Tobacco Smoking as an Etiologic Factor in Disease. I. Cancer*

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Clinicians seem to be in wide disagreement on the relationship between tobacco and cancer. Ochsner (1) and Lickint, (2), for example, considered smoking an important etiologic factor in cancer of the lung. Johnson (3) did not consider specifically the relation between smoking and cancer, but he believed that the only pathologic effect of heavy smoking is congestion of the pharynx. The clinician's point of view is well summarized by the statement of Cameron (4) that for every expert who blames tobacco for cancer of the lung, there is another expert who says tobacco is not the cause.

METHODS OF STUDYING SIGNIFICANCE OF TOBACCO

Clinical histories of individual patients.—The diverse clinical impressions are based to a considerable extent on individual experience and on the clinical histories of individual patients. For example, Hermann (5) observed cancer of the vocal cords in a man 42 years old who smoked heavily and inhaled the smoke. In contrast, no tumor developed in an identical twin who did not smoke. Bogen and Loomis (6) report that bronchogenic carcinoma was found at autopsy in only one woman at the Olive View Sanitarium, and she had given a history of excessive smoking of cigarettes for more than 15 years. Friedell and Rosenthal (7) described eight patients who developed cancer of the mouth following the use of chewing tobacco.

Smoking habits of patients with cancer.—Individual histories are interesting and important in creating clinical impressions, but they only point the way toward studies on groups of patients. Many men have reported on the smoking habits of patients with a particular type of cancer.

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As early as 1915, Abbe (8) in New York reported on 100 private patients with cancer of the mouth. Of these, 90 were men, all of whom except one were heavy smokers. Nearly all of the men used three to twenty cigars a day. This surprisingly high percentage of cigar smokers may be attributed in part to two facts. First, the men were private patients who were presumably in good economic condition and who would be expected to prefer cigars rather than the cheaper cigarettes. Second, the study was made in 1915, when smoking habits of the general population were different from the present. In spite of these two factors, the number of heavy cigar smokers still seems to be unusually high.

Bloodgood (9) reported that nearly all patients with cancer of the tongue used tobacco to excess. He considered tobacco, in whatever form, an important etiologic factor. The literature on the smoking habits of patients with cancer of the lip and of the tongue was reviewed in detail by Haase (10). According to this author, the percentage of smokers among patients with these tumors varied from 100 to 10 per cent in different studies, with an average of 46 per cent. The wide variability in percentages throws doubt on the accuracy and the significance of the statistics.

Jackson and Jackson (11) reported in 1941 that 95 per cent of men with cancer of the larynx were smokers. In spite of this apparently high percentage of smokers, they (12) considered smoking only one of the minor causes of cancer of the larynx. They did not regard it as an essential cause.

Hermann (5) in Essen found that 26 out of 30 male patients (87 per cent) with laryngeal cancer smoked regularly, and most of them heavily; eighteen patients inhaled during smoking. Arkin and Wagner (13) in Chicago reported in 1936 that 90 per cent of 135 patients with cancer of the lung were chronic smokers. These workers, as many others, stress the etiologic significance of inhalation of tobacco smoke. Brockbank (14) in Man-

chester, on the other hand, found only 15 per cent heavy smokers and 21 per cent nonsmokers in 62 patients with pulmonic cancer. Grace (15) states that, in an unusually large series of patients with cancer of the lung, the individuals were heavy cigarette smokers, and almost all were inhalers.

Nearly all of these investigators in different cities report the high incidence of smoking among patients with cancer of the respiratory tract. The findings are suggestive, but the significance of these high percentages cannot be determined without knowing the smoking habits of a control group.

Correlation of increase in smoking and increase in cancer.—Some men used a third method of studying the etiologic significance of smoking. McNally (16) reported that in the United States the cigarette consumption was thirty-four times as much in 1930 as in 1905 (123.8 billion as compared to 3.7 billion). In contrast, the use of cigars declined by 17 per cent during this interval (from 7.6 to 6.3 billion). McNally attributed the reported increase in cancer of the lung to the observed increase in the use of cigarettes. Hoffman (17) also correlated the increase in pulmonic and esophageal cancer with the increased popularity of cigarette smoking. Many other writers, according to Hueper (18), considered that the greater incidence of cancer of the lung was due to the increase in smoking.

TABLE 1

FORM USED IN TAKING THE HISTORIES OF THE SMOKING HABITS OF PATIENTS

	Smoking habits			
	Light	Moderate	Heavy	Duration
Cigarette	10 or less	10–20	More than 20	
Cigar	2 or less	2–4	More than 4	
Pipe	3 or less	3–6	More than 6	
None				

Experimental studies.—These clinical and statistical studies have led many investigators to approach the problem experimentally by studying the carcinogenic effect of smoke or of extracts of tobacco. It is not necessary in this report to review in detail the experimental work, especially since good summaries of the literature were given by Flory (19) in 1941 and Stern and Willheim (20) in 1943. It will suffice to mention the over-all findings of the work on animals.

Most workers obtained no effect or only slight proliferative changes in mice, rats, and rabbits subjected to tobacco tar or to tobacco smoke (21–23).

A few men obtained only a single carcinoma in their entire group of treated animals (24, 25).

In contrast, Roffo (26) painted the ears of rabbits with tobacco tar and derivatives from the tar and reported the development of many tumors which he diagnosed as carcinoma.

Flory (19) obtained tumors of the skin in 50 out of 53 rabbits and in 17 out of 242 mice treated with tar produced by destructive distillation of tobacco, and with tar obtained by smoking tobacco in pipes. In the mice, two tumors were diagnosed as squamous-cell carcinomas, and fifteen as papillomas. Most of the rabbits developed papillomas and a few "carcinomatoid" growths. The latter tumors invaded locally both connective tissue and lymphatic vessels, but they did not metastasize and did not have the property of unrestricted growth. These tumors were not, therefore, considered cancers.

The experimental evidence on the etiologic significance of tobacco in cancer is then equivocal. An editorial in *Lancet* (27) concludes with the understatement that the work with animals has not yet cleared cigarette smoking from suspicion as an etiologic factor.

Smoking habits of patients with cancer and in control individuals.—In the present work the smoking habits of patients with a particular type of cancer were compared with the smoking habits of men in a control group. Several investigators (28, 17, 29, 30) have used this method. Their work will be reviewed later and will be compared with the findings in this report.

METHODS

In 1941, Dr. Baker started the practice at this hospital of having a clerk take a history of the smoking habits of each patient at time of admission by means of a questionnaire shown in Table 1.

In 1948, Drs. Ballard and Dolgoff summarized 5,003 records, selected at random, as to such factors as smoking habits and diagnosis. These men were particularly interested in the relation of smoking with peptic ulcer and heart disease. The data thus obtained were coded and placed on punch cards to facilitate analysis. The punch cards were prepared and handled by Mr. Vernon Graunke and Mr. G. O. Baldo, of Veterans Administration.

The 5,003 records are reviewed in this paper to determine the association of smoking and cancer.

It should be noted that the patients in this study were men, nearly all of whom were veterans of World War I or II or other wars. The patients were admitted during 1942–44.

OBSERVATIONS

All patients as a control group.—In a study such as this, the crucial problem is the choice of a control group. Some factors to be considered in such a

problem have been discussed by Schrek and Allaben (31). One control group that might be used would be the entire group of 5,003 patients studied. By this means, the patients with any particular disease are compared with all the other patients. Let us first try this type of control group.

Cigarette smoking is the principal factor that is considered in this paper. It may be assumed that cancer would not be associated with, or be the result of, mild smoking. Therefore, cigarette smoking for this study was defined as the use of ten or more cigarettes a day. The duration of smoking was not considered at this point.

To compare the incidence of cigarette smoking in the different groups of patients, the graphic method described by Schrek (32) is used and is presented in Figure 1. Each point in the graph shows the number of patients and the percentage

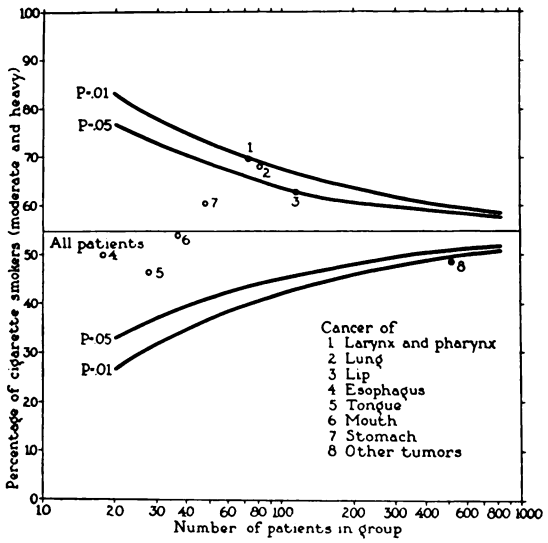

FIG. 1.—A comparison of the percentage of cigarette smoking in all patients with that in patients with cancer of certain sites. The percentage of smokers in the control group consisting of 5,003 patients is 54.8 per cent and is represented by the horizontal line. The curves show the limits of significance. A point on the graph that falls outside these curves differs significantly from the control in its percentage of cigarette smokers.

of cigarette smokers in the group. The percentage of smokers in the control group consisting of all 5,003 patients is 54.8 per cent and is represented by a horizontal line. The distance between the points and the horizontal line represents the difference between the percentages of smokers in each clinical group and the control. To determine whether this difference is statistically significant, curves have been drawn to show the limits of significance. A group of patients represented in the graph by a point that falls outside these curves may be said to differ significantly in its percentage of cigarette smokers from the control.

Of special interest in the graph is the group of patients with "other tumors," that is, tumors other than those of the respiratory and upper digestive tract. This large group of 522 patients had 48.8 per cent smokers, which was significantly lower than the 54.8 per cent for all patients.

The finding of an apparent negative correlation between miscellaneous cancer and cigarette smoking casts doubt on the validity of using all the patients as a control group. In fact, patients with cancer and with other diseases are not comparable in several respects. In the first place, there is the

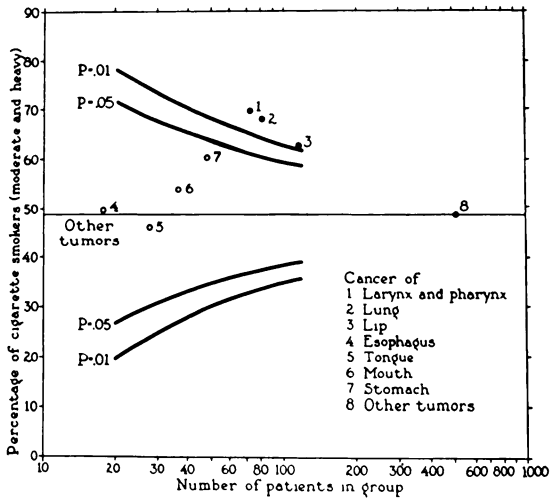

FIG. 2.—A comparison of the percentage of smoking in all patients with tumors with that in patients with cancer of certain sites. Explanation is the same as for Fig. 1.

probable difference in the age distribution of the patients in the two groups. Furthermore, one must take into consideration the fact that this hospital during 1942–44 not only was a general hospital but was, in addition, a cancer center. As a general hospital, patients from Chicago and the vicinity were admitted to it with all types of medical and surgical conditions. As a cancer center for the Veterans Administration, patients with tumors were referred to this hospital from other veterans' hospitals in the entire Midwest. Since smoking habits may be assumed to vary in different parts of the country, one cannot, at least in this hospital, use patients with other diseases as a control for patients with tumor.

It may be concluded, then, that, according to smoking habits, all patients were not a suitable control for comparing with tumor patients. A more suitable control group for studying patients with tumors of the respiratory and digestive tract would seem to be men with "other tumors."

Patients with other tumors as a control group.—In Figure 2, the control group was 522 men with other tumors, of whom 48.8 per cent smoked cigarettes to a moderate or greater extent. This percentage is represented by a horizontal line. As in Figure 1, curves are drawn to show the limits of significance. The percentages of smokers among patients with tumors of the stomach and mouth are higher than the control, but the differences are not statistically significant. This lack of correlation between the incidence of cigarette smoking and of tumors of the upper digestive tract may be due to an insufficient number of patients or to the absence of biologic relationship between smoking and the occurrence of these types of tumors.

In contrast, the groups of patients with tumors of the lung, larynx and pharynx, and the lip have a significantly higher percentage of smokers (68.3, 69.9, and 62.9 per cent, respectively) than the control groups of patients (48.8 per cent).

There is then a correlation between cigarette smoking and the incidence of cancer of the lip and of the respiratory tract. Is the correlation of biologic significance? Before considering this problem, one has to study in more detail the validity of the control group used.

Racial distribution.—In testing the validity of the control group, many factors can be considered. In this study only race and age were tested to determine whether these factors may be responsible for the correlation of cigarette smoking and cancer of the respiratory tract and lip.

The racial distributions of control and clinical groups are presented in Table 2, which shows the percentage of white patients in the different groups of men with cancer. For the control group, 93.1 per cent of the men were white. No significant variations from this percentage were observed for patients with tumors of the lung (89.0 per cent) and of the larynx and pharynx (94.5 per cent). Of the 116 patients with cancer of the lip, however, all or 100 per cent were white. This percentage is significantly higher than that for the control group.

Patients with cancer of the lip differed, then, from patients with "other tumors" in a higher percentage of white men. Is this racial difference in the clinical and control groups responsible for the relatively high percentage of cigarette smokers among patients with cancer of the lip? This question can be answered easily by excluding the colored patients from the control groups (Table 2). The white patients with cancer of the lip had 62.9 per cent cigarette smokers among them as compared to 50.0 per cent for the white men with other tumors. The difference in percentages may be considered as probably statistically significant (P = 0.012). In contrast, the groups of the white patients with cancer of the respiratory tract had significantly elevated percentages of cigarette smokers. It may be concluded that the differences in racial distribution are not responsible for the observed difference in the smoking habits of patients with cancer of the respiratory tract.

TABLE 2

NUMBER AND PERCENTAGE OF MODERATE AND HEAVY CIGARETTE SMOKERS IN WHITE AND COLORED MEN WITH CANCER

Location of tumor	No. of patients			Percentage of white patients	Percentage of cigarette smokers in white patients	Percentage of cigarette smokers in colored patients
	Total	White	Negro			
Other sites	522	486	36	93.1	50.0	33
Lung	82	73	8	89.0	71.2*	50
Larynx and pharynx	73	69	4	94.5	69.6*	
Lip	116	116	0	100.0*	62.9†	

* Percentage is significantly higher than the control percentage for "tumors of other sites" ($P < 0.01$).

† Percentage is probably significantly higher than the control percentage (P = 0.01–0.05).

Incidentally, it may be noted that the data of Table 2 can be tested to determine whether there is any difference in the percentage of cigarette smokers among white and colored patients. In men with "other tumors," for example, cigarette smoking was observed in 50 per cent of the white and only 33 per cent of the colored men. The statistical analysis shows, as might be expected, that colored men had a significantly low percentage of cigarette smokers.

Age distribution.—A second factor that has to be considered is age distribution in the clinical and control groups. A detailed analysis of the age distribution is presented in Figure 3. This graph shows the frequency distribution curves on arithmetic probability paper. This type of graph paper has the advantage of facilitating the comparison of several frequency distributions and permits the representation of a normal distribution by a straight line (Schrek, 33).

The age distribution of the 522 control patients with other tumors is represented in the figure by an irregular curve. The irregularity of the curve indicates that the age distribution is not normal and that the patients are a heterogeneous group. The heterogenicity arises from the fact that the patients in this hospital fall into three distinct categories, namely, veterans of World War I and II and of the Spanish-American War.

A second observation that can be derived from the figure is that the age distributions for the clinical groups differ to an appreciable extent from the control. These differences are greatest in the lower age groups and may possibly be attributed to varying numbers of World War II veterans in the groups.

The age distribution of the control and the clinical groups are also expressed in Figure 3 by means of the average age and the standard deviation. It was found that the arithmetic mean for the ages of the patients with cancer of the lung, larynx and pharynx, and lip (51.46, 52.57, and 52.72 years) do not differ significantly from that for the control group (51.98 years). In contrast, the standard deviation of the three clinical groups (5.98, 6.90, and 7.92 years) are definitely lower than that for the control (10.62). The age distributions for the three clinical groups differ then, at least in one respect, from that for the control.

Evidently, it is necessary to eliminate or minimize the variations in age distributions before comparing the smoking habits in the clinical and control groups. Table 3 presents a detailed analysis of the percentage of cigarette smokers in white patients. It may be concluded from this table that, even when age and race are controlled, the percentage of cigarette smokers in men with cancer of the larynx and pharynx is definitely higher than in the control group ($P = 0.01$). For cancer of the lung, the percentage of cigarette smokers is probably higher ($P = 0.03$).

An incidental observation is that in the patients with tumors in other sites, the older men 50–59 and 60–69 years have a lower percentage of cigarette smokers then men 40–49. This finding may be correlated with McNally's report (16) of an increase in cigarette consumption. The greater popularity of smoking might be expected to affect the younger men more than the older.

Other factors have to be considered in comparing the clinical and control groups. Inasmuch as the patients with tumors are derived from the entire Midwest and from city, town, and farm, it is necessary to consider the geographic distribution of patients. Unfortunately, data on this factor

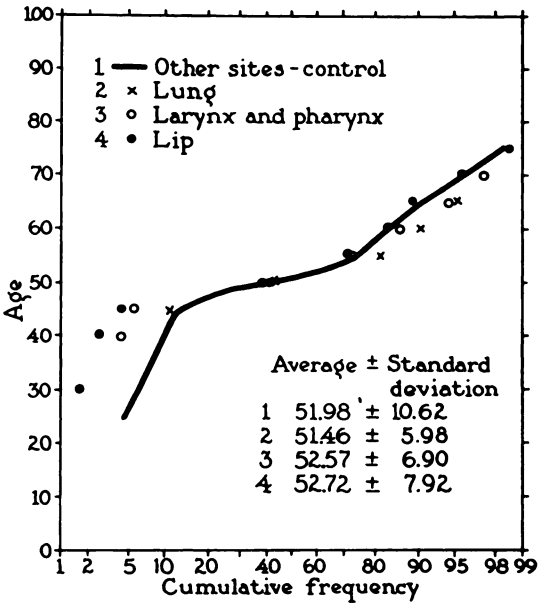

FIG. 3.—The age distribution of patients with cancer of various sites. The irregular curve represents the age distribution of the 522 control patients with other tumors. The irregularity of the curve indicates that the age distribution is not normal and that the patients are a heterogeneous group.

TABLE 3

PERCENTAGE OF MODERATE AND HEAVY CIGARETTE SMOKERS IN WHITE MEN ACCORDING TO AGE AND TYPE OF CANCER

	No. of white men with tumors of				Percentage of moderate and heavy cigarette smokers in white men with tumors of			
Age	Other sites	Lung	Larynx and pharynx	Lip	Other sites	Lung	Larynx and pharynx	Lip
20–	34	0	0	2	50			100
30–	10	0	2	1	40		100	0
40–	171	35	24	47	57.9	77*	58	70
50–	192	30	33	48	49.5	67	82†	56
60–	62	8	8	14	40.3	63	38	71*
70–	17		2	4	18			25
P						0.03	0.01	0.06

* Percentage is probably significantly higher than the control percentage ($P = 0.01$–0.05).

† Percentage is significantly higher than the control percentage for "tumors of other sites" ($P < 0.01$).

were not obtained in reviewing the 5,003 original records. In previous studies in this hospital, Schrek and Allaben (31) found that the groups of patients with cancer of the lung and larynx had the same percentage of southerners and the same percentage of rural dwellers as in control groups. It is probable, then, that there are no significant differences in the geographic distribution of patients with cancer of the respiratory tract and of control patients. The previously observed correlation between the incidence of cigarette smoking and of cancer of the respiratory tract cannot be attributed to the extraneous factor of geographic distribution.

TABLE 4

THE DURATION AND THE AGE AT ONSET OF CIGARETTE SMOKING (MODERATE AND HEAVY) IN PATIENTS

Location of tumor	No. of cases of heavy and moderate cigarette smoking	Age at onset of smoking		Duration of smoking	
		Average	Standard deviation	Average	Standard deviation
Lung	56	21.3	6.7	29.2	8.3
Larynx and pharynx	51	21.8	8.6	30.7	7.9
Lip	73	19.7	6.5	31.2	9.4
Other sites	255	21.5	7.7	27.6	10.4

TABLE 5

CIGARETTE SMOKING IN PATIENTS WITH HISTOLOGICALLY PROVED TUMORS OF THE RESPIRATORY TRACT

Site of tumors	No. of patients	Moderate and heavy cigarette smokers	
		No.	Per cent
Lung:			
Histologically proved cases	47	30	64
Other cases	35	26	74
Total	82	56	68
Larynx and pharynx:			
Histologically proved cases			
Larynx	43	31	72
Pharynx	5	4	80
Larynx and pharynx	3	2	67
Nasopharynx	13	8	61
Total	64	45	70
Other cases	9	6	67
Total	73	51	69

Schrek and Allaben (31) found that men with cancer of the lip had a significantly high percentage of individuals from rural sections (44 per cent as compared to 26 per cent for all cancer patients). The percentage of southerners among patients with cancer was slightly but not significantly higher (30 per cent as compared to 26 per cent). These differences in the geographic distribution of patients with cancer of the lip and of control patients are an additional reason for disclaiming any biologic significance for the high percentage of cigarette smoking in patients with cancer of the lip.

Duration and age at onset of smoking.—In some types of tumors it appears that the development of cancer in an individual depends not only on the carcinogenic agent but also on the age of the individual at the time of the first exposure to the agent. It is, therefore, of importance to investigate the age at which the patients started to smoke.

The history of the duration of smoking was obtained as indicated in the questionnaire in Table 1. Subtracting the duration of smoking from the age of the patient gave an estimate of the age at onset of smoking. It would have been preferable to have interrogated the patient directly as to his age at onset of smoking. There probably was a large percentage of error in the reported duration and in the derived age at onset.

Table 4 presents the average duration and the age of onset for patients in the clinical and control groups. Only the moderate and heavy cigarette smokers are considered in the table. It is seen that the average duration for the four groups of patients is approximately the same (27.6–31.2 years). The slight differences in the averages are not significant. The duration of smoking varied considerably (from 1 to 60 years). This wide range is reflected by the high standard deviations for the duration (7.9–10.4 years). There were no significant differences in the standard deviations. According to these results, the duration of cigarette smoking for patients with cancer of the respiratory tract is not appreciably greater than for patients with other tumors.

The average age at onset of smoking was approximately 21 years for the patients in both the clinical and the control groups. This average seems high, and it may indicate the unreliability of the method used in deriving the age at onset. The standard deviations for the four groups varied from 6.5 to 8.6 years and did not differ significantly from each other.

The present findings failed to confirm an anticipated longer duration of smoking and an earlier age at onset of cigarette smoking for patients with cancer of the respiratory tract.

Histologic classification of tumors.—Not all tumors in the clinical groups were examined by biopsy or autopsy. Table 5 shows the number of patients with histologically proved tumors and the smoking histories of these individuals. It is seen that of the 82 patients with cancer of the lung, more than half (47) had the diagnosis confirmed by biopsy or autopsy. The percentage of cigarette smokers in the proved and nonproved cases were

approximately the same (64 and 74 per cent, respectively).

Of the 73 patients with cancer of the larynx and pharynx, 64 had positive biopsies. The percentage of cigarette smokers in the patients with proved cancers was 70 per cent. It is to be noted that the number of patients with tumors of the pharynx and nasopharynx was so small that it is not possible to obtain satisfactory percentages of cigarette smokers.

Complete smoking habits.—Inasmuch as there appears to be a correlation between moderate and heavy cigarette smoking for cancer of the respiratory tract, it seems necessary to consider in detail the smoking habits of the patients with these tumors.

Figure 4 shows the percentage of mild, moderate (10–20 cigarettes a day), and heavy cigarette smokers for patients in the clinical and the control groups. It is seen that patients with cancer of the respiratory tract had a higher percentage of both heavy and moderate cigarette smokers than the control. In contrast, the group of men with cancer of the lip had a greater percentage of mild and moderate smokers. These findings lend support to the belief that the association between smoking and cancer of the respiratory tract has biologic significance, but the correlation between smoking and cancer of the lip is only incidental.

Figure 4 also compares the nonsmokers in the four groups. For cancer of the lung, of the larynx and pharynx, and of the lip, the percentages of nonsmokers were less than for other tumors (14.6, 13.7, and 10.3 per cent as compared to 23.9 per cent). This finding is not surprising. Since the previous finding was a positive correlation between cigarette smoking and cancer of the respiratory tract and lip, one would expect an associated negative correlation between nonsmoking and the three types of cancer.

Other factors that have to be considered are cigar and pipe smoking. Figure 5 indicates that patients with cancer of the respiratory tract had relatively low percentages of cigar and pipe smoking. These findings, as in the case of the previously observed low incidence of nonsmokers, are apparently the result of the high percentages of cigarette smokers in cancer of the respiratory tract.

DISCUSSION

Review of literature on use of control groups.—The present findings are dependent upon the statistical method of setting up a control group to compare with the clinical group. This method was used for studying the relationship of smoking and cancer by several investigators.

Broders (28) observed that, in a group of 537 patients with cancer of the lip, only 11 were women. He compared the smoking habits of these patients with 500 control men. Both groups had approximately the same percentage of nonusers of tobacco (19.51 and 21.4 per cent). There was,

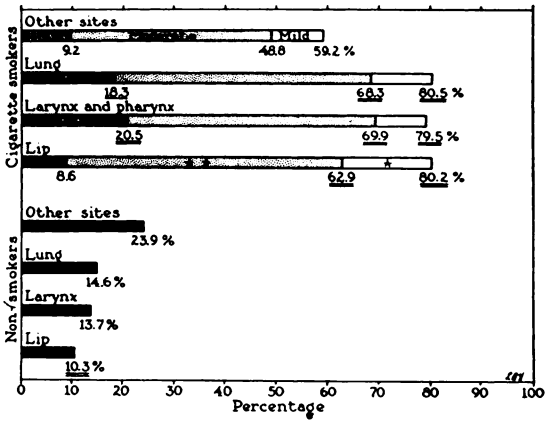

FIG. 4.—This shows the percentage of mild, moderate, and heavy cigarette smokers for patients with cancer of various sites.

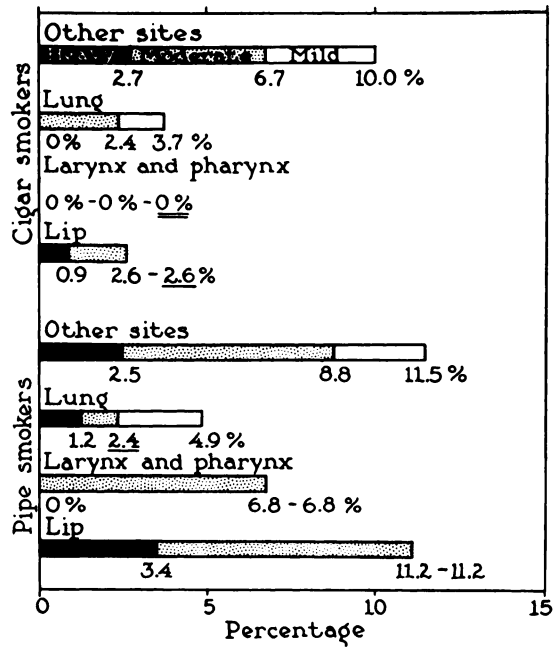

FIG. 5.—This shows the percentage of pipe and cigar smoking for patients with cancer of various sites.

however, a much higher percentage of pipe smokers among the smokers with cancer than in those of the control group (78.48 and 38.03 per cent) and a much lower percentage of cigarette smokers (1.16 as compared to 59.04 per cent in the control). The control group was not, however, entirely a satis-

factory one, as is indicated by the fact that the average age of the control men was 36.07 years, whereas the average age of the cancer patients was 57.3 years. It seems unfortunate that the remarkable differences in the smoking habits of the two groups cannot be properly evaluated because of an insufficient statistical analysis of the data.

In the present work, the group of patients with cancer of the lip did not have an elevated percentage of pipe smokers, nor a low percentage of cigarette smokers. The conflict in the findings do not necessarily mean that there is an error in either the work of Broders or in that of the present authors. Fashions in smoking vary at different times and among different groups of people. If smoking is an etiologic factor in cancer, the variations in the smoking habits will be reflected by changes in the type or the incidence of cancer. For the patients of Mayo Clinic in 1920, pipe smoking may have been a significant etiologic factor in cancer of the lip. For the patients of Hines Veterans Hospital in 1942–44, exposure to sunlight, rather than smoking, appeared to be the major etiologic factor in lip carcinoma.

Hoffman (17) studied the smoking habits of cancer patients in San Francisco, Buffalo, and Boston. He found that the percentage of heavy smokers was 67 among 27 patients with cancer of the lung, 43 among 37 with laryngeal cancer, and 48 among 120 with cancer of the lip. These percentages may be compared with 45.6 heavy smokers in 1,416 male patients with all tumors and 42.3 in 537 men with chronic disease. According to these figures, he failed to obtain any definite correlation between smoking and cancer of the respiratory tract. He minimized, however, this negative finding and attributed it to the small size of the groups, to the poor histories of the smoking habits, and to the presence of other etiologic factors. One also has to consider the suitability of the control group in considering the significance of the negative findings.

Striking results on the correlation of lung cancer and smoking were obtained by Müller (29), who compared the smoking habits of 86 men with cancer of the lung with 86 normal individuals in the same age groups as the patients. The group of patients had a relatively very high percentage of heavy smokers (50.0 as compared to 10.5) and a correspondingly low percentage of nonsmokers (3.5 as compared to 16.3). A heavy smoker was defined as one who used at least 7 cigars, 26 cigarettes, or 36 gm. of pipe tobacco. These findings led Müller to conclude that smoking is an important cause of cancer of the lung.

Recently, Wynder and Graham (30) reported to a cancer meeting in Memphis a comparison of the smoking habits of 200 male patients with cancer of the lung and of 500 control individuals. They found a relatively high percentage of heavy cigarette smokers (95.5 as compared to 50 per cent throughout) and a low percentage of nonsmokers (0.5 as compared to 11). A heavy cigarette smoker was defined as one who had smoked at least 20 cigarettes a day for 20 years. Wynder and Graham, like Müller, found a definite difference in the smoking habits of patients with pulmonic cancer and of control men.

A comparison of the results of the different investigators shows that Müller, Wynder and Graham, and the present authors agree in the finding that cancer of the lung is associated with heavy smoking.

An incidental observation that may be derived from the comparison is the difference in the smoking habits of the control groups of the various studies. For example, nonsmokers in the control groups were 21.4 (Broders), 3.5 (Müller), 11 (Wynder and Graham), and 23.9 per cent (present study). The observed differences are not surprising, since they only indicate that smoking habits vary in different localities and at different times. The finding stresses the need for determining the smoking habits of a suitable control group.

The work of Broders and the others indicates, furthermore, that it is not enough to use a control group for comparison with the cancer patients. It is also necessary to check carefully the control group to see that it is a suitable one for the particular factor under investigation.

Is smoking an etiologic factor in cancer?—From this study and from the work of Müller and Wynder and Graham, it may be concluded that there is a positive association or correlation of cancer of the lung and smoking, particularly cigarette smoking. The correlation is definitely statistically significant, but is it biologically significant? A statistical study cannot prove whether there is a cause-and-effect relationship between two factors. At best, the statistical study can provide circumstantial evidence that a correlation is biologically significant.

Willis (34) summarizes well the conclusions that may be drawn from a statistical study in his statement: "Comparison of the smoking habits of victims of lung cancer with those of control cases obtained by careful questionnaires, like [Müller's, afford strong grounds for suspecting the carcinogenic results of smoking; but, however strongly suggestive, they cannot afford incontrovertible proof—especially in the eyes of smokers themselves!"

The statistical findings are then only circum-

stantial evidence that smoking is an etiologic agent in cancer. Let us evaluate whether the evidence is valid.

The observed correlation between smoking and cancer can be explained in several ways. First, it may be considered that the correlation is a result of fortuitous or chance factors. The tests for statistical significance indicated to a large extent that the observed results are not due to the accidents of sampling.

A second explanation for the correlation is that it was not a direct relationship, but an indirect one and was dependent upon such secondary factors as race, age, occupation, etc. If it were possible to obtain a control group which was exactly the same as the clinical groups in all factors except two—the presence of cancer and smoking—it would be possible to test definitely whether there is a direct relationship between these two factors. Such a control group is frequently approached in experimental work, but rarely in clinical studies.

The chances of obtaining an indirect relationship dependent on secondary factors can be minimized to a considerable degree. The first step is to select the control group with a full and detailed knowledge of the local situation in regard to such factors as the type of patients admitted and the method of taking histories. In this study, for example, it was necessary to consider that cancer and noncancer patients were selected from different localities and populations and, therefore, noncancer patients could not be used as a control.

The second step in considering the possibility of indirect relationship is by testing and comparing the control and the clinical group in as many secondary factors as possible or as seem feasible. In this work it was possible to test age and race. An analysis of these two factors indicated that the control group was unsuitable for cancer of the lip but could be used for cancer of the respiratory tract. When age and race were equalized in the control and clinical groups, there still remained a statistically significant correlation between smoking and cancer of the lung and of the larynx and pharynx.

A third and important step in minimizing indirect relationships is the comparison of the statistical studies in different institutions by different investigators. The uniformity of the findings obtained by Müller and Wynder and Graham, and in the present study is impressive. There still remains a slight possibility that some abstruse secondary factor remained the same in all three investigations and resulted in an indirect relationship between smoking and cancer of the lung.

The correlation between smoking and cancer is, then, probably not due to fortuitous or secondary factors. It seems plausible, therefore, to formulate the hypothesis that there is a direct relationship between cigarette smoking and cancer of the respiratory tract and that cigarette smoking may be a carcinogenic agent.

There is another aspect to the problem. If cigarette smoking is a carcinogenic agent, how dangerous is this habit? This question could not be considered from the present data. Some information can be obtained, however, from other statistics and experiments.

In animal experimentation, application of a strong carcinogenic agent produces tumors in nearly all the animals, but a weak agent causes tumors in only a few animals.

It is well known that cigarette smoking is widespread. The control groups in the present study and in Wynder and Graham's work suggests that about half of the men are moderate and heavy cigarette smokers. According to the mortality statistics of the United States (35), 0.76 per cent of the deaths of men past 40 were due to cancer of the respiratory system. This relatively low percentage of deaths by cancer of the respiratory tract as compared to the high percentage of smokers indicates that smoking is, at most, only a weak carcinogenic agent.

SUMMARY AND CONCLUSIONS

The smoking habits of 82 men with cancer of the lung and 73 men with cancer of the larynx and pharynx were compared with the smoking habits of a control group of 522 patients with miscellaneous tumors. A relatively high percentage of cigarette smokers was found among the patients with cancer of the respiratory tract, as compared to the control. This positive correlation between the incidence of cigarette smoking and the incidence of cancer of the respiratory tract appeared to be both statistically and biologically significant. There is strong circumstantial evidence that cigarette smoking was an etiologic factor in cancer of the respiratory tract.

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