JAMA J AM MED ASSOC
1941, 117, 2215-2222
17487



...ar cysts of the ovaries. Diethylstilbestrol has almost ...inated hysterectomies in cases of functional uterine bleeding. ...re 700 cases of uterine bleeding in our series, in 500 of ...h we would previously have done a hysterectomy. We ...do a hysterectomy just because of uterine bleeding. ...more than 5,000 endometrial biopsies which were taken ...all the way from 1 to 40,000 mg. of diethylstilbestrol had ...given, estrogens, as far as we can observe, do not cause ...cinoma. We have also shown that there is no such thing ...bleeding factor because we have produced uterine bleeding ...children, and in women who have had radium or roentgen ... Estrogenic hormones are apparently the bleeding factor.

Dr. Uball J. Salmon, New York: I regret that the impres... has been created that androgen therapy in women inevitably ...lts in the development of masculinization. This is an unfor... misconception, since it creates an unjustified bias against ...aluable therapeutic agent. We have treated more than 420 ...men with androgens for various gynecologic disorders and ...e encountered some degree of hypertrichosis or hoarseness ...about 7 per cent of the cases. This includes those cases ...ich were treated during the early experimental stage of this ...dy, when we were interested in exploring the biologic proper... of the androgens. With that end in view we had admin... huge doses, in some instances more than 1,500 mg. ...ing one month. Our studies have shown that there is a ...ite threshold for the induction of these masculinization ...nomena, which is about 500 to 600 mg. of testosterone ...ionate a month. The therapeutic dose is very much below ..., varying from 100 to a maximum of 300 mg. a month. ...re are, however, some individual variations in androgen ...eptibility. Brunettes with a slight hypertrichosis appear to ...the most susceptible. The average woman with no ante... ...sutism can be safely given the therapeutic dose ...thout fear of inducing hypertrichosis. We have found that ...quently the smaller doses (100 to 200 mg. a month) will ...ieve satisfactory therapeutic results, particularly in cases of ...menorrhea, premenstrual tension and mastalgia. With these ...aller doses we have encountered no arrhenomimetic effects ...over 200 cases. Furthermore, as regards avoiding these ...henomimetic phenomena, there are certain morphologic signs ...ich indicate androgen saturation. This is determined most ...ply by the vaginal smear, which can be prepared in a few ...utes. The changes in the vaginal cells precede the appear... of the masculinization phenomena, so that the vaginal ...ears can serve as a simple method of guarding against over... ...sage. It is also worthy of note that the arrhenomimetic ...henomena spontaneously regress after the discontinuation of the ...drogens. In regard to the danger of carcinogenesis resulting ...from estrogen therapy, Dr. Geist and I have conducted a study of ...is problem during the past six years on over 200 patients ...ho had been treated with large doses of estrogens, and during ...the last two and one-half years on 180 patients who have been ...planted with estrogen crystals and pellets. In these cases, ...eriodic biopsies of the endometrium and vaginal mucosa failed ...reveal any evidence of any atypical or neoplastic proliferation.

Dr. Samuel H. Geist, New York: The questions raised ...the discussion are so numerous and so broad that it would ...impossible in a short time to attempt even to touch on all ...them. There is one thing that I wish to stress, which ...Dr. Pratt sensed immediately: this work as presented is experi... After all, there must be some venturesome spirits ...among us if we are to establish facts therapeutic or physiologic; ...and we class ourselves as pioneers in this interesting field. It ...only after a long series of experiments by many individuals ...over a period of many years that we shall be able to establish ...the fact that androgens have a definite place in the treatment ...of gynecologic disease. It is possible that they will not. Just ...as the limitations have been put on estrogens so aptly and so ...correctly by Dr. Hamblen, so shall we eventually be able to ...evaluate properly the use and therapeutic indication for andro... ...gens in gynecology.

Dr. E. C. Hamblen, Durham, N. C.: There is only one ...comment which I should like to add: this is in regard to the ...so-called carcinogenic role of estrogens. Reference to possible ...carcinogenic effects by me was only for the purpose of repeat... ...an old clinical warning. It is certain that, in clinical practice, natural estrogenic hormones have not been given, as yet, in such doses and over such periods of time to justify any serious anxiety in this regard. If some of the various estrogenic chemical substances of the diethylstilbestrol type, however, are made available in commerce, their unsupervised employment, i. e. in self medication, their high potency when taken orally and their cheapness may afford a closer approximation of the conditions which have characterized the production of carcinoma by estrogens in experimental animals. Under these circumstances a real danger may be recognized.

---

# BRONCHIOGENIC CARCINOMA

## INCIDENCE IN THE PACIFIC NORTHWEST, WITH A COMMENTARY ON EIGHTY-FOUR CASES

FRANK R. MENNE, M.D.
AND
MELVIN W. ANDERSON, M.D.
PORTLAND, ORE.

Bronchiogenic carcinoma is so designated because of the widely accepted conviction that all primary pulmonary malignant neoplasms of epithelial origin arise from the bronchi or their accessory glands. Most introductory commentaries describe the investigator's interest as being aroused by his encountering an unusual number of cases of bronchiogenic carcinoma. Such experiences with this serious affliction, until recently regarded as extremely rare, have given impetus to numerous dissertations on the subject in many parts of the world.

In like manner, the abrupt appearance of primary cancer of the lung (in 1926) in our autopsy services aroused our interest, and in 1931 we [1] analyzed the basic pathologic, clinical and radiologic characteristics in 16 cases. Shortly thereafter a visit to the different institutes of pathology in Europe elicited, on inquiry, the interesting fact that the percentage of bronchiogenic carcinoma observed at autopsy was increasing in all these institutes.

The literature contains many contributions to the knowledge of the origin, nature and consequences of this form of cancer. Notable among these have been the monograph by Simons,[2] the symposium by Halpert [3] and the contributions by Ochsner and DeBakey.[4] The reader is referred to these for a complete review of the literature. However, there remains some question as to the relative or absolute increase of the incidence, the cause, the exact pathologic classifications and the concomitant symptoms. For this reason additional evidence is herewith presented.

### INCIDENCE

Simons, after an extensive review, expressed the opinion that there was an increase both relative and absolute. This conclusion has been supported by many subsequent investigators. Rice [5] stated that there had been a decided increase in the last five years. Vinson [6] observed a well defined increase ("as frequent as pul-

---

The pathologists of the Northwest cooperated in this study.

From the Department of Pathology of the University of Oregon Medical School.

Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 5, 1941.

1. Menne, F. R.; Bisaillon, Marr, and Robertson, T. D.: Northwest Med. 30:155 (April) 1931.
2. Simons, E. J.: Primary Carcinoma of the Lungs, Chicago, The Year Book Publishers, Inc., 1937.
3. Halpert, Bela: Surgery 8:903 (Dec.) 1940.
4. Ochsner, Alton, and DeBakey, Michael: Carcinoma of Lung, Surg. 42:209 (Feb.) 1941.
5. Rice, Carol M.: J. Lab. & Clin. Med. 21:906 (June) 1936.
6. Vinson, P. P.: Primary Malignant Disease of the Tracheobronchial Tree: Report of One Hundred and Forty Cases, J. A. M. A. 107:258 (July 25) 1936.

89134427

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

monary abscess") during the period 1925 to 1935. Rosedale and McKay [7] found bronchiogenic carcinoma to constitute 7.5 per cent of all carcinoma, being third in the list. Alwens and his associates [8] found a decided rise during the last ten years. Mattick and Burke [9] reported that at the Institute for the Study of Malignant Diseases, of 30,000 persons admitted, showing 18,000 malignant tumors, 73 (1 in every 250) had bronchiogenic carcinoma. This condition occurred with half the frequency of carcinoma of the stomach. A similar comparative observation was reported by Halpert.[2] Brines and Kenning [10] also stated that primary malignant tumor of the lung had developed from obscurity to importance, comprising 10 per cent of all cancer in Germany and being second to carcinoma of the stomach, as observed at autopsy in 3,000 cases. Cramer [11] quoted Peters as pointing out that the bronchiogenic type of neoplasm has advanced from fifth to second place and that in 1930 it constituted approximately 28.05 per cent of all carcinoma in men. Howes and Schenck [12] found 3 per cent of all carcinoma in the Brooklyn Cancer Institute to

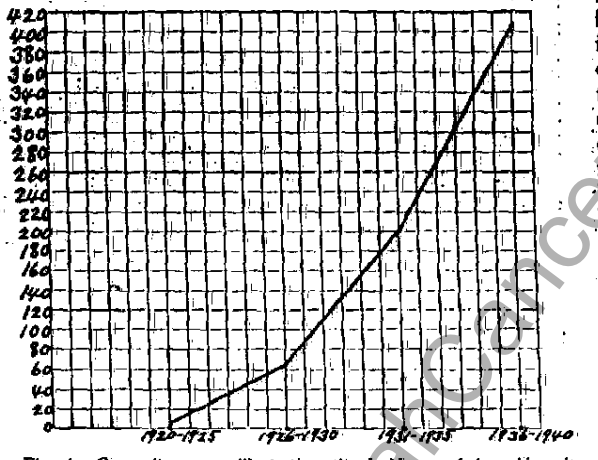


Fig. 1.—Composite curve illustrating the incidence of bronchiogenic carcinoma in the Northwest from 1920 to 1940, as observed at autopsy in 33,945 cases.

be bronchiogenic. Lockwood's [13] percentage was somewhat greater, being 6 to 8. Lockwood further noted that twenty years ago the condition was diagnosed in only 5 per cent of patients during life, while today it is recognized clinically in 80 per cent. It was his conclusion that carcinoma of the lung is on the increase in spite of the improved methods of diagnosis. A report [14] of the Chicago Tumor Institute for a period of two years revealed a smaller incidence of bronchiogenic carcinoma (1.14 per cent of all malignant tumors). Lovelock,[15] while undecided as to the relative or absolute increase, pointed out that European authors often have expressed the view that the increase is relative and not absolute.

Discordant opinions have been voiced by several authors. Stein and Joslin [16] expressed the belief that the increase is due to greater diagnostic accuracy but observed that there was a steady increase as compared with the incidence of carcinoma of the larynx and the lip from 1931 to 1936. Brunn [17] reported 488 instances in 192,271 necropsies (0.24 per cent) from 1898 to 1916. Jaffé [18] noted an incidence of 11.47 per cent of all carcinoma, as compared with one of 10.73 per cent observed in an earlier series of autopsies performed in Vienna (1915 to 1918) and concluded that the increase is more apparent than real. Boyd [19] pointed out that carcinoma of the lung is third in frequency, being exceeded only by carcinoma of the stomach and carcinoma of the large bowel. He recorded 53 instances among 4,500 autopsies (1.2 per cent) from 1925 to 1936 and 64 instances among 2,408 autopsies (2.6 per cent) from 1927 to 1937. This author commented that the worldwide character of the increased incidence has been "phenomenal . . . during the last twenty-five years." However, he concluded that the increase is more apparent than real and that it is due to the recognition of pulmonary carcinoma, the increased facilities for diagnosis and the increased number of autopsies. He further asserted that there was a parallelism between the increase of carcinoma of the lung and the increase of other diseases as revealed by vital statistics. He credited to the use of the bronchoscope and roentgen rays the earlier and more frequent recognition of bronchiogenic carcinoma. In addition, Boyd attributed to the inaccuracy of the differential diagnosis of certain types of bronchiogenic carcinoma from such conditions as Hodgkin's disease and lymphosarcoma a false increase in the incidence of carcinoma of the lung. Middleton [20] regarded the increased span of life and the "clinical and pathologic diagnostic consciousness" as being in part responsible for the apparent gross increase.

Our own experience in the study of the incidence of bronchiogenic carcinoma has been at variance with the conclusion that the increase is more apparent than real. Accordingly, it was decided to determine the occurrence of bronchiogenic carcinoma in the Pacific Northwest. We therefore sent a questionnaire to the members of the Pacific Northwest Society of Pathologists, requesting the incidence observed at autopsy. An analysis of the returns disclosed that from 1920 to November 1940, 33,945 postmortem examinations were made, revealing a total of 517 instances (1.52 per cent) of primary bronchiogenic carcinoma. Some of these were recognized by biopsy and others by combinations of clinical observations, biopsy and final autopsy. For recording the instances, the 20 years was divided into four five-year periods. During the first period, 1920 to 1925, only 3 instances were recorded, 1 at the University of Oregon Medical School (department of pathology) and 2 at the Good Samaritan Hospital. In the second period, 1926 to 1930, 63 cases were noted; from 1931 to 1935, 201, and from 1936 to 1940, 407. The striking increase in the last period as compared with that in the first is undoubtedly due in part to better diagnostic facilities and the presence of pathologists in institutions which had previously had none except in the Vancouver General Hospital, the University of Oregon Medical School and the Good Samaritan Hospital, where both diagnostic facilities and pathologists were available during the entire twenty years. It is significant, however, that during the last two periods, namely 1931 to 1935 and

7. Rosedale, R. S., and McKay, D. R.: Am. J. Cancer 26:493 (March) 1936.
8. Alwens, W.; Bauke, E. E., and Jonas, W.: München. med. Wchnschr. 83:485 (Nov. 6) 1936.
9. Mattick, W. L., and Burke, E. M.: Primary Bronchogenic Carcinoma from Pathologic and Radiologic Points of View, J. A. M. A. 109:2121 (Dec. 25) 1937.
10. Brines, O. A., and Kenning, J. C.: Am. J. Clin. Path. 7:120 (March) 1937.
11. Cramer, H.: Deutsche med. Wchnschr. 63:1259 (Aug. 13) 1937.
12. Howes, W. E., and Schenck, S. E.: Radiology 32:8 (Jan.) 1939.
13. Lockwood, I. H.: South. M. J. 32:30 (Jan.) 1939.
14. Report of the Chicago Tumor Institute, April 1, 1938 to March 31, 1940.
15. Lovelock, J. E.: Brit. M. J. 2:8 (July) 1939.
16. Stein, J. J., and Joslin, H. L.: Surg., Gynec. & Obst. 66:902 (May) 1938.
17. Brunn, H.: Primary Carcinoma of Lung, Arch. Surg. 12:406 (Jan., pt. 2) 1926.
18. Jaffé, R. H.: J. Lab. & Clin. Med. 20:1227 (Sept.) 1935.
19. Boyd, William: Tr. & Stud. Coll. Physicians, Philadelphia, 6: 317 (Feb.) 1939.
20. Middleton, W. S.: Southwestern Med. 24:287 (Sept.) 1940.

Reference Only

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

1936 to 1940, there was an astounding and sharp rise in the incidence. A composite curve (fig. 1) based on the number of carcinomas occurring in the respective five year periods reveals a striking continuous elevation. It has been argued that the greater knowledge of the disease, the increased facilities for diagnosis and the greater number of autopsies adequately explain the greater number of occurrences throughout the two later periods. To ascertain if this was true we compared the yearly percentage of bronchiogenic carcinoma with the number of autopsies in two of the institutions in which trained pathologists had been present during the twenty years and in which diagnostic facilities were standardized in accordance with the developments of the period. It will

In order to determine the accuracy or inaccuracy of the seemingly convincing data, a further analysis of the incidence was made (fig. 3), based on a segregation of the cases of bronchiogenic carcinoma (in the same two institutions) as observed at autopsy during a particular period, into groups of not less than 20.[21] From 1928 to 1933 there were performed at the University of Oregon Medical School 3,129 autopsies, disclosing 23 cases of bronchiogenic carcinoma (0.73 per cent); from 1934 to 1937 there were 2,820 autopsies, disclosing 26 cases (0.92 per cent), while from 1936 to November 1940 there were 2,022 autopsies, disclosing 34 cases (1.68 per cent). Comparatively, in the Vancouver General Hospital from 1928 to 1933 there were 2,111

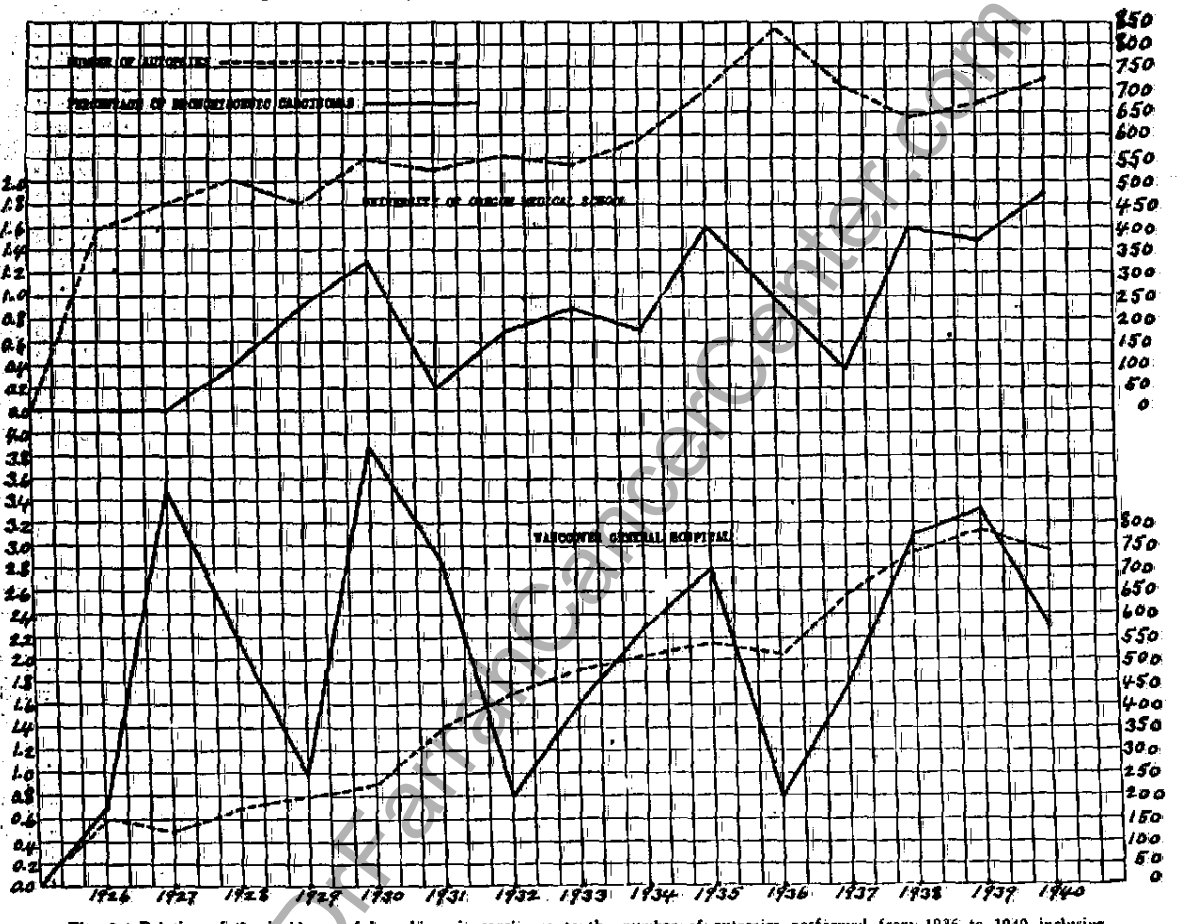


Fig. 2.—Relation of the incidence of bronchiogenic carcinoma to the number of autopsies performed from 1926 to 1940 inclusive.

be noted (fig. 2) that while there was a continuous, steady elevation in the number of autopsies performed throughout the years the percentage of bronchiogenic carcinoma did not parallel the increase in the number of autopsies for a given year and that not infrequently when there was a rise in the number of autopsies there was an actual decrease in the number of bronchiogenic carcinomas. It must be borne in mind that a rising total of autopsies also includes those performed on persons who have died from all causes. Epidemics of influenza or increased numbers of cases of pneumonia and other acute conditions may increase the number of deaths and the percentage of autopsies so that there may be an actual fall in the relative percentage of bronchiogenic carcinoma based on the total number of autopsies performed.

autopsies, disclosing 35 cases of bronchiogenic carcinoma (1.65 per cent), from 1934 to 1937, 2,206 autopsies and 40 cases (1.81 per cent), and in the final period (1938 to November 1940) 2,244 autopsies and 56 cases (2.49 per cent) (fig. 3). There is a striking parallelism in the incidence similar to that seen in figure 2.

The higher percentage at the Vancouver General Hospital in the periods stated may be attributed to less generalization in the performance of autopsies. That is to say, a greater percentage of autopsies may have been performed on all patients with bronchiogenic carcinoma, because of the unusual character of their disease, than

21. In determining the variations due to the laws of chance, as evidenced in a mathematical curve, a reasonably uniform number of not less than 20 must be selected. The greater the number in groupings of this kind, the more accurate is the percentage.

89134429

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

on patients with other conditions, whose death was not due to a malignant tumor. However, the number of cases during these periods at the Vancouver General Hospital was almost twice as great as that at the University of Oregon Medical School. By the same token, the percentage of error in estimating the incidence would be twice as accurate as that used in estimating the incidence at the University of Oregon Medical School. Since there is a striking parallelism, the accuracy of the incidence is enhanced. It would seem, therefore, from the preponderance of evidence submitted in reports in the literature as well as from a careful analysis of our own statistics and those available in the Pacific Northwest, that there is both a relative and an absolute increase of bronchiogenic carcinoma.

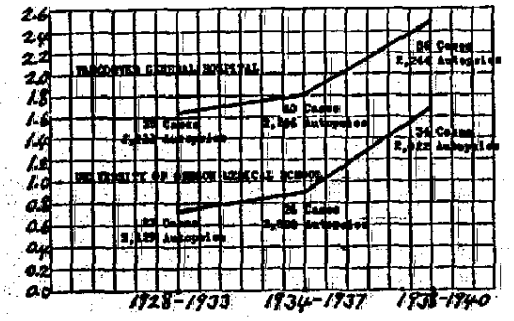


Fig. 3.—Relation of the incidence of bronchiogenic carcinoma to the number of autopsies performed in the University of Oregon Medical School and in the Vancouver General Hospital during three year periods.

## ETIOLOGY

Since it seems evident that there is an absolute increase, the reason for it becomes of paramount importance. (See Simons [2] and others for detailed consideration.) The disease may be in such an early stage and so indefinite in its clinical aspects (Middleton [20]) as to escape detection until therapeutic procedures become extremely difficult. Even when it is recognized in the early stages, radical surgical removal has its dangers both as to mortality and as to altered physiology. All other methods of therapy are still of questionable value. It is accordingly of vital importance to consider the possible causes and to institute proper preventive measures. Unfortunately, study of our own series of cases as well as others yields nothing but speculative opinion as to the possible cause of bronchiogenic carcinoma. Much stress has been laid on the influence of prolonged and severe respiratory infections (e. g. influenza, pneumonia, tuberculosis) by Rice,[5] Vinson,[6] Brines and Kenning,[10] Cramer,[11] Turner and Willis,[22] Dressler and Weigl,[23] Kramer and Som,[24] and others. We also have been convinced that any continuous respiratory irritant or infection producing repeated denuding with reepithelization of the bronchial mucosa will either result or aid in the establishment of a malignant pattern.

Contamination of the air in areas of congested traffic and industry is receiving increased attention. Rosedale and McKay [7] and Dressler and Weigl [23] incriminated chromate dust as provocative in chemical industrial workers. Continued emphasis is being placed on the role of coal dust, chemical agents, radioactive substances and silicosis in mining and other industries (Charr,[25] Stein and Joslin,[16] Turner and Willis,[22] Lockwood,[13] Lovelock,[15] Lynch and Smith [26] and Dressler and Weigl [23]).

More recently investigators have turned their attention to the possible influence of the increased use of smoking tobacco (especially the marked increase in the use of cigarets). Myers [27] pointed to the enormous increase in the number of cigarets consumed in this country. In 1880, 582,718,995 cigarets were consumed, in comparison with 169,847,245,964 in 1937. Myers noted also that the toxic products of the combustion and distillation of tobacco are carbon monoxide, ammonia, formaldehyde, methylamine, methane, methyl alcohol, hydrogen sulfide, pyridine, furfural, arsenic and hydrocyanic acid. Of these the nicotine and tar contents are thought to be the most harmful. The former is an irritant of mucous membranes and the latter is regarded as carcinogenic. Myers [27] stated that "the smoking habits unquestionably increase the liability to cancer of the mouth, throat, esophagus, the larynx and the lungs." Cramer [11] noted that habitual smoking producing chronic inflammation of the mouth, pharynx, larynx and bronchial mucosa was present among the steel workers studied by him. In comparing the influence of tobacco smoking with that of the gases coming from automobile exhausts, Cramer [11] demonstrated that a 5 Gm. cigar yielded 200 mg. of tar (phenanthrene), while an eight hour drive 10 meters behind an automobile resulted in the collection of only 1.5 mg. of a similar tar. This author appeared to be convinced of the influence of tobacco smoking in the causation of bronchiogenic carcinoma. Roffo [28] stated that "the tobacco tars are very strong cancer producing agents and that they are in the "same form as the coal tars and certain substances whose properties are very like those of the hydrocarbons distilled out of coal in their fluorescence and their spectrometry." He produced

*Frequency of Various Symptoms and Signs with the Two Types of Bronchiogenic Carcinoma in Forty-Four of Fifty-Six Cases in Which Autopsy Was Done*

| Salient Symptoms | Group 1 (Carcinoma of Hilar Nodular Type) Number | Group 1 Percentage | Group 2 (Carcinoma of Diffuse Necrotic Type) Number | Group 2 Percentage |
|---|---|---|---|---|
| Cough | 8 | 27.6 | 4 | 26.6 |
| Cough with expectoration | 19 | 65.5 | 9 | 60.0 |
| Hemoptysis | 14 | 48.2 | 3 | 20.0 |
| Dyspnea | 18 | 62.0 | 6 | 40.0 |
| Cyanosis | 4 | 13.7 | 2 | 13.3 |
| Pain | | | | |
| Mediastinal | 6 | 20.6 | 0 | 0 |
| Pleural | 1 | 3.4 | 7 | 46.6 |
| Intercostal | 1 | 3.4 | 0 | 0 |
| Unspecified | 6 | 20.6 | 2 | 13.3 |
| Other than in chest | 7 | 24.1 | 1 | 6.6 |
| Atelectasis | 11 | 37.9 | 3 | 20.0 |
| Empyema | 2 | 6.9 | 1 | 6.6 |
| Pleural effusion | 5 | 17.2 | 5 | 33.3 |
| Abscess of lung | 5 | 17.2 | 3 | 20.0 |
| Gangrene of lung | 2 | 6.9 | 3 | 20.0 |
| Hemothorax | 0 | 0 | 3 | 20.0 |
| Hoarseness | 3 | 10.3 | 1 | 6.6 |
| Cerebral and spinal symptoms | 6 | 20.6 | 0 | 0 |
| Ascites | 1 | 3.4 | 0 | 0 |
| Weakness and weight loss | 8 | 27.5 | 3 | 20.0 |
| Hemopericardium | 1 | 3.4 | 0 | 0 |
| Pancreatic fat necrosis | 1 | 3.4 | 0 | 0 |
| Lymphatic and venous obstruction | 2 | 6.9 | 0 | 0 |
| Total cases studied | 29 | | 15 | |
| | 41 | | | |

22. Turner, E. K., and Willis, R. A.: M. J. Australia 2:866 (Nov. 19) 1938.
23. Dressler, M., and Weigl, A.: Schweiz. med. Wchnschr. 69:763 (Aug. 26) 1939.
24. Kramer, R., and Som, M. L.: Bronchoscopic Study of Carcinoma of Lung, Arch. Otolaryng. 23:526 (May) 1936.
25. Charr, R.: Am. J. M. Sc. 194:535 (Oct.) 1937.
26. Lynch, K. M., and Smith, W. A.: Am. J. Cancer 36:562 (Aug.) 1939.
27. Myers, J. L.: Tr. Am. Laryng. A. 62:340, 1940.
28. Roffo, A. H.: Bol. Inst. de med. exper. para el estud. y trat. d. cáncer 15:406 (Sept.) 1938; cited by Myers.[27]

Document is NOT an official record

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

cancers by the application of tobacco tars to the ears of rabbits. He pointed out that "one can easily see large opportunity of cancerization in a regular smoker who consumes 1 kilogram of tobacco monthly, which means 70 cc. of tar." In this manner Roffo[28] reasoned that "the average smoker loads in one year 840 cc. and in ten years over 8 liters of tar on his buccopharyngo-

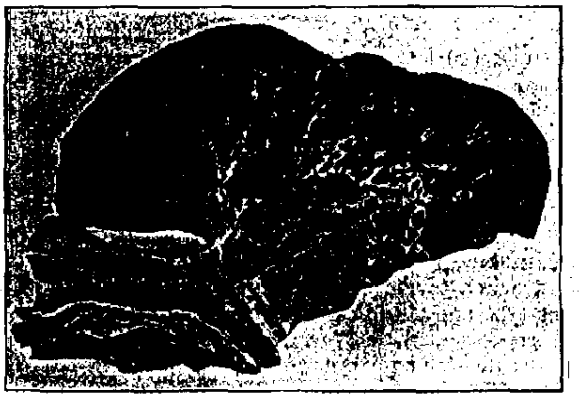

Fig. 4.—Encasement of the left primary and secondary bronchi by the new growth, hilar nodular bronchiogenic carcinoma.

laryngopulmonary membranes, which certainly have not the biologic resistance of the skin of a rabbit." Turner and Willis[22] observed bronchiogenic carcinoma in a gold miner who had influenza and smoked ½ pound (226 Gm.) of black tobacco a week.

Certainly the striking predominance of bronchiogenic carcinoma in men as compared with the incidence among women suggests either that in the industries men come in contact with an irritating substance or that the increased consumption (smoking) of tobacco by men as compared with its use by women is of great significance. It would seem that more careful recording of the histories to how much particular persons smoke would be of great value in determining the causal relation of the use of tobacco to bronchiogenic carcinoma. The average inquiry simply elicits information that the patient is or is not a user of tobacco. It is too early as yet to observe in the statistics of the literature the possible influence that tobacco smoking may exert on the incidence of bronchiogenic carcinoma in women, who are now smoking cigarets, often more excessively than do men. A report by Rice,[8] although it concerned a small number of patients (18 men and 12 women) seemed to indicate an increase among the women.

It seems obvious that the causative agent producing bronchiogenic carcinoma not only is air borne but is in a volatile state, since it involves the two lungs with almost equal frequency. Adequate information concerning correlative inflammatory phenomena in relation to the cause of bronchiogenic carcinoma is not at hand, since the average postmortem examination fails to comb completely the lung structure for initial lesions which might more accurately betray the influence of such phenomena. In the 4 instances of early bronchiogenic carcinoma to be reported by Hunter and his associates,[29] there were no clinical or gross pathologic evidences of such lesions. They were accidentally uncovered in the routine seelction of lung tissue for histologic study. Here then lies a field that needs more intensive tilling. At the time fully developed carcinoma of the lung is recognized there is considerable difficulty in defining cause and effect.

29. Hunter, W. C.: Unpublished data.

## PATHOLOGY

In a previous communication we[1] discussed the extrinsic manifestations of the disease in relation to the existence of bronchiogenic carcinoma. At the time we pointed out that in 75 per cent of the instances there was bilateral chronic fibrous pleuritis indicating a previous inflammatory process of some moment. In addition there were acute empyema and other changes due to metastatic extensions in the mediastinum. In the majority of the instances the disease process had progressed so as to produce retraction of the mediastinal structures in the direction of the involved lung.

We were able to determine two more or less definite outstanding macroscopic types. One, in which the major lesions, at least in the less advanced stages, seemed to be that of maximum hilar accumulation, we designated the hilar nodular type; another, in which there was a diffuse involvement with a minimum of hilar concentration, was termed the diffuse necrotic type (figs. 4 and 5). Among 56 cases of bronchiogenic carcinoma in which autopsy was performed the carcinoma was of the hilar nodular type in 35 (62.5 per cent) and of the diffuse necrotic type in 21 (37.5 per cent). Regional pulmonary or lymphatic metastases occurred in all instances. Distant metastases were observed in 45. Whether this gross classification is of value may be open to question. Simons[2] quoted Aschoff as applying a macroscopic classification as follows: "(1) small nodular masses arising from bronchi of the first to the third order; (2) the infiltrating type in which a large portion of the lung or an entire lobe is involved." Rabin and Neuhof,[30] in a morphologic study of 100 cases (in which autopsy was done), divided bronchiogenic carcinoma into two main types, "circumscribed and noncircumscribed." The foregoing concepts of the pathologic classification of bronchiogenic carcinoma are similar to the one advanced by us in a previous communication.

Our studies led us to conclude that the majority of cancers of the lung arise in the primary and secondary

Fig. 5.—Diffuse character of the involvement of the lung; diffuse necrotic bronchiogenic carcinoma.

divisions of the bronchi. At autopsy confusion of growth and its consequences make localization difficult. Carcinoma of the so-called diffuse necrotic type in general arises in the more distal bronchi; however, variations in type are not entirely due to location but are in part patterns of a varied pathogenesis. Vinson[6]

30. Rabin, C. B., and Neuhof, H. A.: J. Thoracic Surg. 4:147 (Dec.) 1934.

89134431

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

observed primary carcinoma in the trachea in 4 cases and in the bronchi in 87. Kramer and Som [24] concluded that 80 to 90 per cent originated in the bronchi, with 20 per cent of "parenchymal" origin. There is unanimity of opinion as to the more or less equal involvement of the lungs with a slightly increased incidence in the right (ratios given are, e. g., 6:4, 20:16 and 38:33). Of the 56 instances observed by us in detail, carcinoma was in the right lung in 28 and in the left in 27. Kramer and Som [24] in 100 postmortem examinations found the distribution of bronchiogenic carcinoma to be as follows: in the right lung—main bronchus 18, upper lobe 31, middle lobe 1 and lower lobe 12; in the left lung—main bronchus 8, upper lobe 17 and lower lobe 13. Carcinoma is observed in almost twice as many upper lobes as lower lobes. There is as yet no concrete evidence of bronchiogenic carcinoma's arising from atrial lining cells.

### MICROSCOPIC STUDY

Many conflicting views are recorded as to the value and importance of histologic studies from both the academic and the practical point of view. Karsner and Saphir [31] expressed the opinion that the histologic classification of bronchiogenic carcinoma is the most satisfactory. The observations of Fried [32] with respect to the significance of the "reserve" cell type have permeated and influenced the considerations of the histology of bronchiogenic carcinoma. Practically all discussions confirm the existence of definite squamous cell types. The confusion of classification arises in proportion to the degree of anaplasia. Study of the cell structure of the tumors of 56 patients on whom autopsy was done revealed that 31 tumors were distinctly of the squamous cell type, with 9 disclosing keratinization, 15 showing no keratinization and 7 being distinctly anaplastic. Thirteen were found to be of the so-called adenocarcinomatous type, with only 2 showing mucus production. Eight were distinctly of the reserve cell type, 1 of the round cell type and 3 of the spindle or oat-shaped cell type. Again we wish to emphasize, as we did in our previous communication, that epithelial metaplasia with a subsequent malignant formation in the bronchi may result in all of the variable histologic types mentioned. We are of the opinion that with the so-called adenocarcinomatous type, except with growths arising from the mucous glands, the formation of acini is in part dependent on the structure of the lung and is more apparent than real. From the foregoing analysis it is obvious that the more or less confusing types of bronchiogenic carcinoma are decidedly in the minority. We refer in particular to the basal or reserve cell, round cell and spindle cell types. These constitute about 20 per cent of the total. There is, however, no particular confusion in recognizing the distinctly reserve cell type, so that there actually remains less than 1 per cent of primary carcinoma of the lung which may be confused with such lesions as lymphosarcoma. Vinson,[6] using the Broders method of grading, pointed to its advantage in the application of various kinds of therapeutic irradiation. He concluded that the so-called adenocarcinoma is the most radiosensitive.

### PATHOGENESIS

The progressive and subsequent pathologic changes in bronchiogenic carcinoma are obviously primarily dependent on the status quo of lung structure, the bacterial flora and the site of the initial growth. When neoplasia originates in the primary or secondary bronchi, the direction of growth is, as we [1] have pointed out before, usually in the direction of the lumen. With the type designated by us as hilar nodular, analysis disclosed the sequence to be as follows: (1) hypertrophy, hyperplasia and metaplasia of the epithelium of the bronchus (carcinoma in situ); (2) partial or complete occlusion of the bronchus; (3) extension through the bronchial wall, with excitation of wandering cell infiltration and fibrosis; (4) further extension through the lymphatics; (5) involvement of the hilar lymph nodes, and (6) limited and slow massive extension into the lungs. With this type thromboses, coagulation necroses and secondary infectious processes are late in developing. The so-called diffuse necrotic type appears to us to be a manifestation of a more distant initiation in which the more delicate structure of the bronchus or bronchiole permits easier access to the surrounding lymphatics, with greater obstruction to the circulation. Primary carcinoma of this type appears to progress by (1) hypertrophy and hyperplasia of the epithelium (reserve cell type); (2) early extension into peribronchial lymphatics, with intrapulmonary lymphatic stasis; (3) engorgement and thrombosis of blood vessels; (4) secondary lobular pneumonic infection; (5) diffuse carcinosis; (6) coagulation necrosis with miliary abscess formation; (7) bronchiectasis limited to terminal bronchi, and (8) regional hilar node involvement, occurring in considerably less degree and later in the course of the disease. The carcinosis is characterized by spread through a definite lymphatic distribution in the lung as well as by continuity into tissue spaces. Pleurisy with effusion, because of extension to the pleura, is more frequent with this type. Furthermore, because of the earlier and more diffuse involvement of lymphatics and blood vessels, distant metastases (e. g. to the brain) are more common.

### CLINICAL ASPECTS

No attempt will be made in this dissertation to analyze critically the various clinical concepts advanced in the literature by numerous writers. There is, however, universal agreement that the symptoms of bronchiogenic carcinoma are widespread and variable. Most writers on the subject agree that one must recognize two sets of symptoms and signs, those referable to the lungs and those arising from metastases in organs and tissues outside the chest. In our previous communication we attempted to correlate the symptoms, signs and radiologic data characteristic of bronchiogenic carcinoma in general and specifically of two more or less distinctive types (hilar nodular and diffuse necrotic).

In the present series of 84 cases, the average age was 55½ years, with a range of 38 to 77 years. In 78 cases the disease occurred in men and in 6 in women (13 to 1). These data are in agreement with those of the majority of reports. In a number of our cases adequate clinical data were not available, but in 44 of the 56 cases in which autopsy was done they were sufficiently complete to permit comparative evaluation of the signs and symptoms. In 29 of the 44 the carcinoma was of the hilar nodular type, and in 15 it was of the diffuse necrotic type (see accompanying table). An analysis of the salient symptoms and signs disclosed that cough with expectoration was the most frequent symptom, occurring in two thirds of the cases of both types of carcinoma. This was associated with hemoptysis in approximately half of the patients with hilar nodular

31. Karsner, H. T., and Saphir, Otto: Am. J. Path. 6: 553 (Sept.) 1930.
32. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932.

Document Concerning Tobacco

89134432

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

carcinoma (group 1) but in only 20 per cent of the patients with diffuse necrotic carcinoma (group 2). Dyspnea was the second most common symptom. It was especially severe in group 1 (occurring in 60 per cent) and less pronounced in group 2 (occurring in 40 per cent). Cyanosis was present in 13 per cent of the patients and was frequently stated to be a terminal event. The time and location of the pain were significant in that 20 per cent of the patients of group 1 complained of mediastinal pain characterized as dull, substernal and deep seated. This pain was not present in group 2, but the majority of patients in this group evidenced pleural pain, indicative of metastatic or inflammatory involvement of the pleura. The third type of pain in the chest, which is frequently credited to involvement of the intercostal nerves or roots, was present in only 1 patient of group 1.

In 8 instances the type of pain in the chest was unspecified, and in an equal number pain occurred in locations other than the chest. The pain in all 16 was due to metastatic involvement of organs and tissues evidencing distress.

A significant condition definitely related to the pathogenesis was atelectasis in 38 per cent of the patients with the hilar nodular type (group 1) and in 20 per cent of those with the diffuse necrotic type (group 2). Empyema, pulmonary abscess and gangrene, which are complications due to the extension of the growth and are evidences of secondary infection, tended to be more frequent in the patients of group 2. Hemothorax, in our series, occurred only in patients of group 2 (20 per cent). Hoarseness, stated to be a frequent complication of mediastinal extension, was present in 10 per cent of group 1 and in only 1 patient of group 2. Weakness and loss of weight were common complaints in both groups.

In summary, it may be pointed out that approximately half the patients with hilar nodular carcinoma presented symptoms referable primarily to the lungs, while an equal number had symptoms attributable to metastasis. On the other hand, of the patients with diffuse necrotic carcinoma twice as many had symptoms traceable to metastasis as had symptoms referable to the lungs. It is apparent that symptoms originating in the lungs, such as cough, expectoration and dyspnea, occur more frequently in the earlier stages of the disease and are more common in patients with hilar nodular carcinoma. Conversely, the symptoms and signs resulting from pleurisy, pulmonary abscess, empyema, hemorrhage, dyspnea, cough, hoarseness, aphonia and neurotic involvement are more frequent with diffuse necrotic carcinoma. Apparently the last six symptoms are due to the earlier tendency to metastasize as well as to the earlier obstruction of smaller pulmonary units and their surrounding lymphatics and blood vessels. While there may be some criticism as to the feasibility of the clinical and pathologic division of bronchiogenic carcinoma into the types described, it seems to us that the variability of the initial site of bronchiogenic carcinoma may be expected to and does result in fundamentally different clinical and pathologic pulmonary carcinomatous lesions.

## SUMMARY

1. Bronchiogenic carcinoma was observed 517 times during a series of 33,945 autopsies performed in the Pacific Northwest.

2. Statistical analysis based on the number of autopsies, time periods and chance variations indicate an absolute increase in the incidence of primary pulmonary carcinoma in recent years.

3. Emphasis is laid on the etiologic significance of inflammatory processes augmented by volatile irritants, such as tobacco smoke and gaseous products of the industries.

4. Eighty-four instances of bronchiogenic carcinoma were observed in the department of pathology; 78 of the patients were men and 16 women; autopsy was performed in 56 cases.

5. Bronchiogenic carcinomas are classified macroscopically into two types, hilar nodular and diffuse necrotic.

6. Histologic examination of the neoplasm in the 56 cases in which autopsy was done revealed that in 31 it was squamous cell carcinoma, in 13 so-called adenocarcinoma and in 12 reserve cell carcinoma.

## ABSTRACT OF DISCUSSION

DR. HOWARD T. KARSNER, Cleveland: Although not always evident, there is value in analysis of the geographic distribution of disease. Climatic, occupational and perhaps dietary and other factors may be different in some respects in the Pacific Northwest from those which prevail elsewhere. It is therefore of interest to learn that bronchiogenic carcinoma is as common in that region as it is in other parts of the country. The authors review again the discussion concerning an increased incidence of this disease. There can be no doubt of a relative increase, but there may well be some question as to absolute increase. The population of the autopsy room is different from the living population, because it is a population determined by numerous factors of opportunity and interest. In ten years at the Cleveland City Hospital, 1927 to 1937 inclusive, bronchiogenic carcinoma constituted 9.4 per cent of all cases of malignant tumor examined at autopsy. No one would claim that about 1 of 10 living patients with malignant tumors has bronchiogenic carcinoma. If autopsy statistics were a guide in this connection it could be said that carcinoma of the lung arising in an obsolete primary tuberculous focus is on the increase because we have seen 3 such instances in the last year as compared with none in the preceding ten years. It is difficult to employ statistical analyses in determining absolute increase because there is no certain way to provide mathematical corrections that would fully account for improved diagnosis, special attention to the lesion, accurate interpretations of roentgenograms and precision of bronchoscopic examinations and biopsy. Nor are the errors inherent in the improved methods fully evaluated. For example, we have seen within a period of six months pneumonectomy in 2 cases not suitable for biopsy through the bronchoscope but characteristic in every way of bronchiogenic carcinoma. One was metastatic from a thyroid carcinoma treated surgically twenty years before and the other metastatic from an unnoticed malignant granulosa cell tumor of the ovary. No formula has yet been devised that meets all the factors of error, largely because these factors are not yet calculable. An absolute increase cannot be denied, nor is it fully established. The influence of various factors supposed to be responsible for an absolute increase is still in doubt. There is certainly no proved connection with epidemics of influenza, nor is there any frequency of association with pulmonary tuberculosis. Silicosis may be of importance but accounts for relatively few cases. Whatever accounts for the Joachimsthal cases does not prevail widely. If tobacco smoking were of significance, there should be an increasing incidence in women.

DR. BÉLA HALPERT, New Orleans: The contribution of Dr. Menne and Dr. Anderson presents evidence that there is a relative as well as an absolute increase in carcinoma of the lung. Their data from the Pacific Northwest on necropsy material are almost identical with those reported by Rosahn from the East and with our own data from the South. Carcinoma of the lung, in fact, is becoming the second if not the first most common malignant neoplasm in the male. Chronic irritations from infections, inhalation of gases, foreign bodies and

89134433

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055

particularly smoking of tobacco with its nicotine and tar content may play a part, but perhaps more important is the fact that more people are reaching the cancer age. Whether the gross morphologic classification according to location and extent of the growth as suggested by Dr. Menne and the one by Dr. Karsner have any practical value remains to be seen. At present there are no gross criteria by which the cellular structure can be ascertained without microscopic examination. In looking for effective therapy the cellular structure is a decisive factor. It seems certain that successful radiotherapy of carcinoma of the lung is as yet impracticable. So, for the present, the only effective treatment is early recognition and, as suggested by Graham, Rienhoff, Overholt, Ochsner and DeBakey, Churchill and others, surgical removal of the involved lung—pneumonectomy.

DR. L. WALLACE FRANK, Louisville, Ky.: In my intern days, over twenty-five years ago, cancer of the lung was rare. Today it is exceedingly common. About four years ago I came to the conclusion that the probable cause of the increase of pulmonary cancer was related to the rapid increase in the number of automobiles and the increased use of tarred roads. I intended to work out a series of experiments to prove whether or not this was so but in studying the literature found that Campbell of England had already done the work. He studied mice, in which the known incidence of pulmonary carcinoma was 14 per cent. He took one group as controls and over the others blew twice daily the dust and scrapings from the roadways, most of which were made of some tar preparation. The incidence of pulmonary carcinoma in the second group was 76 per cent, compared with 14 per cent in the controls. I am of the opinion that Campbell's studies throw a great deal of light on the cause of the increase of pulmonary cancer.

DR. ISRAEL DAVIDSOHN, Chicago: When one evaluates all the factors which might have some significance in connection with the question of the absolute or relative increase of carcinoma of the bronchi, it seems worth while to point out the fact that until about 1926 the type of bronchiogenic carcinoma now referred to as reserved cell carcinoma was frequently mistaken for a primary sarcomatous growth of the lymph nodes in the mediastinum. The recognition of the true histogenesis of this tumor must of necessity influence the statistics of bronchiogenic carcinoma. I should like to ask the authors whether they have separated in their series the apical carcinoma originating in the peripheral bronchi, which, owing to its invasion of the bones in the region of the upper thoracic aperture and of the nerves, produces a very characteristic clinical picture (the so-called superior pulmonary sulcus tumor of Pancoast).

DR. FRANK R. MENNE, Portland, Ore.: As far as Pancoast's tumor is concerned, we did not encounter it. We have some papillary carcinomas occurring in association with apical scars that will be reported subsequently. I appreciate that several classifications of carcinoma of the lung have been advanced. Of course, when one deals with statistics one gets into trouble. I want to emphasize, however, again the fact that bronchiogenic carcinoma seems to me to be present out of all proportion to our increased knowledge, either clinically or pathologically, of this incidence, irrespective of the locality. I want also again to emphasize the fact that those carcinomas of the lung that are confused with primary tumors of the lymph in the lymph nodes or the lymphocytes or Hodgkin's disease are a small percentage of the bronchiogenic carcinomas that have been present in our experience.

**Lazy Medicine.**—That sort of medicine is lazy medicine. It is easier to get the answer out of a machine or out of laboratory reports than to sit down and think for yourself. Or at least the users of the machine think it is. In any event, it satisfactorily puts off until tomorrow, and perhaps forever, the examination you don't want to make today. The machine is made a substitute for thought. Unfortunately it is not invariably the correct answer which comes out; sometimes the machine speaks with the guile of the Delphic oracle, though the hearer does not realize it. And machine medicine may be not only lazy medicine, it may be dishonest medicine.—Atkinson, Miles: Behind the Mask of Medicine, New York, Charles Scribner's Sons, 1941.

# NORMAL AND ABNORMAL BACTERIAL FLORA OF THE NOSE

LEON ORRIS JACOBSON, M.D.
AND
GEORGE E. DICK, M.D.
CHICAGO

The frequency with which an abnormal bacterial flora was found in cases of frank nasal infection and in the nasal passages of persons without objective changes in the nasal mucosa or subjective symptoms of sinus infection led us to undertake a systematic and comprehensive study of the bacteriology of the nose.

## METHODS

The nasal secretion of 500 consecutive patients admitted to our general medical service was cultured. The age of the patients varied from 4 weeks to 78 years. Cultures were made by inserting a sterile swab far back into the nasal cavity and streaking a blood (sheep blood) agar plate directly. Material from each side of the nose was cultured separately. In some cases cultures were made in the same manner with Löffler's medium. Cultures were made of sterilely obtained antral washings by inoculating nutrient broth, dextrose broth and blood agar plates. Cultures thus obtained were incubated at 37.5 C. for twelve to twenty-four hours, and the organisms were then identified by the appearance of the colonies, appropriate staining procedures and bile solubility tests. In many instances, cultures were made repeatedly during the initial hospitalization, return visits of outpatients or readmission.

## RESULTS

The organisms found in the nasal passages varied considerably except for the constant presence of Staphylococcus albus and diphtheroid bacilli (table 1).

In every instance except 2 in which organisms other than staphylococci, diphtheroid bacilli and Micrococcus catarrhalis were isolated on culture from the nasal passages, abnormal changes or conditions existed in the nasal cavity and/or the paranasal sinuses. The 2 exceptions were the only instances in which green-forming streptococci were isolated from the nasal passages and could not be found on repetition of the culture. No abnormalities were demonstrable either clinically in the nasal cavity or by roentgenogram in the paranasal sinuses in these 2 cases. On the other hand, staphylococci and diphtheroid bacilli were found on culture in every case, whether or not there were objective changes in the nasal passages or the paranasal sinuses. Cultures of nasal secretion taken from patients with the "common cold" or an increased nasal discharge from any cause always showed an increase in the number of colonies of staphylococci and diphtheroid bacilli, regardless of what other organisms, if any, might be present. Children with the "common cold" frequently had pneumococci in the culture.

The organisms cultured from material from the nasal passages (other than staphylococci, diphtheroid bacilli and M. catarrhalis) were associated with many varied abnormalities of the upper respiratory tract. Sinusitis of the acute purulent, chronic purulent or chronic hyperplastic (nonpurulent) type was the condition most frequently encountered. The cultures of nasal secretion (tables 2, 3 and 4) most frequently showed green-forming streptococci, pneumococci or hemolytic strepto-

From the Department of Medicine, The University of Chicago.

89134434

Source: http://industrydocuments.library.ucsf.edu/tobacco/docs/xqkg0055