagnosis.

The important diagnostic methods include roentgenographic, bronchographic, bronchoscopic and cytologic examination of the sputum or bronchial secretions. Roentgenography is of great value in the diagnosis of bronchiogenic lesions, although in the early, nonobstructing lesions the roentgenogram may show no change. Serial roentgenograms are of particular value in the early stages by revealing an increase in the size of the shadow. Not infrequently, relatively small lesions will occlude a large bronchus and produce atelectasis of the lung distal to the point of occlusion. In such an instance a shadow much greater than one would expect from the size of the neoplasm will be seen in the roentgenogram. For this reason an opacity of considerable size does not necessarily signify actual invasion of the lung to that extent but may simply indicate a collapsed atelectatic lung. Centrally located lesions are often difficult to diagnose radiologically because of the confusion with hilar shadows produced by other lesions and by normal structures. Here again, the use of serial roentgenograms is of importance to determine the progress of the lesion. Occasionally, a relatively small lesion in the periphery of the lung will produce a large hilar shadow because of involvement of the mediastinal nodes, the shadow produced by the nodes being much larger than that of the originating lesion. Because of the stasis produced in an area of the lung drained by a bronchus which is occluded by the tumor or because of interference with the blood supply in the center of a rapidly growing tumor, necrosis and infection of the lung may occur with the production of a pulmonary abscess or bronchiectasis. In fact, in a man past 40 years of age an abscess of the lung which cannot be otherwise explained satisfactorily should always be considered of carcinomatous origin until

4. Ikeda, K.: Alveolar Cell Carcinoma of the Lung, Am. J. Clin. Path. **15**: 50, 1945.

disproved. Roentgenographically, pulmonary abscess associated with bronchiogenic cancer not infrequently is evidenced by an irregularity of the wall of the abscess because of the neoplastic tissue which extends into the abscess cavity. Tomographic examination is of value in these cases because of the better visualization and the sharper delineation of the walls of the cavity. Roentgenographic examination of the chest should be performed routinely both because it can be done so simply and because it yields such good results. The importance of routine roentgenograms is shown by the fact that the growth, which was producing no symptoms and consequently was not suspected, was discovered as a part of the routine examination in 5 of our 147 cases in which pulmonary resection was done for carcinoma of the lung. In 121 of the 147 cases (82.3 per cent) the roentgenographic diagnosis was bronchiogenic carcinoma. The diagnosis of pulmonary abscess in 8 cases (5.4 per cent) was the most frequent error, but in almost every case an abscess was actually present in association with the carcinoma.

Although bronchographic study is not essential in all cases of bronchiogenic carcinoma, it is a valuable diagnostic aid in some instances. This is particularly true in lesions located in the periphery of the lung and in those which involve the bronchi of the upper lobe. In the peripherally located bronchi and in the bronchi of the upper lobe which are beyond the vision of the bronchoscopist, visualization of an obstruction in a bronchus is confirmatory evidence of a primary neoplasm. In our series of 147 cases of pulmonary resection, bronchographic examination was performed in 69 (47 per cent).

Of all the diagnostic methods, bronchoscopic examination with biopsy is the most accurate, because this procedure frequently not only permits direct visualization of the tumor but also the section of a piece of tissue for microscopic examination. Unfortunately, the procedure is of no value in a large group of cases because of the peripheral position of the tumor beyond the vision of the bronchoscopist or more frequently because of its position in the bronchi of the upper lobe, i. e., "around the corner," which precludes visualization by routine bronchoscopic methods. By means of a mirror or a special bronchoscope which permits periscopic visualization, many of these tumors can be seen, but biopsy is not possible. At times the induction of artificial pneumothorax by permitting the upper lobe to fall will bring the upper lobe bronchus in more direct line with the main stem bronchus and will permit visualization of an upper lobe bronchus which would not be visible otherwise. In our 147 cases in which pulmonary resection was performed for cancer, bronchoscopic examination was done in 125 cases. In the remaining group, the procedure was not used because of the peripheral location of the tumor. In the 125 cases in which bronchoscopic examination was performed a specimen for biopsy was obtained in 74 (59.2 per cent) with a positive diagnosis in 61 (82.4 per cent). Thus, of 147 cases of cancer of the lung treated by pulmonary resection, a positive diagnosis was obtained by bronchoscopic biopsy in 61 (41.5 per cent). This figure is somewhat lower than many of those reported by others in which a correct diagnosis was made bronchoscopically in as high as 60 to 75 per cent. Our lower incidence (of positive diagnosis by biopsy) may be due to the fact that operative intervention was performed on a large number of patients in whom the lesions were not visible bronchoscopically; although a positive preoperative diagnosis could not be made, the patient was not denied the advantage of operative treatment. This is supported by the fact that the lesion was in the upper lobes in almost half (49 per cent) of our cases of resection.

Another important diagnostic procedure, and one which may prove with increasing experience to be the most important, is cytologic examination of the sputum or bronchial secretions. It is particularly useful in cases in which the tumor is beyond the range of bronchoscopic visualization. From the reports in the literature the method is proving increasingly successful.[5]

The demonstration of tumor cells in the pleural fluid is also of diagnostic value. However, this method is of more prognostic than diagnostic significance; although the presence of tumor cells in the pleural cavity verifies the diagnosis, it usually indicates a hopeless prognosis.

Although Craver[6] has been an ardent advocate of aspiration biopsy in bronchiogenic carcinoma, we believe that this method should not be used in a patient in whom there is a possibility of resection but should be limited to cases in which operative intervention appears definitely contraindicated. A positive diagnosis frequently can be made following aspiration biopsy, but the procedure is undesirable because of the danger of implantation of tumor cells in the tissues traversed by the biopsy needle. We have seen 3 patients in whom implants have occurred along the site of the aspirating needle, a cure being precluded because of the implanted carcinoma on the thoracic parietes, and this complication has been reported by others.[7]

Although an exploratory operation possibly cannot be considered as a diagnostic procedure, it is our belief that in a man past 40 years of age with an unexplained thoracic complaint in whom the existence of a bronchiogenic neoplasm can be neither disproved nor verified, exploration of the chest is justified, especially since the risk is now minimal. Previously, we believed that an operation was not justified unless a positive diagnosis could be made preoperatively, but had we continued to adhere to that contention, we would have denied a number of patients an opportunity for cure. In our series of 246 cases in which an exploratory operation was performed, a positive diagnosis was established prior to operation in 164 (66 per cent).

TREATMENT

The treatment of primary cancers of the lung consists ideally of extirpation of the involved lung before the lesion has extended beyond the confines of the lung. Extirpation of the process offers the only cure. Whereas occasionally a patient may be benefited by irradiation, generally the results from this form of therapy are of little or no value. It may be used as a palliative procedure and may be of value in hopeless cases in the alleviation of symptoms. Certainly, in

5. (*a*) Dudgeon, L. S., and Patrick, C. V.: New Method for Rapid Microscopic Diagnosis of Tumors with Account of Two Hundred Cases so Examined, Brit. J. Surg. **15**: 250, 1927. (*b*) Dudgeon, L. S., and Wrigley, C. H.: On Demonstration of Particles of Malignant Growth in Sputum by Means of Wet Film Method, J. Laryng. & Otol. **50**: 752, 1935. (*c*) Gamba, R., and Lamberti, C. E.: La inclusión de esputos en el diagnóstico de cáncer del pulmón, Prensa méd. argent. **23**: 2711, 1936. (*d*) Barrett, N. R.: Examination of Sputum for Malignant Cells and Particles of Malignant Growth, J. Thoracic Surg. **8**: 169, 1938. (*e*) Herbut, P. A., and Clerf, L. H.: Bronchogenic Carcinoma: Diagnosis by Cytologic Study of Bronchoscopically Removed Secretions, J. A. M. A. **130**: 1006 (April 13) 1946.

6. Craver, L.: Diagnosis of Malignant Lung Tumors by Aspiration Biopsy and by Sputum Examination, Surgery **8**: 947, 1940.

7. Dolley, F. S., and Jones, J. C.: Lobectomy and Pneumonectomy for Lung Suppuration and Malignancy, Journal-Lancet **59**: 162 and 268, 1939.

view of our present knowledge, it is not justifiable to use roentgen therapy in early and operable lesions. Recently, the use of nitrogen mustard, methyl-*bis*(beta-chlorethyl) amine hydrochloride, has been reported to be of possible value in alleviating symptoms in inoperable cases, but we have had little experience with its use.

Contraindications to exploration, we believe, are relatively few. Involvement of the phrenic and recurrent laryngeal nerves has been considered by some a definite contraindication to exploration, but we do not share this opinion. Although in many instances these cases will prove inoperable, we have repeatedly seen persons with this type of involvement in whom at exploration it was possible to resect the lesion. Our indications of definite inoperability are distant metastases, obvious involvement of the carina or trachea and the observation of malignant cells in the pleural fluid. Every other patient should be given the advantage of thoracic exploration, because only in this way can one determine whether the lesion is operable.

The desideratum in the treatment of bronchiogenic carcinoma is curative resection of the lung. However, we are of the opinion that in many instances palliative resection is justified. Even though the patient may subsequently succumb to extension of the malignant

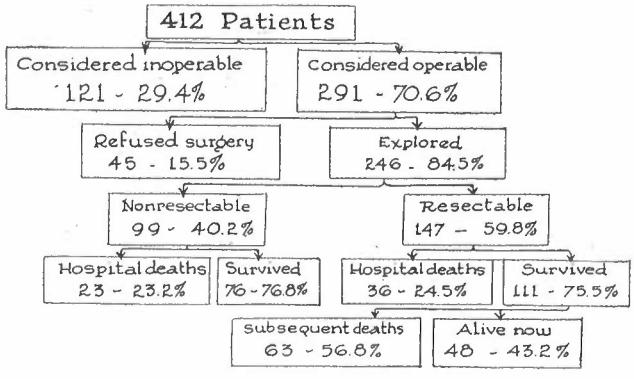

Fig. 1.—Schematic representation of results in present series of 412 cases of pulmonary cancer.

process, removal of the involved lung with its contained tumor, which has undergone necrosis and which has become infected with the development of an abscess, is sufficient justification for the procedure. The remaining days of the patient's life are made more comfortable, and he is spared the sepsis and the continued exudation which would have existed had the lung not been removed. We appreciate the fact that there may not be complete agreement with this point of view, but it seems to us justifiable on a purely humanitarian basis. Moreover, as will be observed later, the survival periods following palliative resection seem to be sufficiently long to justify operative therapy.

No attempt will be made here to discuss technical considerations of the operation, since they have been presented elsewhere.[8] We are still of the opinion that with few exceptions pneumonectomy is the procedure of choice because it permits more thorough extirpation of the involved tissue and the possibly involved hilar lymph node.[9] Simple lobectomy was performed in only 2 of the 147 cases of resection, in 1 because at the time of operation the condition was thought to be inflammatory (this patient has remained well for over five years), and in the other as a palliative procedure. Both the anterior and the posterolateral approaches have been used, but in general the former is preferred because it has seemed to us to have certain advantages over the latter and because it has proved technically satisfactory.

ANALYSIS OF RESULTS

Of the 412 cases reported in this paper, 246 patients (59.7 per cent) were operated on and 166 (40.3 per cent) were not operated on (fig. 1). The latter number includes 121 (29.4 per cent) cases which were considered clearly inoperable at the outset and 45 in which the lesion was considered operable but the patients refused surgical treatment (fig. 1). Of the 246 lesions which were explored, 99 (40.2 per cent) proved to be nonresectable and 147 (59.8 per cent of the number explored, or 35.7 per cent of the total series) were resected. In other words, of every 3 cases of clinical pulmonary cancer 2 will appear to be operable and only 1 will prove to be resectable. Although these incidences are somewhat higher than those found in a collected series of 2,034 cases (29.2 per cent for exploration and 13.4 per cent for resection), they are in accord with those appearing in the more recent reports which reflect an encouraging trend toward higher incidences.[10] However, they are still much too low and emphasize the need for wider recognition of the problem and for earlier diagnosis.

Of the 99 patients in whom the tumor was not resectable, 23 died in the hospital (23.2 per cent) and 76 (76.8 per cent) left the hospital alive. Of the 147 patients in whom resection was performed, 36 (24.5 per cent) died in the hospital and 111 (75.5 per cent) left the hospital alive. Of the latter group, 63 (56.8 per cent) have subsequently died and 48 (43.2 per cent) are still alive, 1 of whom was operated on eleven years ago.

An analysis of the resectable tumors according to whether operation was performed before or after 1942 shows the hospital mortality for these periods to be 46.4 per cent and 19.3 per cent, respectively. It may be reasonably assumed that the lower mortality rate in the later period is due to better operative technic and better preparation and postoperative care of the patient. The relatively high operative mortality for the entire series (24.5 per cent) is, we believe, due in great measure to the fact that resections were performed in patients with extensive disease as well as in those with poor cardiovascular function. This is illustrated by the fact that in order to resect the lesion which had extended beyond the confines of the lung it was necessary to ligate the pulmonary vessels in the pericardium in 18 cases (12 per cent), to resect and suture a portion of the auricle in 8 (5 per cent), to resect a portion of the diaphragm in 9 (6 per cent) and to resect a major portion of the chest wall in 8 (5 per cent). Earlier in our experience many of these cases would have been considered inoperable, but we now believe that the limits of operability can be extended by these procedures and that the effort is justified in order to give the patient his only chance of relief.

The postoperative complications were principally empyema and a blown bronchus. In 18 (12.2 per cent) of the 147 cases empyema developed, and in 8 of these

8. Ochsner, A., and DeBakey, M.: Primary Pulmonary Malignancy: Treatment of Total Pneumonectomy; Analysis of Seventy-Nine Collected Cases, and Presentation of Seven Personal Cases, Surg., Gynec. & Obst. **68**: 435, 1939; Surgical Considerations of Primary Carcinoma of the Lung: Review of the Literature and Report of Nineteen Cases, Surgery **8**: 992, 1940. Ochsner, Dixon and DeBakey.[3b]

9. Ochsner, A., and DeBakey, M.: Significance of Metastasis in Primary Carcinoma of the Lungs, J. Thoracic Surg. **11**: 357, 1942.

10. Ochsner, A.; DeBakey, M., and Dixon, J. L.: Primary Pulmonary Malignancy Treated by Resection, Ann. Surg. **125**: 522, 1947.

(5.4 per cent of the entire group) the bronchus opened. It is our general impression that chemotherapy, whether in the form of sulfonamide drugs or penicillin, has not materially influenced the incidence or the morbidity of these complications.

Further evidence of improvement in the surgical management of these cases with increasing experience is shown by a consideration of the morbidity rate and the length of hospitalization in the patients treated before January 1942 and those treated since that date. In the former group the longest hospital stay was 107 days, the shortest 11 days, and the average 32.3 days. In the latter, the longest period of hospitalization was 118 days and the shortest 6, with an average of 13.5 days. It would seem that the decrease in the hospital stay in the later period is a reflection of better preoperative preparation and more effective postoperative care.

Of the patients who died in the hospital, death occurred within the first twenty-four hours in 33 per cent, from the first to the fifth day in 19.4 per cent, from the sixth to the tenth day in 22.2 per cent, from the eleventh to the fifteenth day in 11.1 per cent and on the eighteenth day in 1 case, and 4 died on the forty-third day. In the 36 cases which ended fatally within the hospital, cardiovascular lesions were responsible for the fatality in 47 per cent. The fact that almost half of the hospital deaths were the result of cardiovascular lesions has prompted us to include a cardiologist in our thoracic team in order to observe these patients preoperatively and postoperatively. It is our belief, however, that the incidence of this cause of death will not be greatly reduced unless the criteria of operability are so strictly limited that patients in whom this complication is likely to occur are excluded from surgical treatment and are thus denied what is admittedly their only chance of salvage.

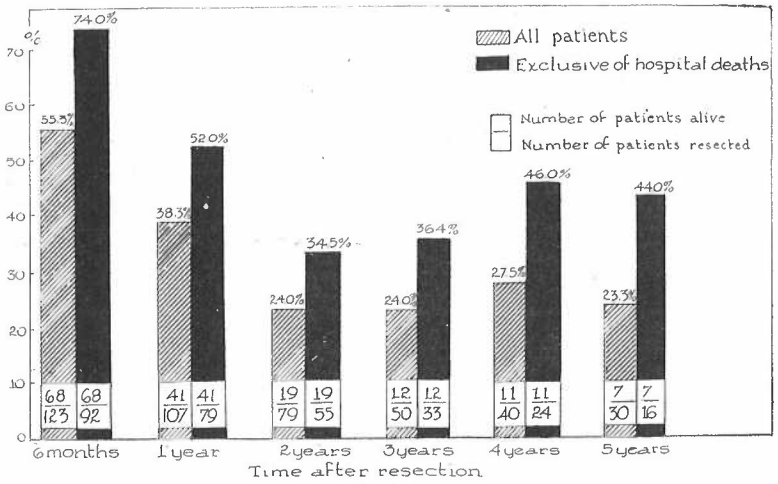

Fig. 2.—Survival rate after resection in present series of pulmonary cancer.

SURVIVAL RATES

In the evaluation of any form of therapy follow-up studies are essential, and this is particularly true for malignant disease. In this series of 147 cases in which resection for pulmonary cancer was done, every patient who was operated on six months or more ago has been followed to date, in the majority of instances the postoperative examination being made by one of us. Because the 123 patients who had been operated on six months ago or longer were treated surgically at varying periods of time during the past eleven years, the number of cases in each category is different, and the numbers become smaller as the possible survival time increases. Patients operated on only a year ago, for instance, obviously have had no opportunity to survive longer than a year. Of the 123 patients operated on six months or more ago, a little over half survived the first six-month period after operation (fig. 2). The 55 deaths in this period, however, include the 36 deaths which occurred in the hospital immediately after the operation. Slightly less than three fifths of the patients, again including those who died in the hospital, died within the first year. After that time, however, the death rate increased much less rapidly. At the end of five years approximately one fourth of the patients (23.3 per cent) who had submitted to resection were still alive (fig. 2). To express it differently, the distribution curve for the survival rate drops rather rapidly within the first two years after operation, but by the third year it becomes stabilized and continues almost as a plateau until the fifth year. It is obvious that a patient with carcinoma of the lung who has survived pneumonectomy for two years has a good chance of being alive at the end of five years.

If hospital fatalities are excluded and an analysis is made only of those patients who left the hospital alive, the distribution curve is similar to the curve for the entire group but is simply at a higher level and thus appears more encouraging; the survival rate at the end of five years then reaches 44 per cent as contrasted with 23.3 per cent when all the patients are included (fig. 2).

Unfortunately, as has already been indicated, there was a large number of cases in this series in which there was gross evidence of extension to other structures, such as the mediastinal lymph nodes or the adjacent viscera. Obviously, when such extension has occurred the chance of a cure is considerably less, because once there has been involvement of the adjacent structures the possibility of removing all the tumor cells, even though these structures are resected, is reduced. Therefore we divided the cases into two groups: those in which there was no gross evidence of extension beyond the lung at the time of operative intervention and those in which the other structures were involved. As was expected the survival rate among the patients with localized growths was significantly greater than that for patients with extension, the figures being 42.9 per cent and 6.2 per cent, respectively, at the end of five years (fig. 3).

Since with increasing experience there has been definite improvement in the operability, hospital mortality and morbidity of pulmonary resection for carcinoma of the lung, it was considered possible that similar improvement might be reflected in the survival rates. Accordingly, the material was analyzed with this objective in mind, the cases having been divided into two groups, depending on whether operative intervention was performed before or after 1942. The analysis of the whole group, as well as the localized and the nonlocalized lesions, reveals no significant differ-

ences in the survival rates before and after 1942. It would therefore seem that improvement in the technical management of the case exerts little influence on the survival rate and that the most important factor in this connection is extent of the growth or the feasibility of complete extirpation of the lesion.

To summarize the operability and survival rate for all cases of carcinoma of the lung according to our present statistics, it may be stated that in a given group of 25 cases, only 15 would meet the criteria of operability and thus be explored, only 9 would prove resectable, almost 7 would survive the operation and only 2 would survive five years or longer (fig. 4). On the other hand, if it were assumed that all the patients were seen early enough that resection could have been performed in all 25 cases, then based on our present statistics, which include many cases with palliative resection and consequently minimal chance of cure, 15 patients would survive six months to a year and 5 plus would survive five years or longer. There is no reason to consider this an impossible goal.

It is of interest to compare these results with those obtained in the treatment of gastric carcinoma. The relative frequency and the clinical importance of gastric cancer have been generally realized for a long time. There has been no comparable appreciation of the frequency and clinical importance of pulmonary cancer. Presumably, then, better results would be expected from treatment in gastric carcinoma than in bronchiogenic carcinoma, for the greater awareness of the problem should permit early diagnosis and therefore more effective therapy in a larger number of cases. Yet this is not the situation. The survival rate in carcinoma of the lung is now actually better than the survival rate in carcinoma of the stomach. The survival rate in carcinoma of the stomach is reported to be about 5 per cent, and our own experience is in accord with this figure. The survival rate in carcinoma of the lung is about 8 per cent. These observations seem to justify two conclusions: 1. The clinical course of bronchiogenic carcinoma is slower than that of gastric carcinoma. 2. With greater awareness of the problem of pulmonary cancer by the members of the medical profession, and with a consequent increase in the proportion of cases diagnosed early, there will be a considerable improvement in the survival rate of the disease.

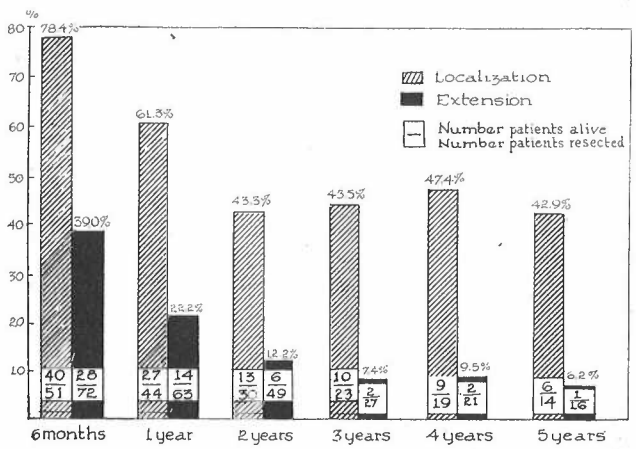

Fig. 3.—Survival rate after resection according to extension and localization of lesion.

SUMMARY AND CONCLUSION

1. An analysis has been made of the experience with primary pulmonary cancer during a period of almost twelve years and in a total of 412 cases, with special emphasis on diagnostic considerations and survival rates.

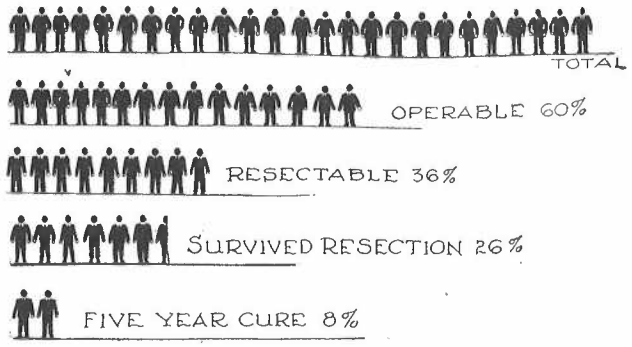

Fig. 4.—Schematic representation of actual survival expectancy in pulmonary cancer based on present experience.

2. Bronchiogenic carcinoma is a common lesion and probably represents about 10 per cent of all carcinomas. It is a disease primarily of men, most frequently in the fifth, sixth and seventh decades of life.

3. The right lung is involved somewhat more frequently than the left. In the present series of cases of resection, the upper lobes of both lungs and the lower lobe of the right lung were involved with equal frequency.

4. The disease begins insidiously, and there is no characteristic clinical picture. The most important factor in making an early diagnosis is the assumption that an unexplained thoracic disorder in a man past 40 years of age is bronchiogenic carcinoma until proved otherwise. Frequently the first manifestation in bronchiogenic carcinoma is an antecedent respiratory infection, the symptoms of which do not subside as they normally should.

5. Routine roentgenologic examination is the most valuable of all diagnostic methods. Bronchoscopic examination, when it permits visualization of the tumor and removal of tissue for biopsy, is perhaps the most accurate. Unfortunately, the lesion in a high proportion of cases (approximately half of the present series) is beyond the range of bronchoscopic visualization. Cytologic examination of the sputum or the material obtained by bronchoscopic aspiration is of increasing diagnostic importance.

6. Although it is extremely desirable to make a positive diagnosis before operation, in many instances (in the present series, 33 per cent) it is necessary to confirm the presumptive diagnosis by exploratory thoracotomy. The incidence of operability in carcinoma of the lung remains discouragingly low and emphasizes the need for wider recognition of the problem and for earlier diagnosis. Of the 412 cases in the present series, 246 (59.7 per cent) were explored and 147 (35.7 per cent) were resected. In simpler terms, of every 3 cases 2 will appear operable and 1 will prove resectable.

7. The surgical mortality has shown progressive improvement. Whereas the total mortality was 24.5 per cent for the entire series, it was 46.4 per cent for the group operated on before 1942 and 19.3 per cent for those operated on since that date.

8. The most frequent cause of death in the cases ending fatally while the patient was in the hospital was cardiovascular disease (47 per cent). This risk must be assumed if patients in whom cardiovascular complications are likely to develop are not to be denied their chance of salvage.

9. Of the patients in whom resection of the lung was possible and who were operated on five years ago or more, 23.3 per cent are still alive. This gives about an 8 per cent five year survival rate for all cases of carcinoma of the lung.

10. Although the results following the surgical treatment of primary malignant neoplasms of the lung are not good at the present time, they are better than those obtained in the treatment of gastric carcinoma, even though this latter lesion has been known for some time and its frequency is generally appreciated by the members of the medical profession. When the physician becomes cognizant of the relative frequency of primary pulmonary malignant neoplasms and recognizes these cases earlier, much better results will be obtained. The fact that a better than 20 per cent five year salvage rate can be obtained in cases of resection, in many of which only palliative resections are performed, indicates that the lesion is relatively slow-growing and that the ultimate outlook is not as pessimistic as it has been considered in the past.

AMERICAN RADIOLOGY

Its Contribution to the Diagnosis and Treatment of Disease

GEORGE W. HOLMES, M.D.
Boston

Radiology is, comparatively speaking, a youth among the great medical specialties. Its entire life history lies within the life span of the average person; it is only half as old as the American Medical Association. Roentgen made his great discovery on Nov. 8, 1895. Radiology may be said to have appeared as a specialty in American medicine in the year 1900 with the organization of the American Roentgen Ray Society. It was not listed as a major specialty by the American Medical Association until 1921. Yet in this relatively short period of time it has revolutionized the practice of medicine. Physicians have always been prompt to utilize great scientific discoveries whenever they seemed to offer help in the diagnosis or treatment of disease. In the long history of medicine there is no record of the acceptance of a scientific discovery with such enthusiasm as that which greeted the roentgen ray. During the year 1896 more than one thousand articles and fifty books on the subject were published;[1] three of these books and many of the articles were on the use of the roentgen ray in medicine.

In the early years discoveries were being made almost daily and were being reported by surgeons, internists, general practitioners, engineers and physicists; and it is still a fact that many of the great advances in radiology are being made by workers outside the specialty. This is true to some extent in any new field, but radiology, perhaps more than any other specialty, is dependent on progress in other branches of medicine and on the instruments which it uses. Each step forward in associated fields has been followed by a corresponding advance in the science of radiology. It has rarely been the leader, but with an increase in the number of young men well trained in the basic sciences who are entering the specialty one may expect the radiologist to take a more active part in medical research. No other specialty with the exception of pathology, which is not a clinical specialty, covers as wide a field. Perhaps it is this very wideness of opportunity that has prevented detailed study, and without detailed study new facts are not discovered. On the other hand, an amazing number of advances in the diagnosis and treatment of disease, covering almost the entire field of medicine, may be directly attributed to the use of the roentgen ray. I shall point out only a few which seem to me to have had the greatest effect on medical progress.

CONTRIBUTIONS TO DIAGNOSIS

Diseases of the Bones and Joints.—The first use of the x-ray in medicine was in the diagnosis of diseases of, or injury to, the bones and joints, and this is still one of its most important uses. So many reports appeared almost simultaneously that it is impossible to give priority to any one author, but the names of some of the early workers have become permanently associated with certain procedures or with certain diseases. Warren's anatomic variations of the hands and feet, Hickey's [2] work on the development of the human skeleton, and Baetjer's contribution to the diagnosis of tumor of the bone are only a few of the first important publications. The great advances which have been made in the treatment of injuries of the bones and joints would not have been possible without the use of the roentgen ray. The painful manipulations formerly necessary to establish a diagnosis are no longer required. The data obtained from a properly conducted roentgenologic examination enable the surgeon to select at once the appropriate treatment, and repeated examinations demonstrate the results of treatment and the progress of healing. All this information is secured with the minimum amount of discomfort to the patient.

Although as early as 1896 records of disease conditions in bone began to appear in the literature, it was not until 1901 that any serious attempt to classify these lesions and to correlate them with the pathologic observations was made. Köhler [3] of Germany and Hickey, Caldwell [4] and Baetjer in this country made outstanding contributions, and later Baetjer and Waters [5] published their important work on tumor of the bone. This, with the investigations of Codman [6] and others, has brought the roentgen diagnosis of lesions of the bone to such a degree of accuracy that it is now considered the most valuable single factor in prepathologic diagnosis.

There are a considerable number of more or less generalized diseases of bone, perhaps best illustrated by hyperparathyroid disease, which have become better understood following the general use of the roentgen ray.

On the Board of Consultation and from the Department of Radiology, Massachusetts General Hospital.

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BRONCHOGENIC CARCINOMA

ITS FREQUENCY, DIAGNOSIS, AND EARLY TREATMENT

Alton Ochsner, M.D., Paul T. DeCamp, M.D., New Orleans, M. E. DeBakey, M.D., Houston, Texas
and
C. J. Ray, M.D., New Orleans

The incidence of bronchogenic carcinoma is increasing more rapidly than that of any other cancer. In 1912 Adler,[1] who was able to collect only 374 cases of cancer of the lung, stated, "On one point, however, there is complete consensus of opinion and that is that primary malignant neoplasms of the lung are among the rarest form of disease." Whereas it was an infrequent lesion 40 years ago, it has become one of the most frequent malignant lesions encountered in men. In the 10 years from 1938 to 1948 the number of fatalities from bronchogenic carcinoma in the United States increased 144%, from 6,732 in 1938 to 16,450 in 1948. In this same period of time the total cancer deaths from all types of cancer, increased 31%, from 149,214 in 1938 to 195,594 in 1948. From 1920 to 1948 the death rate from bronchogenic carcinoma per 100,000 population in the United States increased over 10 times, from 1.1 to 11.3 (Fig. 1). According to Doll and Hill,[2] deaths from cancer of the lung in England increased fifteenfold from 1922 to 1947. There has been considerable controversy concerning the cause of the unprecedented increase in bronchogenic carcinoma. According to Wynder and Graham,[3] excessive and prolonged cigarette smoking is an important factor in the genesis of bronchogenic carcinoma. They found that of their 605 male patients with bronchogenic carcinoma, only 2.6% did not smoke or smoked minimally; whereas over 96% had smoked heavily for over 20 years. In the control male general population these figures were 14.6% and 73.7%, respectively. Levin, Goldstein, and Gerhardt [4] also found that there were more smokers among cancer patients than noncancer patients and that patients with bronchogenic cancer usually smoked cigarettes. Watson [5] found in the Memorial Hospital cases that 37% of the patients with lung cancer and 19% without cancer were heavy smokers. Doll and Hill [2] showed that in a series of patients with cancer of the lung, 11.6% smoked 500,000 cigarettes or more a year; whereas in a noncancer group only 5.6% smoked that many cigarettes. According to these investigators, "About the age of 45, the risk of developing the disease (bronchogenic carcinoma) increases in simple proportion with the amount smoked, and it is approximately 50 times as great among those who smoke 25 or more cigarettes a day as among nonsmokers." Schrek and associates [6] state: "This positive correlation between the incidence of cigarette smoking and the incidence of cancer of the respiratory tract appeared to be both statistically and biologically significant. There is strong circumstantial evidence that cigarette smoking was an etiologic factor in cancer of the respiratory tract." In Iceland, where smoking has only recently become popular, Dungal,[7] states that among 417 cancers found in 1,939 necropsies there were only 12 cases of primary carcinoma of the lung.

For some time two of us [8] have been convinced that there is a causal relationship between the increased incidence of bronchogenic carcinoma and the increased use of cigarettes. There is a distinct parallelism between the

From the Department of Surgery, School of Medicine, Tulane University, and the Ochsner Clinic (Drs. Ochsner, DeCamp, and Ray) and the Department of Surgery, College of Medicine, Baylor University (Dr. DeBakey).
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sale of cigarettes and the incidence of bronchogenic carcinoma (Fig. 1). The annual production of cigarettes per capita population (including men, women, and children) increased from 46.3 in 1903 to 2,541 in 1948. The latter figure excludes those produced for foreign consumption. Because the carcinogenic effect of cigarette smoking does not become evident until after many years of smoking (approximately 20), it is frightening to speculate on the possible number of bronchogenic cancers that may develop as the result of the tremendous numbers of cigarettes consumed in the two decades from 1930 to 1950. From 1920 to 1930 the annual number of cigarettes per capita increased from 480 to 930 (approximately 2 times). In the decade 20 years later, i. e., from 1938 to 1948, during which time the carcinogenic effect of the smoking in the earlier decade should have become evident, the number of bronchogenic carcinomas per 100,000 population increased from 4.2 to 11.3. In the 18 years from 1930 to 1948 the annual number of cigarettes per capita consumed increased from 930 to 2,541 (2.6 times), which suggests that if there is a causal relationship between cigarette smoking and bronchogenic carcinoma the deaths per 100,000 population from this cause may be expected to increase from 11.3 to 29.4 by 1970. With the predicted death rate from bronchogenic carcinoma of 29.4 per 100,000 population in 1970, it may be estimated that the annual deaths from this cause will increase from 16,450 in 1948 to 47,000 in 1970. In 1920 deaths from bronchogenic carcinoma represented 1.1% of all cancer deaths; in 1930, 2.2%, and in 1948, 8.3%. It may be predicted that in 1970 18% of all cancer deaths will be due to bronchogenic carcinoma if present trends continue. Because of increased cigarette smoking it is likely and probable that bronchogenic carcinoma soon will become more frequent than any other cancer of the body, unless something is done to prevent its increase. In 1949 over twice as many patients with bronchogenic carcinoma as with gastric cancer were admitted to the Memorial Hospital.[9]

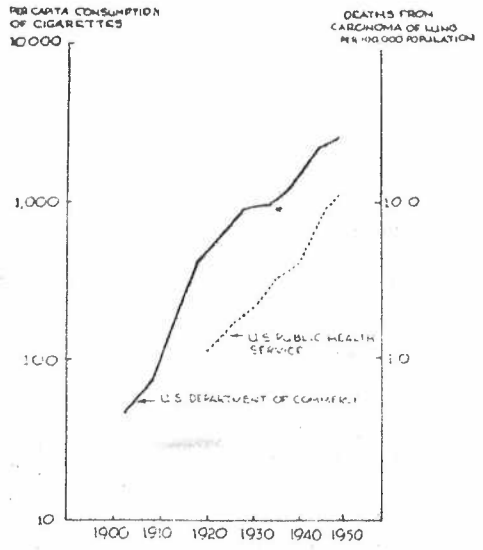

Fig. 1.—Comparison of increasing death rate from bronchogenic carcinoma with the increasing consumption of cigarettes in the United States. * = exported cigarettes deducted in 1933 and subsequently.

Unfortunately, bronchogenic carcinoma begins so insidiously and because with few exceptions it occurs in persons who smoke excessively and have a cigarette cough, relatively little attention is paid to the early manifestations of the disease. Because of this and also because of the fact that the profession generally is not cognizant of the frequency of bronchogenic carcinoma, there may be considerable delay in diagnosis. Overholt and Schmidt[10] stress the importance of the "silent phase" of bronchogenic carcinoma in which there are few or no symptoms. They report 65 cases, 19 of which were malignant and 39 benign. The resectability rate in the former was 79%. Subsequently, Overholt[11] reported 145 cases in which pulmonary shadows were detected on chest surveys, of which 51 were neoplastic and 35 malignant. He states:

> If the patient waits for symptoms and if the delays that follow in the average case are added to this time lost, approximately 90% of the lesions have by that time extended to structures outside the lung. The possibility of cure, therefore, is limited to a meager 10% in the symptomatic stage of the disease. To explore and to carry out excisional treatment during the silent phase will set treatment ahead by months or years. In our clinic when prompt treatment has followed discovery of cancer by survey, all lesions have been resectable and 75% have shown no evidence of lymphatic spread.

All patients in the group are still living. In our series of 948 cases of bronchogenic carcinoma, resection was possible in only 332 cases (35%). The average duration of symptoms in the latter group was 12.3 months. Only three patients were asymptomatic; in one the lesion (by x-ray) was 1 cm. in diameter, and in the other two it was 2.5 cm. Nine patients had symptoms less than one month. In one the lesion measured 2.5 cm.; in five, 6 to 8 cm.; and in three, 10 cm. or over. Nineteen patients had symyptoms from one to two months. In four the lesion measured 2 to 3.5 cm.; in seven, 5 to 7 cm.; in four, 7.5 to 10 cm.; and in four, over 10 cm. Thus, of 332 cases in which pneumonectomy was done, symptoms for two months or less occurred in only 31. Obviously, any malignant lesion in which there is a delay of over a year has relatively little chance of cure.

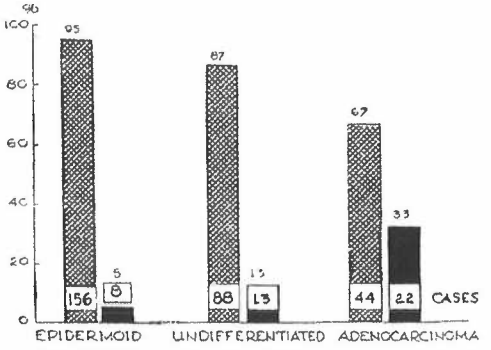

Fig. 2.—Sex incidence by histological types in 331 cases of bronchogenic carcinoma in which resection was done. Hatched bar represents males; black bar, females.

The present report is based on a series of 948 patients with bronchogenic carcinoma observed by us in New

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Orleans at the Ochsner Clinic and at the Charity Hospital. Because Charity Hospital is an institution to which white and Negro patients are admitted with about equal frequency, it is possible to determine fairly accurately the racial incidence of disease. Bronchogenic carcinoma is more frequent in white men than in Negro men, the

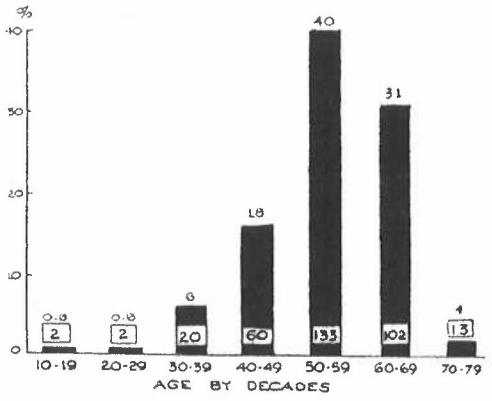

Fig. 3.—Age incidence in 332 cases in which resection was done. Figure in white bar indicates number of cases.

respective percentages of expected incidence being 118 and 80.

Bronchogenic carcinoma is primarily a disease of men, probably due to the fact that the bronchial mucosa in men is more susceptible to malignant change than in women. It has been suggested that since women are beginning to smoke as much as men the incidence in women will increase. However, it is our belief that whereas there will be some increase in the incidence of bronchogenic carcinoma in women, it will always be more prevalent in men. In the present series of patients, 840 were men and only 108 women. The type of lesion varies in the two sexes (Fig. 2). Ninety-five per cent of the patients with epidermoid carcinoma were men, while only 5% were women. On the other hand, 33% of the patients with adenocarcinoma were women, and 67% were men. Undifferentiated carcinomas occurred predominately in men (87%). Of the 288 men in whom pneumonectomy was done, 54% had epidermoid carcinoma, 31% undifferentiated carcinoma, and only 15% adenocarcinoma. Of the 43 women, only 19% had epidermoid carcinoma, 30% had undifferentiated carcinoma, and 51% had adenocarcinoma.

Bronchogenic carcinoma, as other types of carcinoma, is primarily a disease of older persons, the greatest incidence being in the fifth, sixth, and seventh decades (18%, 40%, and 31%, respectively) (Fig. 3).

PATHOLOGY

Primary carcinoma of the bronchus can occur in any part of the bronchial tree (Fig. 4). Over half in our series occurred in the upper lobes. This is of significance, since lesions of the upper lobe bronchi are less likely to be visible on bronchoscopic examination because they are located "around the corner." The two sides were involved with about equal frequency the right 53%, the left 47%. Whereas previously it was thought that primary carcinoma of the bronchus occurred frequently in the main stem bronchus, this contention is not substantiated in our series. Only 13 of the primary carcinomas in the cases in which resection was done were in the main stem bronchus, 188 were in a lobe bronchus, and 123 in the periphery. Of 331 cases in which resection was done, 49.5% of the carcinomas were epidermoid, 30.5% were undifferentiated, and 19.9% were adenocarcinomas. Epidermoid carcinomas were infrequent in women, but adenocarcinomas occurred relatively more frequently in women than in men. Of the 165 epidermoid carcinomas, 4% were in the main stem bronchus, 66% in a lobar bronchus, and 30% in the periphery. Of the 95 undifferentiated carcinomas, 3% were in the main stem bronchus, 54% in a lobar bronchus, and 43% in the periphery. Of the 64 adenocarcinomas, 5% were in the main stem bronchus, 44% in a lobar bronchus, and 51% in the periphery. It is thus seen that, although lobar bronchi are involved more frequently than any other bronchi, adenocarcinomas occur more frequently in the periphery. The relative incidence of adenocarcinoma decreases with advancing age; whereas the incidence of epidermoid carcinoma increases with advancing age. The latter is probably due to the carcinogenic effect of tobacco acting for a longer time. According to Wynder and Graham,[3] "Over 96% of patients with cancer of the lung have smoked for more than 20 years and over 80% have smoked for more than 30 years." Adenocarcinomas probably originate in embryonic rests, as suggested by Graham [12] who states, "Those carcinomas designated as adenocarcinoma, oat cell, and round cell carcinoma arise from an embryonic bronchial bud which has failed to develop into normal tissue and has remained dormant for many years before being transformed into a carcinoma." Because they originate in congenital rests they are likely to become evident at earlier ages. Their incidence is not affected by smoking.

CLINICAL PICTURE

As mentioned previously, the clinical manifestations of bronchogenic carcinoma begin insidiously and are likely to be disregarded both by the patient and his

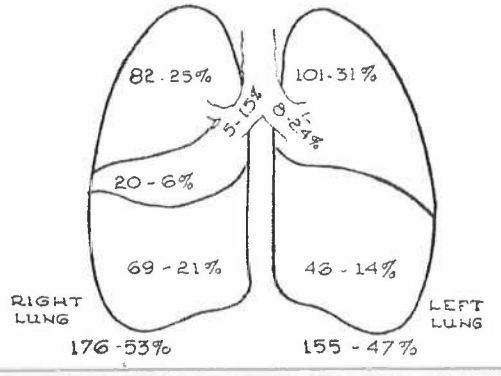

Fig. 4.—Anatomic location of lesion in 331 cases in which resection was done.

physician. Cough is without a doubt the commonest manifestation but is frequently disregarded because it has existed for some time and is thought to be due to irritation from cigarette smoking. Whereas it is true that cigarette smoking can produce a cough and expectora-

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tion, any change in the cough should be considered of significance. Ninety per cent of our patients in whom resections were done had a cough, and in 55% it was the first symptom (Fig. 5). Not infrequently the earliest manifestation of a bronchogenic carcinoma is a respiratory tract infection. A lower respiratory tract infection which does not subside as it normally should suggests a possibility of bronchogenic carcinoma. In 55% of our

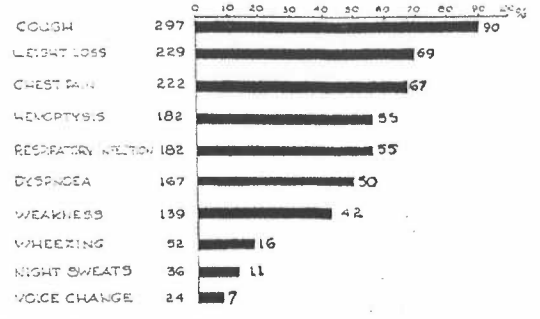

Fig. 5.—Symptoms on hospital admission in 331 patients in whom resection was done. Average duration was 12.3 months.

cases there was a history of a previous respiratory tract infection which was diagnosed either as influenza, viral pneumonia, or nonspecific pneumonitis, and it was the first manifestation in 22%. In each instance there were persistent symptoms after recovery from the acute infection. Hemoptysis is a manifestation which should never be disregarded, and although, when occurring in a man past 40, it does not necessarily mean bronchogenic carcinoma, it is a symptom which must be thoroughly investigated. It was present in 55% of our cases. Thoracic discomfort in a person who previously was well also demands investigation. Initially it is merely a consciousness of one's chest and not pain. The development of wheezing in a person, particularly in a man past 40, is suggestive of bronchogenic carcinoma because it means bronchial obstruction. An unexplained thoracic discomfort in any man past 40 must be thoroughly investigated to exclude bronchogenic carcinoma. Voice change which is the result of involvement of the recurrent laryngeal nerve fortunately occurs infrequently, because it represents extension beyond the lung. It was present, however, in 7% of our patients in whom resections were done. Whereas it has been believed by many to represent a contraindication to operation, we have not considered it as such. Although realizing that recurrent laryngeal paralysis means extension to the mediastinum and the recurrent nerve, it does not mean necessarily that resection cannot be done. Similarly, we do not believe that phrenic nerve paralysis should be considered a contraindication to exploration.

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The late manifestations of primary cancer of the bronchus are fever, pain, digestive disturbances, and emaciation and represent infection, breakdown of the tumor, and extension to other structures. Therefore, they are of little significance as regards early diagnosis or effective treatment.

DIAGNOSIS

Because the symptoms of bronchogenic carcinoma occur so insidiously, it is hoped that an increasing use of routine chest x-rays every six months in men past 40, particularly in heavy smokers, will detect many cases of bronchogenic carcinoma before symptoms occur. Rigler [13] states that peripheral lesions are invariably demonstrable roentgenographically before symptoms and signs are present. Scamman [14] reports that in a total of 536,012 small chest x-rays, 43 cases (7.8 per 100,000) of bronchogenic carcinoma were detected. Overholt [15] in 145 chest lesions detected on mass chest surveys reported 35 cases of primary lung cancer. Boucot [15] found in 156,920 persons surveyed 34 malignant lesions (1 per 5,000). She also found that in a survey of 40,607 apparently healthy workers in industry, 0.14% had a primary lung neoplasm. Because of this, she advocated that "because of the prevalence of lung cancer among men over 45 years of age this particular group should be checked every six months whenever possible." Silent lesions detected by x-ray must be considered as possibly bronchogenic carcinoma, especially in men past 40. Effler, Blades, and Marks [16] found that of 24 such lesions detected in military personnel 4 were malignant. O'Brien, Tuttle, and Ferkarey [17] in 21 patients with solitary pulmonary shadows reported 8 (38%) with bronchogenic carcinoma. Husfeldt and Carlsen [18] found four bronchogenic carcinomas among 33 cases of solitary pulmonary nodules. Sharp and Kinsella [19] in a series of 96 cases of isolated pulmonary nodules, of which 55 were histologically verified, found 11 bronchogenic cancers. Whereas it is possible for a symptomatic lesion to be so situated that it would not be demonstrable on an x-ray

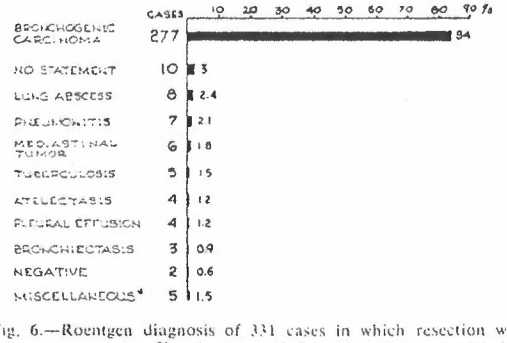

Fig. 6.—Roentgen diagnosis of 331 cases in which resection was done. * Indicates empyema, fibrosis, congenital cystic disease, lymphoblastoma, and elevation of diaphragm.

of the chest, such is unusual. Because the resectability incidence is so high in asymptomatic lesions (100%, with 75% showing no lymphatic spread [19]) and is so low in patients with symptoms (35% in our series, 70% of which already had extension beyond the lung), it cannot be overemphasized that every pulmonary shadow must be viewed with suspicion and exploration insisted on much more frequently than previously.

In patients with symptoms the diagnosis of bronchogenic carcinoma is usually not difficult if one only thinks of its possible existence. One of the most valuable diagnostic methods is roentgenography, not only because of the ease with which it can be performed, but also because it gives a high percentage of abnormal findings (Fig. 6). Roentgenography will demonstrate a shadow produced by the tumor resulting from infiltration

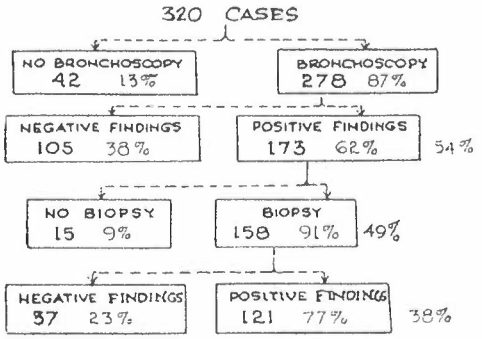

Fig. 7.—Results of bronchoscopic examinations in 320 cases in which resection was done.

of the pulmonary parenchyma or by atelectasis. The latter occurs whenever a bronchus is completely occluded by the tumor; air cannot pass beyond the site of the obstruction, and air from the alveoli distal to the tumor is absorbed. In this instance the shadow produced is much greater than would be produced by the tumor. It must be remembered, therefore, that all patients with massive shadows do not necessarily have extensive lesions. An even earlier roentgenographic manifestation is obstructive emphysema, which occuss as a result of an incompletely obstructing tumor of the bronchus. Because the bronchi are expansile and change their size during inspiration and expiration, a tumor which completely occludes the bronchus during expiration, at which time the bronchus is contracted, incompletely occludes the bronchus during inspiration, thus permitting the entrance of air into the bronchus and lung distal to the tumor but not permitting the exit of air during expiration. In this way an overdistention of the lung distal to the tumor occurs. In the present series of cases in which resection was done, a bronchogenic carcinoma was suspected roentgenologically in 84%, demonstrating the high incidence of correct diagnoses by this method. In those lesions located in the upper lobe bronchi, bronchography may be of value in demonstrating a bronchial obstruction which is suggestive of a bronchogenic neoplasm.

Early in our experience with bronchogenic carcinoma, bronchoscopy was thought to be the most valuable method of diagnosis, but it is now generally accepted that although bronchoscopy should be done in all instances, the percentage of carcinoma diagnoses made by this procedure is relatively small because most bronchogenic cancers are either in the periphery or in the upper lobe bronchi. Bronchoscopy should be done in every instance, however, not only because a biopsy study can be made of the lesions which are visible, but also because considerable information can be obtained by inspection of the trachea, carina, and the main stem bronchi, which may be of value in determining operability. However, in the present series, a diagnosis of carcinoma was made bronchoscopically in only 38% of the cases (Fig. 7).

A relatively newer method, cytological examination of sputum or bronchial secretions, has become a most valuable diagnostic procedure and should be employed in all suspected cases. In 112 cases of proved primary cancer of the lung in our series, cytological examination indicated cancer in 76 (68%). There was only one false indication. This is, however, a difficult diagnostic procedure. It requires the services of a very good pathologist, one trained in cytological diagnosis and also willing to spend many hours looking for malignant cells.

TREATMENT

The treatment of bronchogenic carcinoma is pneumonectomy with complete en bloc removal of all the mediastinal nodes. Although Churchill and Sweet [20] have recently emphasized the desirability of lobectomy, we are convinced that lobectomy is not the method of choice in the treatment of bronchogenic carcinoma and should be used only when a pneumonectomy is contraindicated. All patients with bronchogenic carcinoma should be carefully studied preoperatively to determine their pulmonary function, in order to evaluate their ability to withstand the removal of an entire lung. Unless pulmonary studies suggest that a pneumonectomy will not be tolerated, lobectomy should not be done. Only by pneumonectomy and en bloc removal of all the mediastinal nodes can a high incidence of cure be obtained, and it is just as essential to remove the mediastinal nodes in bronchogenic carcinoma as it is to remove regional lymph nodes in carcinomas elsewhere.

Unfortunately, largely due to the fact that the medical profession still considers bronchogenic carcinoma an infrequent lesion and does not consider it as a possibility in a man past 40 in whom a relatively insignificant and mild thoracic discomfort has developed, the diagnosis is frequently delayed. In fact, in our series, there was an average delay of 12.3 months from the onset. Less than 10% had symptoms of two months or less, and only 0.9% were asymptomatic. Probably because of this, 385

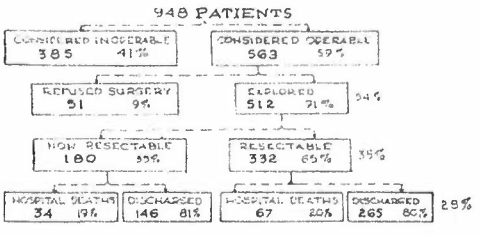

Fig. 8.—Results in the management of 948 patients with bronchogenic carcinoma.

(41%) of the 948 patients were obviously inoperable when first seen (Fig. 8). Five hundred sixty-three were considered operable, of which 51 (9%) refused surgery and 512 (91%) were explored (54% of the entire group seen). Of the 512 explored, resection could not be done in 180 (35%) because of extensive involvement of the

20. Churchill, E. D.; Sweet, R. H.; Soutter, L., and Scannell, J. G.: Surgical Management of Carcinoma of the Lung; a Study of the Cases Treated at the Massachusetts General Hospital from 1930 to 1950, J. Thoracic Surg. **20**: 349, 1950.

heart or large vessels. Of this group 34 (19%) died in the hospital, the high mortality rate being due to associated disease and not to the exploration. Of the 332 patients in whom resection was done (65% of those explored and 35% of the entire group), 67 died in the hospital (20%) and 265 were discharged from the hospital (28% of the entire group).

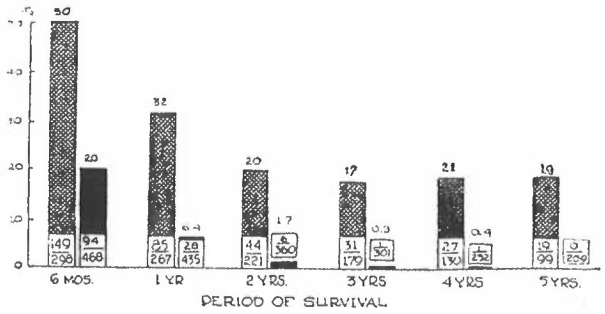

Fig. 9.—Comparison of survival rates in patients in whom resection was done and in patients in whom it was not done. Hatched bar indicates patients in whom resection was done and black bar, patients in whom it was not done. Figure in top half of white bar indicates number of patients alive; figure in bottom half, total number of patients.

It is interesting to compare the incidence of exploration and resectability in the private and Charity Hospital series. In 46% of the cases of the entire goup, no operation was deemed advisable; exploration was done in 54% and resection in 35%. These same percentages in the private group were 34, 66, and 43%, respectively; while in the Charity Hospital series, they were 63, 37, and 23%, respectively. It is evident that the Charity Hospital patients are more likely to neglect themselves and are less likely to consult a physician, even though facilities are available to them at no cost. There has been a slight increase in the incidence of resectability throughout the years from 1935 to 1951, but this has been principally in the Charity Hospital series. Whereas resection was possible in only 8% of the patients at Charity Hospital in the period 1935 to 1941, resection was done in 33% from 1949 to 1951. These respective percentages in the private series are 42% and 49%.

Although 332 resections were done, unfortunately in most cases the lesion was extensive and had already involved some other structure. In 232 the resection was termed a palliative resection, which means that the tumor had already extended beyond the lung, either to involve the mediastinal nodes or the mediastinal pleura, pericardium, heart, chest wall, or diaphragm. In only 90 cases was the lesion apparently limited to the lung. Extensive involvement necessitated extensive resection, as illustrated by the fact that 33 of the patients required intrapericardial ligation of the major vesels, 13 had suture of an auricle, 13 resection of a major portion of the chest wall, and 11 resection of a major portion of the diaphragm.

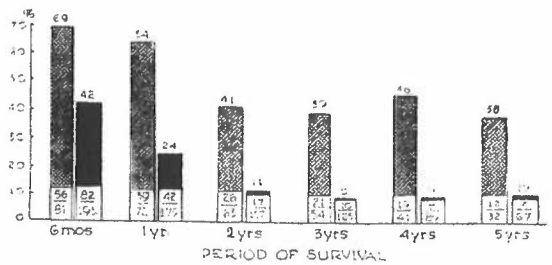

Fig. 10.—Comparison of survival rates after resection according to extension and localization of the lesion. Hatched bar indicates cases of localized disease and black bar, cases of extensive disease. Figure in top half of white bar indicates number of patients alive; figure in bottom half, number of patients in whom resection was done.

Although there was an over-all mortality rate of 20%, the mortality rate has decreased in more recent years. Whereas in the period 1935 to 1941 the mortality rate was 48%, from 1942 to 1946 it was 20%, and from 1947 to 1951 it was 17%. The decrease in mortality rate has been noticed particularly in the more advanced cases, in which there is extension of the carcinoma beyond the lung. The mortality rate in the cases in which the lesion was limited to the lung was 14% and in the cases in which it had extended beyond the lung, 22%. The mortality rate in the latter group in the period 1935 to 1941 was 63%; whereas in the period 1947 to 1951 it was 18%.

Of the 67 hospital deaths, 45% (30 cases) were due to cardiovascular disorders, of which most were cardiac disorders (25 cases). Thirty per cent (18 cases) were due to respiratory disorders, eighteen per cent (12 cases) to hemorrhage, and seven per cent to miscellaneous causes. The fact that the greatest number of patients were in the sixth decade of life, in which cardiovascular disease is prevalent, undoubtedly accounts for the high incidence of cardiovascular deaths, and there will always be an irreducible minimum of deaths from this cause. Because of this, it is imperative that careful cardiovascular surveys of all patients with bronchogenic carcinoma should be made before operation in order to reestablish good vascular function.

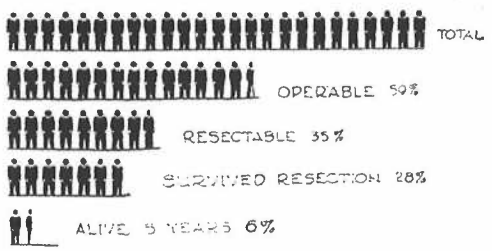

Fig. 11.—Management and results in 948 patients with bronchogenic carcinoma.

The period of survival of patients subjected to resection can be seen in figure 9. These figures are significant because they do not take into consideration deaths from other causes, and since most of these patients were of advanced ages, deaths from other causes are likely. It is our belief, however, that only by considering the survivals after a period of time can one evaluate the results obtained. It is of interest that whereas there is a rapid decrease in the survival rate for two years following pulmonary resection, a plateau is reached after that period of time, and approximately the same percentage are alive at the end of five years as were alive at the end of two years. In other words, a patient who has survived for two years following a pneumonectomy for bronchogenic carcinoma has a good chance of being alive at the end of five years.

As might be imagined, there is a good deal of difference between the curative and palliative resections. Of

the patients in whom "palliative resection" was done, 42% were alive at the end of six months, as compared with 69% of those in whom curative resection was done (Fig. 10). At the end of a year these respective percentages were 24% and 54%. At the end of five years they were 10% and 38%. It is thus seen that even among the advanced patients who are treated by pneumonectomy, 1 out of 10 is alive at the end of five years; whereas among those patients in whom there is no evidence of gross extension beyond the lung, approximately 4 out of 10 are alive at the end of five years.

The value of resection in bronchogenic carcinoma is illustrated when one compares the survival rates obtained in the group of patients submitted to resection with the survival rate of those patients in whom resection was not done. Obviously the latter group is composed of much more advanced patients, generally because they were either inoperable when first seen or the lesion was not resectable when operated on. However, there were patients in whom the lesion appeared clinically resectable but who refused operation. All patients who were not subjected to resection were treated with other therapeutic palliative procedures, such as x-ray, nitrogen mustard, other chemotherapeutic agents, or a combination of all. Whereas at the end of six months 50% of the group in which resection was done were alive, only 20% of the group in which resection was not done were alive (Fig. 9). At the end of a year these respective percentages were 32% and 6.4%; at two years, 20% and 1.7%; at three years, 17% and 0.3%. One patient out of 252 in whom resection was not done survived four years, but died shortly thereafter. No patient survived five years; whereas 19% of the patients subjected to resection were alive at the end of five years.

The results from treatment of bronchogenic carcinoma are not as satisfactory as they should be because of our 948 patients only 59% were operable, 35% were resectable, 28% survived resection, and only 6% were alive at the end of five years (Fig. 11). This is, indeed, a low salvage rate, but is undoubtedly due to the fact that there was considerable delay in the establishment of diagnosis and the institution of radical therapy. The fact that an average of over a year elapsed from the onset of the first symptoms until therapy was instituted accounts for the low incidence of resectability and the extremely low incidence of five-year salvage. It is our belief that as soon as the profession becomes cognizant of the frequency of bronchogenic carcinoma and considers the possibility of its existence in all men past 40 who have an unexplained thoracic discomfort earlier diagnoses will be made. It is also our hope that with an increasing interest in screening methods, such as mass chest roentgenography, many lesions will be detected before the patient has any clinical manifestations of the condition. As has been shown by Overholt and others,[21] the incidence of resectability in this group can approach 100%. It is further hoped that physicians will urge all patients, especially men past 40 who smoke heavily, to have thoracic roentgenography done every 6 to 12 months and that whenever a shadow is detected prompt exploration should be done if bronchogenic carcinoma cannot be excluded within a short period of time.

3503 Prytania St. (Dr. Ochsner).

21. Overholt,[39] Rigler,[36] Scamman,[37] Boucot.[35]

EFFECT OF CANCER ON LIVER ENZYMES

Jesse P. Greenstein, Ph.D., Bethesda, Md.

There are two general approaches that the chemical analyst may employ in the study of malignant disease. The first of these is the direct chemical analysis of tumors, and comparison of such findings with those obtained in identical fashion on normal tissues and organs. The second approach is the chemical analysis of the tissues, circulating fluids, secretions, and excreta of cancerous patients, and comparison of such findings with those obtained on the same materials from normal persons. In the former case, it is expected that such information will yield a picture of the chemical processes inherent in the neoplastic transformation of tissues. In the latter case, it is expected that such information will give a description of the systemic effects induced by a tumor on the host that bears it, at a site or sites removed from the tumor, and in a state free of metastatic involvement. It is with this second of the chemical analytic approaches that this paper will deal.

Many striking and clear-cut phenomena have been noted in the study of the effects induced in the cancerous patient as a consequence of the presence of a tumor. The unhappily familiar cachexia of patients with advanced neoplastic disease is a clinical symptom of these effects, sometimes exaggerated, sometimes partly masked, as a result of secondary causes, such as bacterial infection, generalized toxemia, malnutrition, and psychic depression, but nevertheless fundamentally due to systemic alterations produced by the tumor on the host. In view of the complexities involved in the study of such effects in the human patient, a great deal of the efforts in this area of cancer research has been conducted on experimental animals.

EXPERIMENTAL APPROACH

The experimental studies that my colleagues and I undertook several years ago were essentially naive and empirical.[1] We investigated a number of chemical and enzymatic systems under the same conditions in the tissues of normal and of cancerous experimental animals which were located at a distance from the tumor. Most of the tumors borne by these animals were of the trans-

Chief, Biochemistry Laboratory, National Cancer Institute, National Institutes of Health, United States Public Health Service, Bethesda, Md.

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1. Greenstein, J. P.: Biochemistry of Cancer, New York, Academic Press, Inc., 1947.