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

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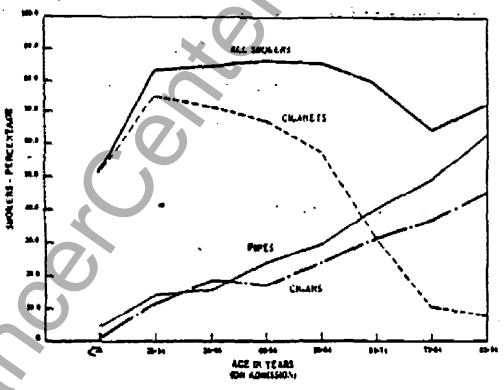
The published literature on use of tobacco and its possible association with human cancer fails to show clearcut consistent observations. Reviews of the literature for the past twenty years reveals that it is often conflicting and that it consists for the most part of studies which are inconclusive because 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 Breese and David Robbins.
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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.

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This report is based on a study 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	58.0	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 t ata 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)		Cigaret (2)		Pipes (3)		Cigars (4)	
		%	P	%	P	%	P	%	P
Lung cancer compared with—	230	84.7	....	66.1	....	13.5	....	11.2	....
Other cancer (except lip)	666	82.9	0.35	48.0	0.01	25.8	0.01	20.2	0.01
Lung nontumors	124	81.1	0.29	33.1	0.01	25.5	0.09	17.4	0.01
Other noncancer	481	78.3	0.05	44.1	0.01	25.3	0.01	22.7	0.01
Lip cancer compared with—	143	84.5	....	45.2	....	48.1	....	26.5	....
Other cancer (except lung)	666	82.9	0.56	48.0	0.49	25.8	0.01	20.2	0.11
Lip nontumors	51	74.0	0.09	45.0	0.78	20.7	0.02	34.9	0.23
Other noncancer	334	78.1	0.23	46.4	0.81	23.8	0.01	19.6	0.09

* 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.			25 Yr. and Over			
		(1) No.	(2) % *	P	(3) No.	(4) % *	P
Cigaret Smokers								
Lung cancer compared with—	236	25	11.7	....	149	54.1	....
Other cancer (except lung and lip)	666	74	13.0	0.02	225	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	33.7	....
Other cancer (except lung and lip)	666	26	3.9	0.02	162	22.9	0.01
Lip nontumors	51	5	10.6	0.33	11	21.5	0.04
Other noncancer	334	35	5.8	0.34	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 Pt	Lip Cancer Cases	Lip Cancer Rate*	Lip Cancer Pt
Nonsmokers compared with:	293	23	8.6	....	20	6.9	....
Cigaret smokers ‡.....	600	148	20.7	0.01	37	5.9	0.35
Pipe smokers ‡.....	358	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 Pt	Lip Cancer Cases	Lip Cancer Rate*	Lip Cancer Pt
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	0.46	34	15.7	0.01
Cigar smokers ‡.....	116	14	12.8	0.18	17	11.0	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.

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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

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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

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