FILE NAME: Kent (KNT)

DATE: 1950 May 27

DOC#: KNT116

DOCUMENT DESCRIPTION: Journal Article - Tobacco Smoking as a Possible Etiologic Factor in Bronchiogenic Carcinoma - The Journal of the American Medical Association

early smoking epi papers

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 143, No. 4 — CHICAGO, ILLINOIS — MAY 27, 1950

COPYRIGHT, 1950, BY AMERICAN MEDICAL ASSOCIATION

TOBACCO SMOKING AS A POSSIBLE ETIOLOGIC FACTOR IN BRONCHIOGENIC CARCINOMA

A Study of Six Hundred and Eighty-Four Proved Cases

ERNEST L. WYNDER
and
EVARTS A. GRAHAM, M.D.
St. Louis

General Increase.—There is rather general agreement that the incidence of bronchiogenic carcinoma has greatly increased in the last half-century. Statistical studies at the Charity Hospital of New Orleans (Ochsner and DeBakey),[1] the St. Louis City Hospital (Wheeler)[2] and the Veterans Administration Hospital of Hines, Ill. (Avery)[3] have revealed that at these hospitals cancer of the lung is now the most frequent visceral cancer in men.

Autopsy statistics throughout the world show a great increase in the incidence of bronchiogenic carcinoma in relation to cancer in general. Kenneway and Kenneway,[4] in a careful statistical study of death certificates in England and Wales from 1928 to 1945, have presented undoubted evidence of a great increase in deaths from cancer of the lung. In this country statistics compiled by the American Cancer Society show a similar trend during the past two decades.[5]

Tobacco as a Possible Cause of Increase.—The suggestion that smoking, and in particular cigaret smoking, may be important in the production of bronchiogenic carcinoma has been made by many writers on the subject even though well controlled and large scale clinical studies are lacking. Adler[6] in 1912 was one of the first to think that tobacco might play some role in this regard. Tylecote,[7] Hoffman,[8] McNally,[9] Lickint,[10] Arkin and Wagner,[11] Roffo[12] and Maier[13] were just a few of the workers who thought that there was some evidence that tobacco was an important factor in the increase of cancer of the lungs. Müller[14] in 1939, from a careful but limited clinical statistical study, offered good evidence that heavy smoking is an important etiologic factor. In 1941 Ochsner and DeBakey[15] called attention to the similarity of the curve of increased sales of cigarets in this country to the greater prevalence of primary cancer of the lung. They emphasized the possible etiologic relationship of cigaret smoking to this condition. In a recent paper Schrek[16] concluded that there is strong circumstantial evidence that cigaret smoking is an etiologic factor in cancer of the respiratory tract and finds that his data are in agreement with the results of a preliminary report presented by Wynder and Graham at the National Cancer Conference in February 1949.[17]

Purpose of Study.—The purpose of the present study was to attempt to determine, so far as possible by clinical investigations, statistical methods and experimental studies, the importance of various exogenous factors that might play a role in the induction of bronchiogenic carcinoma. In this regard we intended to learn the relative importance of previous diseases of the lungs, rural and urban distribution of patients, various occupations and hereditary background as well as smoking habits. By obtaining all this information, we hoped to determine whether any of these factors, either singly or in combination, have had an effect in increasing the incidence of bronchiogenic carcinoma.

In the present paper the chief emphasis will be placed on our findings in regard to smoking.

METHOD OF STUDY

The results of this study are based on 684 cases of proved bronchiogenic carcinoma. It should be emphasized that the results in this report have not been obtained from hospital records since we learned at the outset of our study that the routine records did not supply satisfactory answers to our questions. It was therefore decided to seek the desired information by special interviews. Six hundred and thirty-four patients reported on in this paper have been personally interviewed, and in 33 cases we obtained the information by mailing a questionnaire.[18] In the remaining 17 cases information for the questionnaire was obtained from a person who had been intimately acquainted with the patient throughout his adult life.

From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

This study has been aided by a grant from the American Cancer Society. Other phases of it will be presented in subsequent publications.

1. Ochsner, A., and DeBakey, M.: Surgical Considerations of Primary Carcinoma of the Lung, Surgery **8**: 992-1023 (Dec.) 1940.
2. Wheeler, R.: Personal communication to the authors.
3. Avery, E. E.: Personnal communication to the authors.
4. Kenneway, N. M., and Kenneway, E. L.: A Study of the Incidence of Cancer of the Lung and Larynx, J. Hyg. **36**: 236-267 (June) 1936. Kenneway, E. L., and Kenneway, N. M.: A Further Study of the Incidence of Cancer of the Lung and Larynx, Brit. J. Cancer **1**: 260-298 (Sept.) 1947.
5. Statistics on Cancer, New York, American Cancer Society, Statistical Research Division, 1949, p. 19.
6. Adler, I.: Primary Malignant Growths of the Lungs, and Bronchi, New York, Longmans, Green and Co., 1912.
7. Tylecote, F. E.: Cancer of the Lung, Lancet **2**: 256-257 (July 30) 1927.
8. Hoffman, F. L.: Cancer of the Lung, Am. Rev. Tuberc. **19**: 392-406 (April) 1929.
9. McNally, W. D.: The Tar in Cigarette Smoke and Its Possible Effects, Am. J. Cancer **16**: 1502-1514 (Nov.) 1932.
10. Lickint, F.: Der Bronchialkrebs der Raucher, München med. Wchnschr. **82**: 1232-1234 (Aug. 2) 1935.
11. Arkin, A., and Wagner, D. H.: Primary Carcinoma of the Lung, J. A. M. A. **106**: 587-591 (Feb. 22) 1936.
12. Roffo, A. H.: Der Tabak als Krebserzeugende Agens, Deutsche med. Wchnschr. **63**: 1267-1271 (Aug. 13) 1937.
13. Maier, H. C.: Personal communication to the authors.
14. Müller, F. H.: Tabakmissbrauch und Lungencarzinom, Ztschr. f. Krebsforsch. **49**: 57-85, 1939.
15. Ochsner, A., and DeBakey, M.: Carcinoma of the Lung, Arch. Surg. **42**: 209-258 (Feb.) 1941.
16. Schrek, R.; Baker, C. H.; Ballard, G. P., and Dolgoff, S.: Tobacco Smoking as an Etiological Factor in Disease: I. Cancer, Cancer Research **10**: 49-58 (Jan.) 1950.
17. Wynder, E. L., and Graham, E. A.: Tobacco and Bronchiogenic Carcinoma: Preliminary report to the National Cancer Conference, Memphis, February 1949.
18. The questionnaires were sent to male and female patients with cancer of the lungs from Dr. W. L. Watson's Thoracic Surgery Service at Memorial Hospital, New York.

Through the cooperation of many hospitals and physicians throughout all parts of the country who permitted us to interview their patients, it is felt that a fairly good cross section of the entire United States has been obtained. The list of cooperating institutions and physicians is presented below.[19]

In order to make this survey as uniform as possible, each interviewer used the questionnaire shown in table 1.

In regard to smoking habits, we considered it particularly essential to learn how much a patient had smoked formerly, even though he might not smoke at all or smoke little at the time of the interview. The reason for this is the well known existence of a time lag between the exposure to a carcinogenic substance and the appearance of cancer. Many patients coming into the hospital with chronic disease of the lungs had stopped smoking months, or even years, previously. We therefore asked the patients to estimate the average use of tobacco during the last twenty years of their smoking period. The control patients were questioned in an identical manner; thus any possible error lying in this method of estimating smoking habits was balanced.

In questioning patients about occupations, we attempted to learn all the occupations of a given patient, the years during which he had held these jobs and to what type of dusts or fumes he had been exposed. Similar details were obtained in regard to other possible exposures, such as those a patient might have had in connection with certain hobbies.

Classification of Smoking.—In order to facilitate a statistical analysis of the results, the arbitrary classification of smoking habits given in table 2 was established. If a patient smoked for less than twenty years, his amount of smoking was adjusted to a twenty year period. Thus a patient smoking 20 cigarets for ten years only was classified as smoking 10 cigarets daily (class 2). Such adjustments were rarely necessary, since only a few patients had smoked for less than twenty years.

If a man smoked habitually more than one type of tobacco during the last twenty years, the various types were added together to make up his classification. Thus a man who smoked 1 package of cigarets daily, as well as 2 cigars, was classified as a class IV, or an excessive, smoker.

Histologic Types.—To insure an undoubted diagnosis, microscopic confirmation of the presence of carcinoma was obtained in all cases. Some difficulty arose in the histologic classification because of the variation of terms employed by pathologists in the different hospitals who examined the specimens. For example, what some pathologists would designate as an adenocarcinoma others would classify as an undifferentiated carcinoma. Likewise, the term oat cell or round cell carcinoma was at times used, a designation which is not recognized by some pathologists. In some cases pathologists called a lesion, from biopsy section, merely a carcinoma, unclassified. It may be said, however, that in general by far the most prevalent histologic types were the epidermoid or squamous carcinoma and its variant the undifferentiated carcinoma. These are the most common types found in males. In females the adenocarcinoma has so far been nearly as common as the other types. It is unquestionably the epidermoid and undifferentiated carcinomas which have shown the

TABLE 1.—*Etiologic Survey*

Name:..... Age:.....

1. Have you ever had a lung disease? If so, state time, duration and site of disease:
   Pneumonia Asthma Tuberculosis Bronchiectasis
   Influenza Lung Abscess Chest Injuries Others
2. Do you or did you ever smoke? Yes ☐ No ☐
3. At what age did you begin to smoke?
4. At what age did you stop smoking?
5. How much tobacco did you average per day during the past 20 years of your smoking?
   Cigarettes.....Cigars.....Pipes.....
6. Do you inhale the smoke? Yes ☐ No ☐
7. Do you have a chronic cough which you attribute to your smoking, especially upon first smoking in the morning? If so, for how long? Yes ☐ No ☐
   Duration.....
8. Do you smoke before or after breakfast? Before ☐ After ☐
9. Name the brand or brands, and dates, if any given brand has been smoked exclusively for more than five years.
   Change frequently? ☐

First brand—from 19.... to 19....

Second brand—from 19.... to 19....

10. What kind of jobs have you held? Have you been exposed to dust or fumes while working there? (Use back of page for detailed description of possible exposure)

From	To	Position	Dust or Fumes

11. Have you ever been exposed to irritative dusts or fumes outside of your job? In particular have you ever used insecticide spray excessively? If so, state time and duration.
    Yes ☐ No ☐ Type.....Duration.....
12. How much alcohol do you or have you averaged per day? State time and duration in years.
    Whiskey..... Beer.....Wine.....
13. Where were you born and where have you lived most of your life? State the approximate time span you have lived in a certain locality. Up to what grade did you attend school?
    Birthplace.....Home.....Educational Level.....
14. State the cause of death of your parents, and of brothers and sisters if any.
15. *Site of Lesion* *Microscopic Diagnosis* *Papanicolaou Class* *Etiological Class*

Interviewer .....

19. CALIFORNIA: Private patients of Drs. L. Brewer, Daniels, F. Dolley, D. Dugan, H. Garland, E. Holman, J. Jones, W. Rogers, P. Samson, B. Stephens. Hospitals: Birmingham General, French, Good Samaritan, Letterman General, Los Angeles County, Southern Pacific General, Stanford, United States Marine, United States Naval, University of California, Wadsworth General. COLORADO: Private patients of Drs. A. Brown, F. Condon, J. Grow, F. Harper, M. Peck. Hospitals: Colorado General, Denver General, Fitzsimmons, Fort Logan Veterans, General Rose, St. Lukes. DISTRICT OF COLUMBIA: Private patients of Drs. B. Blades, E. Davis. Hospitals: Georgetown, George Washington, Walter Reed. ILLINOIS: Hospitals: Cook County, Veterans Administration, Hines, Ill. MARYLAND: Hospitals: Johns Hopkins, United States Naval. MASSACHUSETTS: Private patients of Drs. D. Harken, R. Overholt. Hospitals: Boston City, Massachusetts General, New England Deaconess. MICHIGAN: Hospitals: Dearborn Veterans. MISSOURI: Private patients of Drs. J. Flance, A. Goldman, R. Smith. Hospitals: Jefferson Barracks Veterans, Jewish, St. Louis City, St. Louis County. NEW JERSEY: Hospitals: Berthold S. Pollack, Newark City. NEW YORK: Private patients of Drs. W. Cahan, H. Maier, J. Pool, W. Watson. Hospitals: Bellevue, Veterans Administration, Brooklyn Cancer Institute, Kings County Memorial, Montefiore, New York City Cancer Institute, New York Hospital, Presbyterian, Roswell Park Memorial Institute. OHIO: Hospitals: Veterans Administration. PENNSYLVANIA: Private patients of Dr. J. Johnson. Hospitals: Jefferson Medical College, Temple University, University of Pennsylvania. UTAH: Private patients of Drs. W. Rumel, Cutler. Hospitals: Holy Cross, St. Marks, Salt Lake County General, Veterans Administration, Dr. W. H. Groves, Latter-Day Saints.

greatest increase in recent years. For this reason we were particularly interested in studying these types separately from the adenocarcinomas. The present report includes 605 male and 25 female patients with epidermoid, undifferentiated and unclassified carcinomas and 39 male and 15 female patients with adenocarcinoma. In order to determine possible sex variations in the etiology of cancer of the lung, results in men and women are reported separately.

Control Study I.—To check all possible bias on the part of the interviewers who saw only patients believed to have bronchiogenic carcinoma, it was deemed advisable to conduct a control study in which a nonmedical investigator would interview every patient admitted to the Chest Service of Barnes Hospital without knowing the diagnosis in advance. Two interviewers [20] were used for this purpose. When the final diagnosis was determined, all cases of cancer of the lungs (75 men) were separated from the other cases (132). Control patients under the age of 30 were excluded since there were no cases of cancer in this age group. Seventeen male patients for whom no definitive diagnosis could be made were also omitted.

In addition these interviewers interrogated patients with cancer of the lung at other St. Louis hospitals,[21] also without previous knowledge of diagnosis. Here the interviewers were given the names of several patients with diseases of the chest in a comparable age group, of whom at least 1 was suspected to have bronchiogenic carcinoma. The patients with proved cancer of the lung (25 men) and the other patients (54 men) were added to the Barnes Hospital groups, thus collectively making up control study I.

To determine the smoking habits, as well as the other data contained in the questionnaire of our study of other hospital patients, the nonmedical investigators also questioned patients without cancer of the lungs on the general surgical and medical services at Barnes Hospital, the Jefferson Barracks Veterans Hospital and the St. Louis City Hospital. This group, called "general hospital population," consists of 780 patients. Also a total of 552 female patients without cancer of the lungs have been interviewed as control patients on our surgical and medical services.

Two objects were to be realized by this control study. One was to learn of possible exposures to exogenous irritants of a large group of patients without cancer of the lung and the other to test the validity of the interviews made by those who knew the suspected diagnosis in a given case in advance.

Age Distribution in Control Cases: For proper statistical evaluation of a study of this kind it is obvious that the age distribution should be the same in the control cases as in the cases of cancer of the lungs. Since no patients with cancer of the lungs below 30 or above 80 years of age were seen, no controls beyond these ages have been included. The controls comprised the unselected patients as they entered the Barnes Hospital and other St. Louis hospitals. For that reason their age distribution is not identical with that of the patients with cancer. In order to be able to evaluate the cases without cancer on the basis of the same age distribution as that found in the cases of cancer, the following adjustments were made:

The combined results include data on 780 cases without cancer. Among these there is the following age distribution: 30 to 39, 18.7 per cent; 40 to 49, 21 per cent; 50 to 59, 26.9 per cent; 60 to 69, 20.5 per cent, and 70 to 79, 12.8 per cent. (For the age distribution in the 605 cases of cancer see table 5.)

The smoking classifications of the control cases have been made proportional to the age distribution among the cases of cancer by multiplying the percentage value of each smoking classification for each age group of the controls by the proportion of cases of cancer in that age group. For example, in the age group 30 to 39 of the controls there were 146 (18.7 per cent) patients, of whom 20 (13.6 per cent) were nonsmokers. However, since of the patients with cancer only 2.3 per cent fell into this age group, the value of 13.6 per cent was made proportional to the age distribution in the cases of cancer (2.3 per cent).[22] In a similar manner the smoking values for the control group aged 40 to 49 were made proportional to 17.4 per cent. Finally, the quotients of the smoking classifications in each age group were added to make the percentage values shown in figure 3. The detailed data which compare the smoking classifications of the two groups according to age are shown in table 6. It was from those data that the proportional values were obtained.

TABLE 2.—*Classification of Smoking Habits*

Group 0.....	Nonsmokers (Less than 1 cigaret per day for more than 20 years) *
1.....	Light smokers (From 1 to 9 cigarets per day for more than 20 years) * †
2.....	Moderately heavy smokers (From 10 to 15 cigarets per day for more than 20 years) *
3.....	Heavy smokers (From 16 to 20 cigarets per day for more than 20 years) *
4.....	Excessive smokers (From 21 to 34 cigarets per day for more than 20 years) *
5.....	Chain smokers (35 cigarets or more per day for at least 20 years) *

* Pipe and cigar smokers have been included by arbitrarily counting 1 cigar as 5 cigarets and 1 pipeful as 2½ cigarets.
† Includes minimal smokers (from 1 to 4 cigarets a day, or the equivalent in pipes or cigars for more than 20 years).

The 100 cases of cancer and the 186 cases of control study I were made proportional in the same manner.

Control Study II.—In addition to the control study just cited, it was thought to be valuable to have other physicians carry out similar interviews using our questionnaire. It was thought that the results would serve as an effective control for the cases collected under our own supervision.

At this time we are reporting preliminary results based on 83 patients interviewed at the Bellevue Hospital, Columbia University Division (New York), by Dr. H. G. Turner [23]; at the Boston City Hospital by Dr. G. W. Ware [24]; at the Crile Veterans Hospital (Cleveland, Ohio) by Dr. C. T. Surington, and at the Veterans Administration Hospital, Hines, Ill., by Dr. E. J. Shabart.

RESULTS

The first data to be presented are based on 605 proved cases of bronchiogenic carcinoma in men, other than adenocarcinoma. Five hundred and ninety-five of these cases have been diagnosed on the basis of tissue biopsy,

20. Betty G. Proctor, A.B., and Adele B. Croninger, M.A.
21. City Hospital, Jewish Hospital and Veterans Administration Hospital.
22. $\frac{13.6 \times 2.3}{100} = 0.312$. This is the quotient which, added to the others determined in the same manner, makes the data shown in figure 3.
23. Of the service of Dr. James B. Amberson.
24. Of the service of Dr. John W. Strieder.

9 on the basis of examination of sputum and 1 on the basis of study of the pleural fluid.[25]

Comparison of Independent Studies.—Before the smoking habits of the 605 patients with cancer of the lungs are compared with those of the general hospital population, it might be well to compare the results in the two control studies and the group of 422 patients (study III) interviewed and collected by one of us

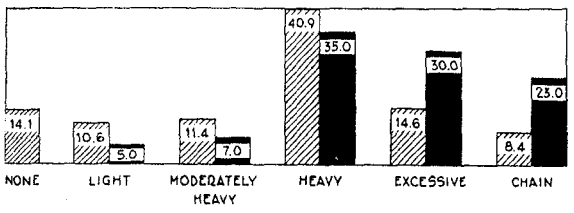


Fig. 1.—Control study I. Amount of smoking in percentage among 100 male patients with cancer of the lungs (solid bars) and 186 male patients with other chest diseases (lined bars) having the same age and economic distribution.

(E. L. W.) to determine any possible bias in cases in which the suspected diagnosis was known in advance and whether the data are sufficiently similar to warrant their discussion as a group.

Control Study I: This group consists of 100 patients with cancer of the lungs and 186 with diseases of the chest other than cancer interviewed by two nonmedical investigators who had no previous knowledge of the diagnosis in a given case. The data show no nonsmokers (fig. 1) among the cancer group, while there are 14.1 per cent nonsmokers among the patients with other thoracic diseases. Ninety-five per cent of the patients with cancer are in the classification of moderately heavy to chain smokers and 53 per cent are excessive and chain smokers, while among the patients without cancer, 75.3 and 23 per cent, respectively, fell among these smoking groups.

Control Study II: The data in table 3 cover 83 male patients with cancer of the lungs interviewed independently by physicians in other cities. Among each small group of cases some variation is, of course, to be expected. In each of the individual groups nearly half or more of the patients are excessive or chain smokers. Grouping the data of the four independent investigators together, we find 2.4 per cent nonsmokers and 93.9 per cent moderately heavy to chain smokers (fig. 2), while

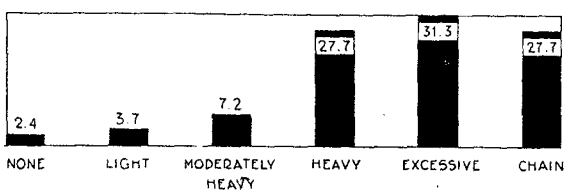


Fig. 2.—Control study II. Percentages for amount of smoking in 83 cases of cancer of the lungs collected independently by Dr. E. J. Shabart (Chicago), Dr. C. T. Surington (Cleveland), Dr. H. G. Turner (New York) and Dr. G. W. Ware (Boston).

59 per cent are excessive and chain smokers. The results of the two control studies correspond closely to one another as well as to the results of study III (table 4).

The results in relation to the areas or hospitals where the cases were observed show uniformity. Small differences between the groups may well be explained on the basis of the small size of each series. The mountain state series includes 13 patients of Mormon faith. Mormons in general were found to smoke much less than our general hospital population. Among the Mormon patients with cancer of the lung, however, there was only 1 nonsmoker (72 years old). The others were long-time users of tobacco.

Comparing the three studies, we note little difference. For example, nonsmokers account for 0.0 per cent in control study I, 2.4 per cent in control study II and 1.4 per cent in study III. The percentage of heavy to chain smokers in these three groups is 88, 86.7 and 85.2 respectively, while the percentage of excessive and chain smokers totals 53, 59 and 49 respectively.

Since we thus have not been able to determine any essential difference in the amount of smoking in the three studies, we shall from here on refer to the total results of 605 cases.

Age Distribution.—The age distribution of cancer of the lungs in the present series shows 2.3 per cent of the patients to be under 40 years of age, while 79.3 per cent were 50 years or older (table 5). This distribution readily shows that it would be of little value to study the smoking habits of the younger age groups for the purpose of control studies, since in them, for reasons still unknown to us, cancer of the lungs is a rare phenomenon.

TABLE 3.—*Control Study II: Amount of Smoking in 83 Cases of Proved Cancer of the Lung as Determined by Investigators Using the Same Questionnaire as that Used in the Cases of this Study*

	Bellevue Hospital (Turner)	Boston City Hospital (Ware)	Crile Veterans Hospital (Surington)	Hines Veterans Hospital (Shabart)
Cases	22	16	15	30
Amount of Smoking:				
None	1	0	1	0
Light	2	0	0	1*
Moderately heavy	2	3	1	0
Heavy	6	2	6	9
Excessive	8	5	7	6
Chain	3	6	0	14

* Minimal smoker. (For definition see previous classification of smokers.)

Combined Data on Amount of Smoking.—The data on the amount of smoking among 605 patients with cancer of the lungs and 780 male patients with other diseases reflect the results of the individual studies reported. It may also be noted that there is no essential difference in the amount of smoking between the general hospital population and patients with diseases of the chest who do not have cancer. The total results show that whereas there are 14.6 per cent nonsmokers among the male general population there are 1.3 per cent nonsmokers among the male patients with cancer of the lungs; and while there are 54.7 per cent heavy to chain smokers and 19.1 per cent excessive and chain smokers among the general hospital group there are 86.4 and 51.2 per cent, respectively, among the patients with cancer. All these differences seem highly significant.

The results on the amount of smoking according to age groups (table 6) show that in general the patients with cancer of the lungs in their forties and early fifties have smoked more heavily than the older patients with this disease. This observation does not seem to apply to the few patients in their thirties. The age group 70 to 79 has the greatest percentage of light and moderately heavy smokers.

25. Eight of these cases were diagnosed in Dr. Papanicolaou's laboratory on conclusive evidence of carcinoma. One sputum and one pleural fluid examination were made at the Boston City Hospital.

The frequency of nonsmokers in the age groups shown for the patients without cancer is significantly different from that among patients with cancer in the same age groups. However, in the 30 to 39 age group the smoking habits of the patient with cancer are difficult to evaluate since too few patients of this age have been seen.

TABLE 4.—*Study III: Amount of Smoking Among Male Patients With Cancer of the Lung in Relation to Area or Hospital Where Cases Were Observed (Wynder)**

	Smoking Classification, %						
Areas or Hospitals	V	IV	III	II	I	0	Average Age
Barnes (76)	18.4	31.5	43.4	5.3	0.0	1.3	54.8
Los Angeles (50)	12.0	32.0	12.0	12.0	0.0	4.0	59.5
San Francisco (50)	20.0	28.0	36.0	14.0	2.0	0.0	54.9
Mountain states (50)	14.0	26.0	36.0	18.0	4.0†	2.0	60.1
St. Louis (25)	20.0	36.0	32.0	12.0	0.0	0.0	58.2
Eastern and northern states (50)	16.3	23.6	40.0	20.0	0.0	0.0	56.1
New York City (66)	20.0	40.0	32.3	7.7	0.0	0.0	55.8
Memorial Hospital (55)	23.6	27.3	29.1	10.9	5.5†	3.6	57.6
Total (422)	18.2	30.8	36.7	11.4	1.4	1.4	56.7

* This table does not include any cases represented in control studies I and II.
† Includes 1 minimal smoker.

TABLE 5.—*Age Distribution in 605 Cases of Cancer of the Lung in Men*

Age Groups	Percentage of Cases
30-39	2.3
40-49	17.4
50-59	42.6
60-69	30.9
70-79	6.8

TABLE 6.—*Percentage Distribution of Amount of Smoking in Respect to Age Groups Among 780 Men in the General Hospital Population and 605 Men with Cancer of the Lungs* *

	Age Groups									
	30-39		40-49		50-59		60-69		70-79	
No. of Cases	(146)	(14)	(164)	(105)	(210)	(258)	(169)	(187)	(100)	(41)
Amount of smoking; class: 0	13.6	7.1	9.7	0.0	14.8	1.6	14.3	1.1	25.0	2.4
1	5.5	7.1	9.7	1.9	7.1	1.6	18.7	1.1	13.0	12.2
2	17.1	14.3	18.9	3.8	17.6	7.4	20.6	13.6	21.0	24.4
3	41.0	42.9	37.1	29.5	43.3	36.0	28.7	38.0	16.0	29.3
4	14.3	28.6	14.0	28.6	10.5	34.1	10.6	30.5	15.0	17.1
5	8.2	0.0	10.3	36.2	6.7	19.4	6.8	15.5	10.0	14.6

* The percentages for the general male hospital population are given in the left hand columns.

In comparing the amount of smoking among the various age groups, one must also consider the type of tobacco used, which has undergone a marked shift particularly when the youngest and oldest age groups are considered.

Statistical Analysis of Data.—The statistical analysis of these data has been carried out by Dr. Paul R. Rider, professor of mathematics at Washington University, and H. David Hartstein, M.A., instructor of statistics at Washington University.

On the assumption that smoking has no effect on the induction of cancer of the lungs, the probability (p) of a deviation from expectation as great or greater than that observed is as follows:

Control Study I: Class O, p is 0.0002; class O plus class I, p is 0.0002; classes 3 to 5 inclusive, p is 0.0226, class 4 plus class 5, p is 0.0002; class 4, p is 0.0046, and class 5, p is 0.0016.

Combined Results: The values for the combined results of 605 patients with cancer of the lung as compared with 780 men in the general hospital population are as follows: class O, class O plus class 1, classes 3 to 5 inclusive, class 4 plus class 5, class 4 and class 5 have p values which are in all cases less than 0.0001.

Their conclusion is as follows: "On the basis of the statistical data for both the control study I and the combined results, when the nonsmokers and the total of the high smoking classes of patients with lung cancer are compared with patients who have other diseases, we can reject the null hypothesis that smoking has no effect on the induction of cancer of the lungs. If smoking does not have anything to do with the induction of cancer of the lungs, then the observed deviation could occur only with the probability (p) as shown above."

Miscellaneous Data.—Nearly all (98.7 per cent) the cigaret smokers of the cancer group, but fewer pipe (62.5 per cent) and cigar (18 per cent) smokers, stated that they inhaled consciously. Seventy-eight and a half per cent of cancer patients interviewed stated that they usually began to smoke before breakfast.

Type of Tobacco: Among the general hospital population pipes and cigars were smoked most prominently

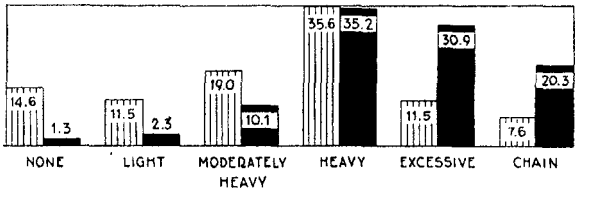


Fig. 3.—Percentages for amount of smoking among 605 male patients with cancer of the lungs (solid bars) and 780 men in the general hospital population without cancer (lined bars) with the same age and economic distribution.

in the older age groups. For example, only 4.3 per cent of the smokers in the age group 30 to 39 used chiefly pipes or cigars, 11.0 per cent in the age group 40 to 49, 12.9 per cent in the age group 50 to 59, 30 per cent in the age group 60 to 69 and 38 per cent in the age group 70 to 79. Only those patients were tabulated as either pipe or cigar smokers who smoked a given type of tobacco predominantly over the last twenty years of their smoking period. Among the age-adjusted general hospital population we find 12.4 per cent pipe smokers and 7.8 per cent cigar smokers and among the patients with cancer 4.0 per cent and 3.5 per cent respectively (fig. 4).

The average age of the pipe smokers with cancer of the lung was 60.5, with a range of 52 to 78, and the average age of the cigar smokers with cancer of the lung was 63.1, the range being from 53 to 76. The average number of pipes smoked by the cancer patients was 15.6 and the average number of cigars 6.8 per day for the last twenty years of their smoking history. This amount of smoking is decidedly higher than that found among the general cigar and pipe smokers.

Duration of Smoking: The duration of smoking in years dates to the first time the patient began smoking habitually to any degree. Of 605 patients with cancer in our series, 96.1 per cent had smoked for twenty years or more, 85.4 per cent for thirty years or more, 68.2 per cent for thirty-five years or more and 50.2 per

cent for forty years or more. One patient with epidermoid cancer began to smoke at 45 (20 cigarets a day), and clinical symptoms of cancer of the lungs developed at 50 (class I smoker). He had no other exposure to irritants. Only three of the patients with bronchiogenic cancer began to smoke after the age of 25 (fig. 5).

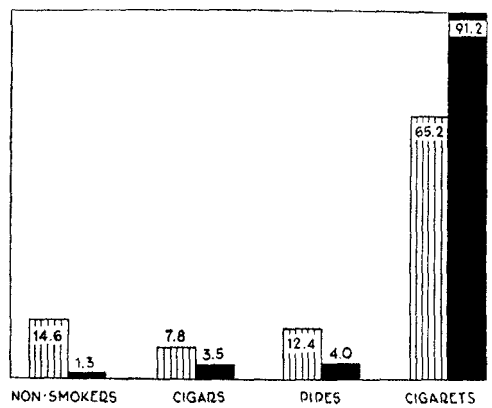


Fig. 4.—Smoking habits and type of tobacco smoked (in percentages) in 605 cases of cancer of the lungs (solid bars) and 780 men in the general hospital population (lined bars) with a similar age and economic distribution.

Adenocarcinoma in Men: Among 39 men[26] with adenocarcinoma there were 4 nonsmokers (10.3 per cent), a percentage higher than that found for the other types of bronchiogenic carcinoma. There were 7 chain smokers (18 per cent), significantly more than in the general male hospital population. Ten and three-tenths per cent were excessive, 38.5 per cent heavy, 15.4 per cent moderately heavy and 7.7 per cent light smokers. Among the latter there were 2 minimal smokers.

Data on Women:[27] Among 13 women with adenocarcinoma and 2 designated as having terminal bronchiolar carcinoma there was not 1 heavy smoker. Thirteen were nonsmokers and 2 light smokers. Among 25 patients with epidermoid and undifferentiated carcinoma, however, there were 15 smokers of many years' duration as well as 10 nonsmokers. Among those who smoked there were 1 light, 4 moderately heavy, 6 heavy, 2 excessive and 2 chain smokers.

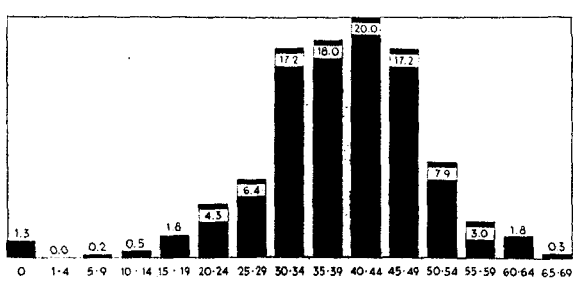


Fig. 5.—Percentages for duration of smoking in years, starting with the time when the patient first began to smoke habitually, in 605 cases of cancer of the lungs.

To determine the smoking habits among women in the general hospital population 552 patients without cancer of the lung have been interviewed at this hospital. The data resulting from this study show that but few women in the cancer age have been heavy smokers for many years and that most of the heavy smokers are young women. On the basis of our arbitrary smoking classification, we found 79.6 per cent of the women to be nonsmokers while 11.3 per cent were moderately heavy to chain smokers, and only 1.2 per cent of the controls in the cancer age[28] were excessive or chain smokers for at least twenty years (fig. 6).

COMMENT

Universal Increase.—If one feels that the greatly increased incidence of cancer of the lungs is real and that this increase is most marked in men, one may theorize that the change has been due to an external factor, or group of factors, nationally prevalent but applicable to men more and over a longer period than to women.

Influence of Tobacco.—Since in a small percentage of cases cancer of the lungs occurs in nonsmokers and minimal smokers and since it obviously does not develop in every person who has been a heavy smoker for a long time, it is apparent that smoking cannot be the only etiologic factor in the induction of the disease. From the evidence presented, however, the temptation is strong to incriminate excessive smoking, and in particular cigaret smoking, over a long period as at least one important factor in the striking increase of bronchiogenic carcinoma for the following reasons: (1) it

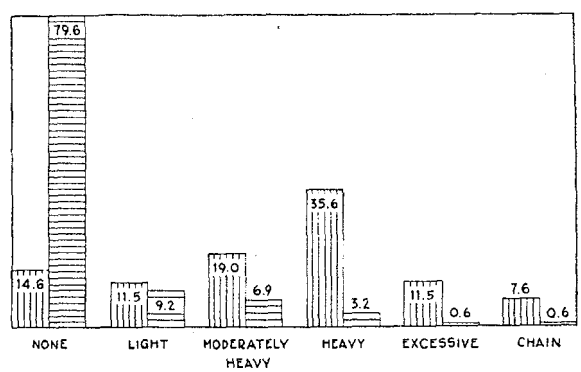


Fig. 6.—Amount of smoking in percentage among 780 male patients (vertically lined bars) and 552 female patients (horizontally lined bars) of the general hospital population with the same age and economic distribution as found among cases of cancer of the lungs.

is rare to find a case of epidermoid or undifferentiated carcinoma in a male patient who has not been at least a moderately heavy smoker for many years; (2) the use of cigarets is much greater among patients with cancer of the lungs than among other patients of the same age and economic groups; (3) the sex distribution of cancer of the lungs roughly corresponds to the ratio of long-term smoking habits of the two sexes (see section on "Duration of Smoking"); (4) the enormous increase in the sale of cigarets in this country approximately parallels the increase of bronchiogenic carcinoma.[29]

Amount of Smoking.—The data have clearly shown that the average patient with cancer of the lungs smokes much more heavily than the average patient of the same age and economic group with some other disease. This contrast becomes even greater if our observation of Mormons is considered, who as a group smoke far less than the general hospital population; Mormons with cancer of the lung were, with one exception, considerable smokers.

26. Includes 3 cases of Dr. C. T. Surington and 1 case of Dr. H. G. Turner.
27. Includes 4 cases of Dr. H. G. Turner and 3 cases of Dr. G. W. Ware.
28. See table 5.
29. It is taken for granted, of course, that by itself such parallelism would mean little since similar curves could be drawn for many other commodities.

The fact that patients with bronchiogenic cancer in their forties and fifties had smoked more heavily than those in whom the cancer developed at a later age may indicate that the greater the irritation the sooner will cancer develop in a susceptible person. Such an observation obviously does not apply to the individual case but rather to the age groups taken collectively. Too few patients below the age of 40 have been seen in order to evaluate this age group.

In general it appears that the less a person smokes the less are the chances of cancer of the lung developing and, conversely, the more heavily a person smokes the greater are his chances of becoming affected with this disease.

Type of Tobacco.—The majority of patients with cancer of the lungs are cigaret smokers rather than pipe or cigar smokers, the ratio being over and above that found in the general population. This fact may be due to one of the following reasons:

1. Cigaret smoke is more frequently inhaled than is that of either pipes or cigars. Obviously the lungs of an inhaler are exposed to a greater concentration of smoke than those of a person who does not consciously inhale.

2. Because of the greater physical and economic convenience, more persons are heavy smokers of cigarets than of either pipes or cigars. Among the latter one finds more minimal and light smokers than among the former.

3. Certain irritative substances may be present in cigarets in greater amounts than in pipes or cigars. The role of paper, the use of insecticides during the growth of the tobacco and other ingredients warrant further research in this regard.

Duration of Smoking.—One of the chief reasons many investigators have thought that tobacco has no effect on the development of cancer of the lungs has been their belief that women today smoke as much as men and that if tobacco plays a role the sex ratio of the disease should be about equal. The data presented demonstrate that it makes little difference how many women smoke today or have smoked for the past ten years, since results have shown that over 96 per cent of patients with cancer of the lungs have smoked for more than twenty years and that over 80 per cent have smoked for more than thirty years.

It is, of course, difficult to tell whether the important point in this regard is the fact that these persons have smoked for many years or that they have been heavy smokers for a brief period, because we have noted that also among the general male hospital population nearly all smokers have been smoking since their youth. For this reason it is difficult to evaluate the one case in our study in which the patient smoked only from his forty-fifth to his fiftieth year, at which time clinical signs of cancer developed. If one may judge from control data on women, it would appear that a long duration of smoking is at least one important factor in the induction of cancer of the lungs. The relatively low incidence of the condition in women might be explained by the fact that few women in the cancer age have smoked for an extensive period.

On the basis of a twenty year period of smoking, it may be of interest to note that, while only 1.2 per cent of the women were excessive or chain smokers, by contrast 19.1 per cent of the male controls were in those smoking groups, a ratio which points in the same direction as the sex ratio of lung cancer.

Lag Period.—If smoking is to be regarded as an important etiologic factor in the development of cancer of the lungs, apparently a time lag exists for this disease as well as for carcinoma of the bladder, known to occur years after cessation of exposure to aniline. We have now seen 3 cases in which clinical signs of cancer of the lung appeared ten years or more after the patient stopped smoking. The 3 patients had smoked for thirty years or more, and none gave a history of occupational or other irritative exposures. Two of them had stopped smoking because of a bothersome chronic cough and 1 because of concomitant heart disease. In 1 of the patients, a 67 year old warehouse clerk, clinical symptoms of cancer developed thirteen years after the cessation of smoking. The phenomenon of the lag period is of course well known in cancer research.

Adenocarcinoma in Men.—Since the great increase in cancer of the lungs has mostly involved the epidermoid and undifferentiated carcinomas, it would appear that the exogenous factors possibly affecting these types of cancer play a lesser role, if any, in the induction of adenocarcinomas of the lung in men. As yet we have not seen a sufficient number of cases of this type of cancer to warrant definitive conclusions. It appears, however, that on the basis of present data one is more likely to find nonsmokers or minimal smokers with this type of cancer than with the other types. At the same time, however, the percentage of chain smokers among men with adenocarcinomas of the lung is greater than among the general hospital population. It seems, therefore, that tobacco smoke has also some influence on the induction of adenocarcinoma in men, even though, as judged from the incidence, the influence on this type is much less marked than on the other types of bronchiogenic carcinoma.

Cancer of the Lungs in Women.—Many observers have commented on the fact that bronchiogenic carcinoma, while on the increase among both men and women, is increasing more rapidly among men. In 100 consecutive cases collected by Lindskog [30] in 1938 to 1943 the ratio was 4.5 to 1, and in another series collected in 1947 and 1948 the ratio had reached 24 to 1.[31] At Barnes Hospital the ratio in our last 150 cases has been 18.5 to 1. This shift in ratio has been noted in varying proportions throughout the country. Such a radical change warrants a careful analysis.

The insufficient number of cases of cancer of the lungs in women in our survey does not allow definite conclusions at this time. So far, however, smoking seems to have had no apparent effect on the incidence of adenocarcinoma in women. It is of great interest that we have observed 10 cases of epidermoid and undifferentiated carcinoma of the lungs of women who were nonsmokers with no history of occupational or other irritative exposure. This percentage of nonsmokers in women with cancer of the lung is much higher than that found among men. Proper explanations for this finding remains to be advanced. At the same time it appears strongly suggestive that heavy smoking plays a significant role in the induction of epidermoid and undifferentiated carcinoma of the lungs in women, since the percentage of heavy smokers is considerably higher in the cancer group than in the general hospital control group.

30. Lindskog, G. F.: Bronchiogenic Carcinoma, Ann. Surg. **124**: 667-674 (Oct.) 1946.

31. Lindskog, G. F., and Bloomer, W. D.: Bronchiogenic Carcinoma, Cancer **1**: 234-237 (July) 1948.

CONCLUSION AND SUMMARY

1. Excessive and prolonged use of tobacco, especially cigarets, seems to be an important factor in the induction of bronchiogenic carcinoma.

2. Among 605 men with bronchiogenic carcinoma, other than adenocarcinoma, 96.5 per cent were moderately heavy to chain smokers for many years, compared with 73.7 per cent among the general male hospital population without cancer. Among the cancer group 51.2 per cent were excessive or chain smokers compared to 19.1 per cent in the general hospital group without cancer.

3. The occurrence of carcinoma of the lung in a male nonsmoker or minimal smoker is a rare phenomenon (2.0 per cent).

4. Tobacco seems at this time to play a similar but somewhat less evident role in the induction of epidermoid and undifferentiated carcinoma in women. Among this group a greater percentage of nonsmokers will be found than among the men, with 10 of 25 being nonsmokers.

5. Ninety-six and one-tenth per cent of patients with cancer of the lungs who had a history of smoking had smoked for over twenty years. Few women have smoked for such a length of time, and this is believed to be one of the reasons for the greater incidence of the disease among men today.

6. There may be a lag period of ten years or more between the cessation of smoking tobacco and the occurrence of clinical symptoms of cancer.

7. Ninety-four and one-tenth per cent of male patients with cancer of the lungs were found to be cigaret smokers, 4.0 per cent pipe smokers and 3.5 per cent cigar smokers. This prevalence of cigaret smoking is greater than among the general hospital population of the same age group. The greater practice of inhalation among cigaret smokers is believed to be a factor in the increased incidence of the disease.

8. The influence of tobacco on the development of adenocarcinoma seems much less than on the other types of bronchiogenic carcinoma.

9. Three independent studies have resulted in data so uniform that one may deduce the same conclusions from each of them.

ADDENDUM

Since the data presented in this paper were tabulated, 45 additional interviews of male patients with epidermoid or undifferentiated cancer of the lung have been obtained. Eight of these patients have been interviewed by Dr. J. L. Ehrenhaft from the University of Iowa Hospital, 9 were given our questionnaire by Lt. Col. J. M. Salyer from Fitzsimons General Hospital and 7 were reported on by Dr. E. J. Shabart from the Veterans Administration Hospital, Hines, Ill. Among these 24 cases there were no nonsmokers or light smokers, 7 heavy smokers, 13 excessive smokers and 4 chain smokers. Twenty-one additional patients have been interviewed by Miss Croninger on the Barnes Hospital Chest Service. Among these there were 1 nonsmoker (a 72 year old blacksmith), 10 heavy smokers, 6 excessive smokers and 4 chain smokers. These 45 cases, which include reports independently made at two additional centers (University of Iowa and Fitzsimons General Hospital), show the same trend noted in the larger series.

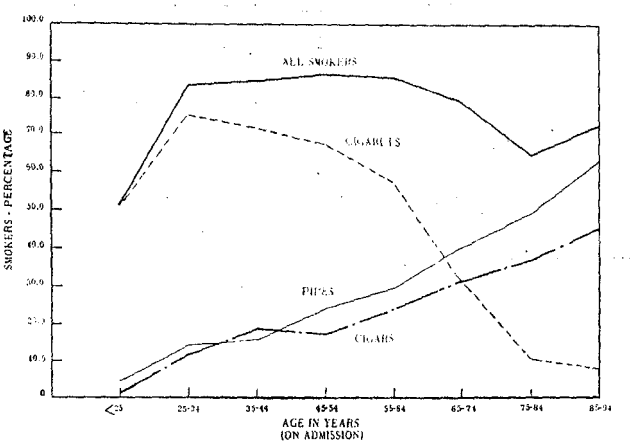
CANCER AND TOBACCO SMOKING

A Preliminary Report

MORTON L. LEVIN, M.D.
HYMAN GOLDSTEIN, M.D.
and
PAUL R. GERHARDT, M.D.
Albany, N. Y.

The published literature on use of tobacco and its possible association with human cancer fails to show clearcut consistent observations. Reviews of the literature for the past twenty years reveals that it is often conflicting and that it consists for the most part of studies which are inconclusive because of lack of adequate samples, lack of random selection, lack of proper controls or failure to age-standardize the data. Potter and Tully [1] have reported a higher proportion of smokers in patients with cancer of the "buccal cavity" and "respiratory tract" among males "over the age of 40" who were seen at Massachusetts cancer clinics.

Since 1938 a history of tobacco usage has been obtained routinely from all patients admitted to the Roswell Park Memorial Institute, Buffalo. These histories are part of the regular clinical history and are taken before the final diagnosis has been established. This procedure is considered especially important from the standpoint of excluding bias. Approximately half the patients admitted to the institute are subsequently found not to have cancer. Special attention with respect to the history of smoking has not been paid to any single group of conditions, so that these records may be presumed to be free from bias which might result from preconceived ideas as to relation between smoking and a particular form of cancer.



Percentage of patients who had ever smoked by type of smoking.

The histories record the date smoking began, duration, type of smoking and amount per day. The reliability of the quantitative aspects of smoking obtained by a history is of course highly variable. It is presumed, however, that such errors are not selective with respect to presence or absence of cancer, especially since only patients suspected by their physicians of having cancer are admitted to the Institute.

With technical assistance of Elizabeth Brezee and David Robbins.
From the Bureau of Cancer Control, Division of Medical Services, New York State Department of Health.
Dr. Louis C. Kress, Dr. Joseph G. Hoffman and Miss Olive C. Ralston, of the staff of the Roswell Park Memorial Institute, assisted by making available the records of the institute and by making suggestions as to the planning of the study.

1. Potter, E. A., and Tully, M. R.: The Statistical Approach to the Cancer Problem in Massachusetts, Am. J. Pub. Health **35**: 485-490, 1945.

This report is based on a study of 1,045 male cancer patients and 605 male noncancer patients. The cancer sites selected were lung, lip, pharynx, esophagus, colon, rectum and a scattered number of other sites. The noncancer patients were those with symptoms referable to the same sites but which proved not to be due to cancer. Only the users of cigarets, pipes and cigars are considered here, since the number of patients who used snuff or chewing tobacco was negligible. Smokers engaging in more than one form of smoking entered into separate analysis for each such form, so that the sum of smokers is less than the sum of smokers of each type. The factor studied was whether or not the patient had ever smoked, regardless of whether he was a smoker at the time of admission.

Over 80 per cent of all patients were smokers (table 1). Prevalence of smokers, regardless of type, did not vary strikingly with age past the age of 25 (see the accompanying figure). Prevalence of cigaret smokers, however, decreased with age, and that of pipe smokers and cigar smokers increased with age. Obviously, comparison of groups with differing age composition would show different proportions of cigaret, pipe and cigar smokers because of this factor alone. Accordingly, comparisons should be made of age-specific prevalence rates or of prevalence rates standardized for age

TABLE 1.—*Prevalence of Smokers Among Male Cancer and Noncancer Patients by Type of Smoking*

	No. of Cases	Percentage of Smokers * All Types	Cigarets	Pipes	Cigars
Cancer	1,045	84.8	56.0	30.3	22.4
Noncancer	605	77.8	46.0	24.3	20.8
P †	.....	0.01	0.01	0.01	0.47

* Age standardized.
† P denotes probability here and in tables 2 and 3.

by applying the age-specific rates to a standard population. The latter device was adopted, using the entire series of 1,650 patients as the standard population.

The significant observations are summarized in tables 1, 2, 3, 4 and 5. There were more smokers among cancer patients than noncancer patients, because of an excess of cigaret and pipe smokers among the former (table 1). This excess was due entirely to the increased percentage of cigaret smokers among patients with cancer of the lung and the increased percentage of pipe smokers among patients with cancer of the lip (table 2). These differences, in turn, were confined to those who had smoked cigarets or pipes for twenty-five years or longer (table 3).

It should be noted that the prevalence rates of smokers in columns 2 and 4 of table 3 are age-standardized rates, obtained by applying the age-specific rates for each subgroup to the age distribution of the total group of 1,650 male patients. Since length of smoking is related to age, this statistical procedure was necessary to exclude the possibility that the greater percentage of "25 years or more" smokers in the cancer groups was due solely to the greater proportion of older persons in these groups. The failure to find comparable differences in smokers of less than twenty-five years' duration may be due to the relatively small percentage of such smokers which may be expected in an older population. Further study of large numbers of younger patients may alter this observation.

In tables 4 and 5 the data are presented to show the relative prevalence of lung and lip cancer among nonsmokers and among cigaret, pipe and cigar smokers in the patient population. There were more than twice as many cases of lung cancer among cigaret smokers as among any other group. Pipe smokers and cigar

TABLE 2.—*Prevalence of Smokers Among Male Patients by Type of Smoking and Diagnostic Group*

Diagnosis	No. of Cases	Percentage of Smokers * Any Type (1) %	P	Cigaret (2) %	P	Pipes (3) %	P	Cigars (4) %	P
Lung cancer compared with—	236	84.7	....	66.1	....	13.5	....	11.2	....
Other cancer (except lip)	666	82.9	0.53	48.0	0.01	25.8	0.01	20.3	0.01
Lung nontumors	124	81.1	0.39	53.1	0.02	25.5	0.09	13.4	0.64
Other noncancer	481	78.3	0.03	44.1	0.01	25.3	0.01	22.7	0.01
Lip cancer compared with—	143	84.5	....	45.8	....	48.1	....	26.5	....
Other cancer (except lung)	666	82.9	0.58	48.0	0.48	25.8	0.03	20.3	0.11
Lip nontumors	51	74.0	0.09	43.0	0.78	30.7	0.02	34.9	0.22
Other noncancer	554	78.1	0.23	46.4	0.81	23.8	0.01	19.6	0.08

* Age standardized.

smokers had no more cancer of the lung than did nonsmokers. Lip cancer was significantly increased among pipe smokers but not among cigaret smokers. Cases of lip cancer were increased also among cigar smokers.

In table 4 persons who smoked more than one type of tobacco are counted in each category. In table 5 only those who smoked but one type of tobacco are considered. The observations in table 4 with respect to lung cancer are the same as in table 5, i. e., only cigaret smokers show any significant increase of lung cancer over nonsmokers. For lip cancer, only pipe smokers show a significant increase over nonsmokers.

No other site of cancer that was included in this study was found to be associated with any particular type of smoking. However, not all sites of cancer were

TABLE 3.—*Prevalence* of Cigaret and Pipe Smokers Among Male Patients by Duration of Smoking and Diagnostic Group*

Diagnosis	No. of Cases	Duration of Smoking: Under 25 Yr. (1) No.	(2) %*	P	25 Yr. and Over (3) No.	(4) %*	P
Cigaret Smokers							
Lung cancer compared with—	236	25	11.7	....	148	54.1	....
Other cancer (except lung and lip)	666	74	13.0	0.62	233	34.9	0.01
Lung nontumors	124	19	16.3	0.23	54	36.9	0.01
Other noncancer	481	92	14.3	0.34	128	29.8	0.01
Pipe Smokers							
Lip cancer compared with—	143	8	7.8	....	60	35.7	....
Other cancer (except lung and lip)	666	26	3.9	0.02	162	22.9	0.01
Lip nontumors	51	5	10.6	0.35	11	21.5	0.04
Other noncancer	554	35	5.8	0.24	87	17.9	0.01

* Age standardized.

studied. It is planned to continue analysis of the records of the Roswell Park Memorial Institute to provide data regarding all types of malignant tumors.

These data indicate that, in a hospital population, cancer of the lung occurs more than twice as frequently among those who have smoked cigarets for twenty-five years than among other smokers or nonsmokers of comparable age. Pipe smokers apparently experience

an almost equal increase in the incidence of lip cancer, compared with other smokers or nonsmokers. It is somewhat surprising to find that the type of smoking, i. e., cigarets for lung cancer, pipe for lip cancer, is the associated factor, rather than the actual use of tobacco.

The data suggest, although they do not establish, a causal relation between cigaret and pipe smoking and cancer of the lung and lip, respectively. The statistical association may, of course, be due to some other unidentified common factor between these types of smoking and lung and lip cancer. Cancer is now generally considered a disease attributable to multiple causative factors. Among these are "irritants." The generalization has been advanced [2] that, although not all irritants are carcinogenic, all carcinogens are irritants, that is, capable of inducing chronic reparative hyperplasia. Berenblum [2a] has shown also that an irritant (croton resin; basic tar fraction) which is noncarcinogenic alone may nevertheless increase the percentage of tumors produced when its action is combined with that of a carcinogen. Thus, some experimental basis exists for explaining the apparent effect of cigaret and pipe smoking, although the true nature of the association with lung and lip cancer remains to be determined.

TABLE 4.—*Comparison of the Proportion* of Cases of Lung and Lip Cancer Among Male Nonsmokers and Smokers of 25 Years' Duration or More at Roswell Park Memorial Institute, 1938-1948*

	No. of Persons	Lung Cancer Cases	Lung Cancer Rate*	Lung Cancer P†	Lip Cancer Cases	Lip Cancer Rate*	Lip Cancer P†
Nonsmokers compared with:	293	23	8.6	....	20	6.9	....
Cigaret smokers ‡.....	600	148	20.7	0.01	37	5.9	0.55
Pipe smokers ‡.....	353	33	8.6	1.00	60	13.4	0.01
Cigar smokers ‡.....	263	22	8.5	0.97	39	12.5	0.03

* Standardized for age against age distribution of total males.

† Probability of the observed difference between smokers and nonsmokers occurring by chance alone.

‡ Multiple smokers, e. g., persons smoking more than one type of tobacco plus those smoking only one type.

TABLE 5.—*Comparison of the Proportion* of Cases of Lung and Lip Cancer Among Male Nonsmokers and Smokers of 25 Years' Duration or More at Roswell Park Memorial Institute, 1938-1948*

	No. of Persons	Lung Cancer Cases	Lung Cancer Rate*	Lung Cancer P†	Lip Cancer Cases	Lip Cancer Rate*	Lip Cancer P†
Nonsmokers compared with:	293	23	8.6	....	20	6.9	....
All smokers ‡.....	761	148	17.1	0.01	73	8.9	0.29
Cigaret smokers ‡.....	479	115	20.9	0.01	22	5.1	0.29
Pipe smokers ‡.....	166	19	10.6	0.48	34	15.7	0.01
Cigar smokers ‡.....	116	14	12.8	0.18	17	11.6	0.13

* Standardized for age against age distribution of total males.

† Probability of the observed difference between smokers and nonsmokers occurring by chance alone.

‡ Persons smoking only one type of tobacco.

2. (*a*) Berenblum, I.: Irritation and Carcinogenesis, Arch. Path. **38**: 233-244 (Oct.) 1944. (*b*) Pullinger, B. D.: First Effect on Mouse Skin of Some Polycyclic Hydrocarbons, J. Path. & Bact. **50**: 463-471, 1940.

Safeguarding the Profession.—Every physician should aid in safeguarding the profession against admission to it of those who are deficient in moral character or education.—Section 3, Chapter III of the PRINCIPLES OF MEDICAL ETHICS of the American Medical Association.

EPINEPHRINE, PREGNENOLONE AND TESTOSTERONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

C. MAYNARD GUEST, M.D.
Albany, N. Y.
WILLIAM H. KAMMERER, M.D.
RUSSELL L. CECIL, M.D.
and
SOLOMON A. BERSON, M.D.
New York

Reports of the effectiveness of cortisone (Kendall's compound E, or 17-hydroxy-11-dehydrocorticosterone) and of pituitary adrenocorticotropic hormone (ACTH) in the treatment of rheumatoid arthritis and spondylitis [1] have given rise to the hope that substances known to stimulate endogenous production or liberation of pituitary adrenocorticotropic hormone might also be effective in these conditions. Vogt [2] demonstrated in several different species of animals that the amount of active cortical material released into the suprarenal vein in one minute is many times that which can be extracted from both adrenal cortices by present methods. The administration of epinephrine was found to increase the amount of cortical material which could be recovered from suprarenal venous blood by several hundred per cent.[3] Her results suggested that epinephrine, administered in doses approaching the amounts that might be liberated normally within the body, stimulates the adrenal cortex directly. Long [4] concluded that the action of epinephrine on the adrenal cortex is indirect and is dependent on the presence of the anterior pituitary gland. Thorn [5] has emphasized the fact that epinephrine is effective in stimulating the pituitary-adrenal system in man. He and his collaborators [6] showed that epinephrine increases 11-oxysteroid and 17-ketosteroid excretion and lowers the total circulating eosinophil count by 50 per cent or more in normal subjects but not in those with pituitary or adrenocortical insufficiency. Almy and Laragh [7] confirmed the observation that epinephrine consistently produces eosinopenia in normal persons. Thorn [8] suggested using 0.5 mg. of epinephrine subcutaneously every six hours in patients with rheumatoid arthritis and referred to improvement which he had obtained in

From the Medical Service of the Veterans Administration Hospital, the Arthritis Clinic, New York Hospital, and the Department of Medicine of Cornell University Medical College, New York, and Bronx, N. Y.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet. Mayo Clin. **24**: 181, 1949.

2. Vogt, M.: The Output of Cortical Hormone by the Mammalian Suprarenal, J. Physiol. **102**: 341, 1943; Some Aspects of the Physiology of the Secretion of the Adrenal Cortex with a Bearing on Clinical Medicine, Exper. Med. & Surg. **5**: 279, 1947.

3. Vogt, M.: Observations on Some Conditions Affecting the Rate of Hormone Output by the Suprarenal Cortex, J. Physiol. **103**: 317, 1944.

4. Long, G. N. H.: Recent Studies on the Function of the Adrenal Cortex, Bull. New York Acad. Med. **23**: 260, 1947.

5. Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency, Springfield, Ill., Chas. C Thomas, Publisher, 1949.

6. Thorn, G. W.; Bayles, T. B.; Massell, B. F.; Forsham, P. H.; Hill, S. R.; Smith, S., and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**: 529, 1949.

7. Almy, T. P., and Laragh, J. H.: Reduction in Circulating Eosinophils Following Epinephrin, Insulin and Surgical Operations, Am. J. Med. **6**: 507, 1949.

8. Thorn, G. W., In discussion on Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of the Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis, read before the Sixty-Second Annual Meeting of the Association of American Physicians, Atlantic City, N. J., May 3, 1949.