METHODOLOGIC VARIABLES

Subject Selection—

1. Males and/or females
2. Occupational groups
3. Hospitalized cases
4. Autopsy series
5. Total lung cancer deaths in an area
6. Samplings of nationwide lung cancer deaths

Control Selection—

1. Age matching vs. age groups
2. Healthy individuals
3. Patients hospitalized for other cancers
4. Patients hospitalized for causes other than cancer
5. Deaths from cancers of other sites
6. Deaths from other causes than cancer
7. Samplings of the general population

Method of Interviewing—

1. Mailed questionnaires
2. Personal interviewing of subjects (or relatives) and controls
   a) By professional personnel
   b) By non-professional personnel

Tobacco-use Histories—

1. By type of smoking (separately and combined)
2. By amount and type
3. By amount, type, and duration
4. By inhalation practices

Other Variables Concurrently Studied—

1. Geographic distribution
   a) Regional
   b) Urban-rural
2. Occupation
3. Marital status
4. Coffee and alcohol consumption
5. Other nutritional factors
6. Parity
7. War gas exposures
8. Other pathologic conditions
9. Hereditary factors
10. Air pollution
11. Previous respiratory conditions

This listing of methodologic variations is by no means complete, nor does it imply that the individual retrospective studies should be criticized for their choice of study methods and factors for observation. The individual points of criticism have usually applied to one or two studies but not to all.

It is indeed striking that every one of the retrospective studies of male lung cancer cases showed an association between smoking and lung cancer. All have shown that proportionately more heavy smokers are found among the lung cancer patients than in the control populations and proportionately fewer non-smokers among the cases than among the controls. Furthermore, the disparities in proportions of heavy smokers between "test" groups and controls are statistically significant in all the studies. The differences in proportions of non-smokers among the two groups are also statistically significant in all studies but one (236); in the latter study, although there were fewer non-smokers among lung cancer patients, the difference was very small.

In the studies which dealt with female cases of lung cancer, similar findings are noted in all of them with one exception (238). In this latter study, although significantly more heavy smokers were found among the lung cancer cases than among the controls, the proportion of non-smokers among the cases was distinctly higher than among the controls. This is the only inconsistent finding among all the retrospective studies. Its meaning is not clear but the authors have indicated that non-response among their female cases was 50 percent.

The weight to be attached to the consistency of the findings in the retrospective studies is enhanced when one considers that these studies exhibit considerable diversity in methodologic approach.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Müller 1939 (250)	Germany	M	86 Lung cancer decedents, Bürger Hospital, Cologne.	86 Healthy men of the same age	Cases: Questionnaire sent to relatives of deceased. Controls: Not stated.
Schairer and Schoeniger 1943 (309).	Germany	M	93 Cancer decedents autopsied at Jena Pathological Institute, 1930–1941.	270 Men of the city of Jena aged 53 and 54 (average age of lung cancer victims = 53.9).	Cases: Questionnaire sent to next of kin (195 for lung cancer). Controls: Questionnaire sent to 700.
Potter and Tully 1945 (280)	U.S.A.	M	43 Male patients aged over 40 in Massachusetts cancer clinics with cancer of respiratory tract.	1,847 Patients of same group with diagnoses other than cancer.	Cases and controls interviewed in clinics
Wassink 1948 (363)	Netherlands	M	134 Male clinic patients with lung cancer.	100 Normal men of same age groups as cases.	Cases: Interviewed in clinic. Controls: Not stated.
Schrek et al., 1950 (311)	U.S.A.	M	82 Male lung cancer cases among 5,003 patients recorded, 1941–48.	522 Miscellaneous tumors other than lung, larynx and pharynx.	Smoking habits recorded during routine hospital interview.
Mills and Porter 1950 (237)	U.S.A.	M	444 Respiratory cancer decedents in Cincinnati, 1940–45 and in Detroit, 1942–46.	430 Sample of residents matched by age in Columbus, Ohio, from census tracts stratified by degree of air pollution.	Cases: Relatives queried by mail questionnaire or personal visit. Controls: House-to-house interviews.
Levin et al., 1950 (207)	U.S.A.	M	236 Cancer hospital patients diagnosed lung cancer.	481 Patients in same hospital with non-cancer diagnoses.	Cases and controls: Routine clinical history taken before diagnosis.
Wynder & Graham 1950 (381).	U.S.A.	M–F	605 Hospital and private lung cancer patients in many cities.	780 Patients of several hospitals with diagnoses other than lung cancer.	Nearly all data by personal interview; a few cases by questionnaire; a few from intimate acquaintances. Some interviews with knowledge or presumption of diagnosis, some with none.
McConnell et al., 1952 (236)	England	M–F	100 Lung cancer patients, unselected, in 3 hospitals in Liverpool area, 1946–49.	200 Inpatients of same hospitals, matched by age and sex, without cancer, 1948–50.	Personal interviews by the authors of both cases and controls, with few exceptions.
Doll and Hill 1952 (82)	Great Britain.	M–F	1,465 Patients with lung cancer in hospitals of several cities.	1,465 Patients in same hospitals, matched by sex and age group; some with cancer of other sites, some without cancer.	Personal interviews of cases and controls by almoners.
Sadowsky et al., 1953 (301)	U.S.A.	M	477 Patients with lung cancer in hospitals in 4 states.	615 Patients in same hospitals with illnesses other than cancer.	Personal questioning by trained interviewers.

Wynder and Cornfield 1953 (379).	U.S.A.	M	63 Physicians reported in A.M.A. Journal as dying of cancer of the lung.	133 Physicians of same group dying of cancer of certain other sites.	Mail questionnaire to estates of decedents
Koulumies 1953 (192)	Finland	M–F	812 Lung cancer patients diagnosed at one hospital in 16 years.	300 Outpatients of same hospital aged over 40, living in similar circumstances, and without cancer, February and March 1952.	Cases and controls questioned about smoking habits when taking case histories.
Lickint 1953 (211)	Germany	M–F	246 Lung cancer patients in a number of hospitals and clinics.	2,002 Sample of persons without cancer living in the same area and of same sex and age range as cases.	Personal interviews by staff members of cooperating hospitals and clinics, corresponding in time to interviews of cases.
Breslow et al., 1954 (38)	U.S.A.	M–F	518 Lung cancer patients in 11 California hospitals, 1949–52	518 Patients admitted to same hospitals about the same time, for conditions other than cancer or chest disease, matched for race, sex, and age group.	Cases and controls questioned by trained interviewers, each matched pair by the same person.
Watson and Conte 1954 (365).	U.S.A.	M–F	301 All patients of Thoracic Clinic at Memorial Hospital who were diagnosed lung cancer, 1950–52.	468 All patients of same clinic during same period with diagnoses other than lung cancer.	The 769 consecutive patients of case and control groups were questioned by the same trained interviewer.
Gsell 1954 (138)	Switzerland	M	135 Men with diagnosis of bronchial carcinoma.	135 Similar hospital patients with diagnoses other than lung cancer, and of the same age.	Personal interviews, all by the same person.
Randig 1954 (283)	Germany	M–F	448 Lung cancer patients in a number of West Berlin hospitals, 1952–1954.	512 Patients with other diagnoses, matched for age.	Controls were interviewed at about the same time as the cases, each case-control pair by the same physician.
Stocks and Campbell 1955 (337).	(Preliminary; see 1957 report below.)				
Wynder et al., 1956 (375)	U.S.A.	F	105 Patients with lung cancer in several New York City hospitals, 1953–55.	1,304 Patients at Memorial Center with tumors of sites other than respiratory or upper alimentary, 1953–1955.	Cases: Personal interview or questionnaire mailed to close relatives or friends Controls: Personal interview.
Segi et al., 1957 (316)	Japan	M–F	207 Patients with lung cancer in 33 hospitals in all parts of the country, 1953–55.	5,636 Patients free of cancer in 420 local health centers, selected to approximate the sex and age distributions of cases.	Cases and controls by personal interview using long questionnaire on occupational and medical history and living habits.
Mills and Porter 1957 (238)	U.S.A.	M–F	578 Residents of defined areas dying of respiratory cancer, 1947–55.	3,310 Population sample approximately proportional to cases as regards areas of residence, and 10 years or more in the area.	Cases: From death certificates, hospital records, and close relatives or friends. Controls: Personal home visits or telephone calls, usually interviewing housewife.
Stocks 1957 (335)	England	M–F	2,356 Patients suffering from or dying with lung cancer within certain areas.	9,362 Unselected patients of the same area admitted for conditions other than cancer.	Cases: Histories taken at the hospital or from relatives by health visitors. Controls: Personal interview in hospital.

TABLE 2.—*Outline of methods used in retrospective studies of smoking in relation to lung cancer*—Continued

Investigator, year, and reference	Country	Sex of cases	Number of persons and method of selection		Collection of data
			Cases	Controls	
Schwartz and Denoix 1957 (313).	France	M	602 Patients with bronchopulmonary cancer in hospitals in Paris and a few other cities.	1,204; 3 groups: patients in same hospitals with other cancer, with non-cancer illness, and accident cases, matched by age group.	Personal interviews in the hospital; cases and controls at about the same time by the same interviewer.
Haenszel et al., 1958 (150)	U.S.A.	F	158 Lung cancer patients available for interview in 29 hospitals, 1955–57.	339 Patients in same hospital and service at same time, next older and next younger than each case.	Personal interviews by resident, medical social worker, or clinic secretary.
Lombard and Snegireff 1959 (222).	U.S.A.	M	500 Men dying of lung cancer, microscopically confirmed, 1952–53.	4,238 Controls in 7 groups including volunteers, hospital and clinic patients, random population sample, and house-to-house survey samples.	Personal interviews by trained workers.
Pernu 1960 (277)	Finland	M–F	1,606 Respiratory cancer patients in 4 hospitals and from cancer registry between 1944 and 1958.	1,773 Cancer-free persons recruited by Parish Sisters of 2 institutes in all parts of the country.	Cases: From case histories or mailed questionnaires. Controls: Questionnaires distributed by Parish Sisters.
Haenszel et al., 1962 (147)	U.S.A.	M	2,191 Sample of 10 percent of white male lung cancer deaths in the U.S. in 1958.	31,516 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.
Lancaster 1962 (199)	Australia	M	238 Hospital patients with lung cancer	476 Two groups, one with other cancer, one with some other disease, matched by sex and age.	Personal interviews of both cases and controls in hospitals.
Haenszel and Taeuber 1963 [1] (152).	U.S.A.	F	749 Sample of 10 percent of white female lung cancer deaths in the U.S. in 1958 and 1959.	34,339 Random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Population: Personal interview by Census enumerators.

[1] To be published.

Germane to this concordance is a recent study (386) of Seventh Day Adventists, a religious group in which smoking and alcohol consumption are uncommon. On the basis of expectancy of male lung cancer incidence derived from the control population, only 10 percent of the cases expected were actually found among Seventh Day Adventists.

FORM OF TOBACCO USE

In considering the details of the individual retrospective studies listed in Tables 2 and 3, 13 of the studies, combining all forms of tobacco consumption, found a significant association between smoking of any type and lung cancer (138, 199, 211, 250, 277, 280, 283, 309, 316, 363, 365, 379, 381); 16 studies yielded an even stronger association with cigarettes alone as compared to pipe and/or cigar smoking (38, 82, 147, 192, 207, 222, 236, 237, 238, 277, 283, 301, 311, 314, 335, 379) when these forms of smoking were considered separately and in combinations for males. The females, in the studies investigating the relationship of smoking and lung cancer among them, were almost invariably cigarette smokers so that comparisons with other forms of tobacco use were not indicated.

AMOUNT SMOKED

Twenty-six of the studies quantitated the amount of smoking per day either by combining weights of tobacco consumed in any form, or, more often, by quantities of the specific forms of tobacco. In each of the studies investigating male lung cancer, the degree of association increased as the amount of smoking increased (38, 82, 138, 147, 150, 192, 199, 211, 222, 236, 250, 277, 280, 283, 301, 309, 311, 314, 316, 335, 363, 365, 379, 381). One retrospective study (82) by Doll and Hill found a sharper difference in amount smoked between cases and controls among recent smokers (10 years preceding onset of the disease) than in a comparison of the maximum amount ever smoked. The authors cautioned against accepting this finding as being against their hypothesis of a gradient of risk (which would more properly be tested by the whole life history of "exposure to risk") by citing the inaccuracies resulting from "requiring the patient to remember habits of many years past."

Of the 11 retrospective studies with data on females and tobacco use by amount smoked daily, six (211, 236, 277, 283, 365, 381) showed trends of increasing association with amount smoked daily, but had too few cases for reliability of the trend. However, five studies (82, 150, 152, 335, 375) did have large numbers of female lung cancer cases for analysis by smoking class; three of these (150, 152, 375) were directed towards female cases only. In each of these latter five studies, the degree of association increased with the amount of cigarettes smoked daily.

Four of the retrospective studies dealt with *ex-smokers* as well (147, 152, 211, 314); in one of these (314), where relative risks were derived indirectly by the Cornfield method (61), and in another by conventional use of standardized mortality ratios (147), male ex-smokers showed a lower risk than

TABLE 3.—*Group characteristics in retrospective studies on lung cancer and tobacco use*

Authors	Reference	Year	Males						Females						Remarks
			Cases			Controls			Cases			Controls			
			Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	Number	Percent non-smokers	Percent heavy smokers [1]	
Müller	(250)	1939	86	3.5	65.1	86	16.3	36.0	(*)	(*)	(*)	(*)	(*)	(*)	
Schairer & Schoeniger	(309)	1943	93	3.2	31.2	270	15.9	9.3	(*)	(*)	(*)	(*)	(*)	(*)	16 female cases not analyzed.
Potter & Tully	(280)	1945	43	7.0	30.2	1,847	26.0	23.0	(*)	(*)	(*)	(*)	(*)	(*)	
Wassink	(363)	1948	134	4.8	54.8	100	19.2	19.2	(*)	(*)	(*)	(*)	(*)	(*)	Percentages estimated from chart.
Schrek et al	(311)	1950	82	14.6	18.3	522	23.9	9.2	(*)	(*)	(*)	(*)	(*)	(*)	
Mills & Porter	(237)	1950	444	7.2	(**)	430	30.5	(**)	(*)	(*)	(*)	(*)	(*)	(*)	
Levin et al	(207)	1950	236	15.3	(**)	481	21.7	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Quantity smoked not considered.
Wynder & Graham	(381)	1950	605	1.3	51.2	780	14.6	19.1	40	57.5	25.0	552	79.6	1.2	
McConnell et al	(236)	1952	93	5.4	38.5	186	6.5	23.2	7	57.1	(**)	14	78.6	(**)	
Doll & Hill	(82)	1952	1,357	0.5	25.1	1,357	4.5	13.4	108	37.0	11.1	108	54.6	0.9	Percentage "heavy" smokers understated.
Sadowsky et al	(301)	1953	477	3.8	(**)	615	13.2	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Gradient with amount smoked.
Wynder & Cornfield	(379)	1953	63	4.1	67.6	133	20.6	29.3	(*)	(*)	(*)	(*)	(?)	(*)	
Koulumies	(192)	1953	812	0.6	58.9	300	18.0	25.0	(**)	(**)	(**)	(*)	(*)	(*)	
Lickint	(211)	1953	224	1.8	35.8	1,000	16.0	4.8	22	64.0	4.5	1,002	90.4	0.1	
Breslow et al	(38)	1954	518	3.7	74.1	518	10.8	42.7	(**)	(**)	(**)	(**)	(**)	(**)	Data include 493 males, 25 females.
Watson & Conte	(365)	1954	265	1.9	71.7	287	9.7	51.6	36	58.3	2.8	181	82.0	1.1	
Gsell	(138)	1954	135	0.7	68.1	135	16.0	14.0	(*)	(*)	(*)	(*)	(*)	(*)	
Randig	(283)	1954	415	1.2	34.2	381	5.9	17.9	33	51.5	3.0	131	70.3	0	
Stocks & Campbell	(337)	1955	(See reference (335) below)												
Wynder et al	(375)	1956	(*)	(*)	(*)	(*)	(*)	(*)	105	56.2	16.2	1,304	66.0	3.4	
Segi et al	(316)	1957	166	(**)	(**)	2,124	(**)	(**)	(**)	(**)	(**)	(**)	(**)	(**)	Quantities smoked stated as averages only. Differences are statistically significant.
Mills & Porter	(238)	1957	484	8.4	26.0	1,588	27.6	5.3	94	83.0	4.3	1,722	73.3	0.5	Percent "heavy" smokers understated. Only 50% survey response among female cases.
Stocks	(335)	1957	2,101	1.9	28.2	5,960	8.7	22.3	255	57.6	17.2	3,402	68.6	10.7	
Schwartz & Denoix	(313)	1957	602	1	58.2	1,204	9.5	36.2	(*)	(*)	(*)	(*)	(*)	(*)	
Haenszel et al	(150)	1958	(*)	(*)	(*)	(*)	(*)	(*)	158	51.9	14.6	339	69.6	8.2	

Lombard & Snegireff	(222)	1959	500	1.6	(**)	4,238	11.0	(**)	(*)	(*)	(*)	(*)	(*)	(*)	Authors' calculations for heavy smoking based on lifetime number of packs of cigarettes.
Pernu	(277)	1960	1,477	6.6	34.5	713	37.2	20.8	129	85.3	26.4	1,060	91.6	0.7	Quantities given only in grams per day.
Haenszel et al	(147)	1962	2,191	3.4	41.9	(*)	16.2	12.0	(*)	(*)	(*)	(*)	(*)	(*)	Population sample of 31,516 used as base. Not a case-control study.
Lancaster	(199)	1962	238	2.5	86.1	476	20.1	71.2	(*)	(*)	(*)	(*)	(*)	(*)	
Haenszel & Taeuber	(152)	[2] 1963	(*)	(*)	(*)	(*)	(*)	(*)	749	60.9	11.5	[2]	67.3	2.5	Population sample of 34,339 used as base. Not a case-control study.

[1] For this table heavy smokers are defined as those smoking 20 or more cigarettes per day.
[2] To be published.
*Does not apply.
**Data not given.

current smokers but greater than non-smokers. In a third study (152) of lung cancer in women, the ex-smoker risk was lower than the current-smoker risk but approximately equal to that for the non-smoker.

DURATION OF SMOKING

Duration of smoking was considered in 12 of the retrospective studies (82, 150, 207, 222, 236, 283, 301, 311, 316, 335, 375, 381). In only six of them, however, were the data treated in such a way as to permit evaluation of the relationship between duration of smoking and lung cancer—two studies in males (207, 301); two in males and females (82, 236); and two in females only (150, 375). Among the studies of male lung cancer, Levin (207), correcting his data for age, found a relationship between the number of years of cigarette smoking and lung cancer. McConnell (236) found a significant difference in duration of smoking between cases and controls, but was reluctant to draw any definite conclusions. On the other hand, Doll and Hill (82), in their age- and sex-matched study, showed a distinct and statistically significant association between the duration of smoking among males. In a well-conceived analytic study, Sadowsky et al. (301), recognizing that duration of smoking is a function of age, controlled the age variable, and found an increasing prevalence rate of lung cancer with an increase in duration of smoking among all age groups (age at diagnosis).

Among the studies including data on female lung cancer, McConnell had too few female cases to resolve the question of duration of smoking (236) and Doll and Hill, though finding differences between cases and controls, could not establish statistical significance (82). In the two investigations in which only female lung cancer cases were studied (150, 375), neither showed an independent association between duration of smoking and lung cancer. Haenszel states, however, that "among women, the association of starting age and duration of tobacco use with current rate is so strong that it may be unrealistic to expect to find a separate duration effect in retrospective studies of limited size" (150).

AGE STARTED SMOKING

Closely related to duration of smoking and thus pertinent to the length of time that subjects have been exposed to tobacco smoke is the variable of age when smoking was started. Relatively few of the retrospective studies have dealt with this variable. Koulumies (192) found that males with lung cancer had started smoking significantly earlier in life. In fact, 143 of his 845 cases or 17 percent began to smoke below 10 years of age as compared to 6.5 percent among his matched controls. The study of male cases and controls by Breslow et al. (38) found a definite trend in the same direction. Pernu (277) found a statistically significant difference in age at start of smoking, with a higher proportion of the male lung cancer group starting at under 15 years of age. Lancaster (199) indicated that the male lung cancer patients began to smoke at a significantly younger age. One other study (283) showed no difference.

Of the three investigations of female lung cancer which explored this variable, there were too few smokers in one study for a test of significance (277), and in the remaining two (150, 283), no differences were found.

INHALATION

If the association between smoking, particularly cigarette smoking, and lung cancer is a causal relationship, then inhalation should provide more exposure than non-inhalation and should thus contribute significantly to the lung cancer load. Four retrospective investigations were addressed to this question. In the earlier Doll and Hill study (82), no difference in the proportion of smokers inhaling was found among male and female cases and controls. However, four subsequent studies of men (38, 211, 222, 313) found inhalation of cigarettes significantly associated with lung cancer. Although in Breslow's study (38) of age-, sex- and race-matched case and control patients, the variable "quantity-smoked" was not held constant in the comparison when type of smoking though not quantity was controlled, an association was found between inhalation and lung cancer. In the study by Schwartz and Denoix (313) who held constant both type of smoking and amount of cigarettes smoked, the relationship of inhalation was significant for those smoking cigarettes alone but not for the smokers of both cigarettes and pipes. Furthermore, although inhalers among lung cancer patients averaged a significantly higher number of cigarettes per day than did the controls, the relative risk differences between inhalers and non-inhalers, calculated by the Cornfield method (61), become smaller and almost equal each other at the highest cigarette consumption levels. Lombard and Snegireff (222) demonstrated similar relative risk ratios.

HISTOLOGIC TYPE

The earliest retrospective study which considered histologic type of lung cancer was by Wynder and Graham (381) in 1950. These authors presented data on smoking habits of male and female adenocarcinomatous patients and for female patients with epidermoid cancers which were but 25 in number. With this partial analysis only a hint of a higher proportion of smokers among female epidermoid cases could be derived. Of the 1,465 lung cancers in the Doll and Hill retrospective study (82), 995 were histologically confirmed (916 males and 79 females). Of the confirmed cases, 85 percent of the males and 71 percent of the females were of the epidermoid or anaplastic types. Although no statistically significant difference in smoking habits was elicited for the several types, a relatively higher proportion of non-smokers and light smokers were found among patients of both sexes with adenocarcinoma.

Following the presentation by Kreyberg of a Typing Classification of the epidermoid and oat cell or anaplastic types as Group I and the adenocarcinoma and bronchiolar or alveolar cell types as Group II, and the suggestion of a relationship between Group I and smoking (196), several ensuing retrospective studies dealt with this question.

Breslow's study revealed a higher percentage of non-smokers among the patients with adenocarcinoma than among those with epidermoid types (38). In rapid succession six additional retrospective studies analyzed the relationship between histologic type of lung cancer and smoking. The 1956 study of female lung cancers by Wynder et al. (375) indicated that adenocarcinomata apparently had little or no relationship to smoking but that a relationship did exist between smoking and the epidermoid and anaplastic types. Schwartz et al. (313), similarly, in 1957, found a highly significant

association between smoking of cigarettes, amount of smoking as well as inhaling, and the epidermoid and anaplastic types of tumors. No such association with "type cylindrique" was noted. In that same year Doll and Hill furnished Kreyberg with lung cancer slides from 933 British patients. Kreyberg, without knowledge of the patients' smoking history or clinical data, separated these into two groups. A strong correlation was found between smoking history and histologic type; smoking and amount were highly associated with the epidermoid and anaplastic types, and non-smokers were predominantly among the adenocarcinomatous types (86).

In this study of lung cancer in women, Haenszel, et al. (150) found statistically significant relative risk gradients for amount of cigarette smoking among Group I cancer patients. No increased risk was established for Group II cancers. In his later study of a current mortality sample of white males for 1958, Haenszel found relative risk gradients for the several smoking classes for both adenocarcinomas and epidermoid cancers (147). A parallel study of white females for the current mortality sample of 1958 and 1959 showed essentially the same findings, except possibly for a lower effect on adenocarcinomas among smokers of less than one pack daily (152).

Haenszel points out that in both these studies a "true differential in risks" for the two histologic types could well have been diluted seriously by reporting and classification errors which were definitely known to exist from reinquiry of a sub-sample of deaths (152). (For current evaluation, see section on Typing of Lung Tumors.)

RELATIVE RISK RATIOS FROM RETROSPECTIVE STUDIES

Retrospective studies are usually designed to establish the probability of association of an attribute A with disease X; or, given disease X, what is the probability that A will be found in association (P [A|X])? Procedurally, one compares a supposedly representative group of patients with disease X, with another group as controls, in regard to the percentages of individuals with and without the attribute A. This procedure may reveal significant differences leading to judgments of association but it does not yield an estimate of the magnitude of the relative risk of disease X among those with attribute A and those without. A method which estimates this relative risk, developed by Cornfield (61), has been referred to several times earlier and can be applied to data derived from retrospective studies if two assumptions, inherent in the first procedure of judging the association, are made: (a) that patients with disease X interviewed or otherwise studied are a representative sample of all cases with disease X, and (b) that the controls without disease X or who have escaped disease X are a representative sample of all persons without disease X. An estimate of the prevalence of disease X in the population is a requisite.

Such an approach was utilized by a number of investigators in retrospective studies on lung cancer. Doll and Hill (82) made similar calculations and found a linear gradient of deaths from lung cancer for men and women increasing with amount of tobacco smoked daily. Sadowsky et al. (301) found similar increases in risk for amount smoked daily in virtually all but the oldest age groups and calculated an age-standardized risk ratio of 4.6:1 for all smokers compared to non-smokers. These authors also

utilized the data of Wynder and Graham (381) and Doll and Hill (82) for calculating similar risk ratios, deriving ratios of 13.6:1 and 13.8:1, respectively. Their calculations of estimated prevalences by quantity smoked daily for age groupings similar to their own also showed linear increases of risk.

Breslow et al. (38) treated their retrospective data similarly and developed relative risk ratios of 7.7:1 for males aged 50–59 years and 4.6:1 for those aged 60–69. In considering heavy smokers (40 or more cigarettes per day), they showed relative risk ratios of 17:1 and 25.5:1, respectively. Randig (283) also demonstrated a linear progression of risk with increasing amounts of daily tobacco consumption and an over-all ratio of 5.1:1 for all smokers to non-smokers among males and 2.2:1 for females. Schwartz and Denoix (313) reported similar findings in amount smoked daily and a risk ratio of smokers to non-smokers of approximately 8:1. Lombard and Snegireff (222) approached their data in a different way, utilizing "lifetime number of packs of cigarettes consumed" as a measure of exposure. Their estimated prevalence rates also increase linearly with amount smoked. The risk ratio which can be calculated from their tabulated data ranges from 2.4:1 for light smokers to 34.1:1 for heaviest smokers.

Haenszel, in his two studies on male and female lung cancer mortality as related to residence and smoking histories, calculated relative risk ratios of 4.1:1 for one pack or less daily and 16.6:1 for more than one pack a day among males (147), and 2.5:1 and 10.8:1, respectively, among females (152). Table 4 summarizes the relative risk findings of the nine studies.

TABLE 4.—*Relative risks of lung cancer for smokers from retrospective studies*

Author and Reference	Year	Sex	Relative risk—Smokers: non-smokers
Sadowsky et al. (301)	1953	M	4.6
Doll and Hill (82)	1952	M	13.8
Wynder and Graham (381)	1950 [1]	M	13.6
Breslow et al. (38)	1954	M	7.7 age 50–59 4.6 " 60–69 17.0 " 50–59 } very heavy smokers 25.5 " 60–69 }
Randig (283)	1954	M–F	5.1 M 2.2 F
Schwartz and Denoix (313)	1957	M	8.0
Lombard and Snegireff (222)	1959	M	2.4 light smokers 34.1 heavy smokers
Haenszel (147)	1962	M	4.1<1 pack/day 16.6>1 pack/day
Haenszel (152)	Unpublished	F	2.5<1 pack/day 10.8>1 pack/day

[1] Calculated by Sadowsky et al. (301) from other authors' data.

Prospective Studies

It has been pointed out that in retrospective studies the usual approach is to determine the frequency of an attribute among cases and controls. This measure does not provide estimates of the risks of developing the disease

among individuals with and without the attribute unless one makes assumptions referred to above. The validity of such assumptions may at times be suspect, for the cases may not be representative of the total population with the disease nor the controls representative of the population without the disease. Thus, some retrospective studies may not truly assess the existent risks with reasonable accuracy. However, when *all* the cases of a disease in an area and a representative sample of the population without the disease are included in a study, the estimates of risk bear high validity.

Despite the criticisms leveled at the retrospective method in general and its obvious defects as practiced by some investigators, a number of the retrospective studies on lung cancer have indeed overcome most of the criticisms of major import leveled at the method. These criticisms and their implications will be treated specifically below in the section on an Evaluation of the Association Between Smoking and Lung Cancer. Suffice it to say at this point that certain shortcomings of the retrospective survey approach, some real and some exaggerated, led several courageous investigators to undertake the necessarily protracted, expensive, and difficult prospective approach.

The first prospective study encompassing total and cause-specific mortality in a human population was initiated in October 1951 among British physicians by Doll and Hill (83, 84). There then followed in rather rapid succession, five additional independent studies in the United States and Canada (25, 87, 88, 96, 97, 157, 162, 163), all but one of which continue to be active. The earlier study, by Hammond and Horn, among 187,783 white males aged 50–69 years, initiated between January and May 1952, was terminated after 44 months of follow-up (162, 163). This has been succeeded by the current Hammond study which broadened its age-base (35–89 years) and contains 1,085,000 persons (in 25 states) of whom 447,831 are males (157).

These studies have been described in detail, analyzed, and evaluated in Chapter 8 of this Report where a discussion of differences in total mortality between smokers and non-smokers has been presented, and are summarized in Table 1 of that chapter. All the prospective studies thus far have shown a remarkable consistency in the significantly elevated mortality ratios of smokers particularly among the "cigarettes only" smoking class. Of special interest is the fact that in a number of the studies the magnitude of the association between cigarette smoking and total death rates has increased as the studies have progressed. This has particularly been true for lung cancer. The presently calculated total mortality ratios have been presented in Table 2 of Chapter 8 of this Report.

With reference to the smoking and lung cancer relationship, each of the seven prospective studies has thus far revealed an impressively high lung cancer mortality ratio for smokers to non-smokers. Examination of Table 5, which presents in summary form the lung cancer mortality ratios for the seven studies by smoking type and amount, derived both from the published reports of these studies and current information from the investigators wherever available, reveals a range of ratios from 6.0 to 25.2 with a median value of 10.7 for all smokers irrespective of type or amount. For smokers currently using cigarettes only at the time of enrollment in the studies, the ratios range from 4.9 to 20.2 with a mean value of 10.4 as derived from a summation of observed and expected values of most recent data.

Several of the studies have fortunately provided data for a measure of the "dose of exposure" relationship (84, 88, 96, 157, 163). It can readily be seen from Table 5 that the mortality ratios increase progressively with amount of smoking. The pivot level appears to be 20 cigarettes per day. Cigar and/or pipe smokers (to the exclusion of cigarettes) manifest ratios lower than any of the cigarette smoking classes, including combinations of cigarettes with pipes and/or cigars (25, 84, 88, 157, 163). One study provided data on occasional smokers (163). These have a ratio very close to that of non-smokers. Ex-smokers of cigarettes (83, 88, 163) fall into levels of risk ratios below those for current smokers of cigarettes depending upon the length of the interval since smoking was stopped. In the Doll and Hill study (83), the ex-smoker ratio was less than the current smoker ratio even when cessation had occurred less than 10 years before entry into the study. This, however, was not true for the first Hammond and Horn study (163). In this latter study, if smoking had ceased more than 10 years before entry, the lung cancer mortality ratios were lower than for current smokers at the corresponding daily consumption levels, but if cessation of smoking had occurred less than 10 years before entry, the ratios were virtually identical to those for current cigarette smokers at the corresponding daily consumption levels. The Dorn material (87, 88), currently brought up to date (89), provides a measure of relative risk by amounts of smoking prior to stopping. The ratios thus elicited are again below those for current cigarette smokers of corresponding daily amounts.

At this time it is difficult to assess the effect of other variables such as duration of smoking and starting age on lung cancer mortality since cross-classification by these variables, and amount smoked as well, leads to cells with small numbers of deaths. Most prospective studies have thus far confined themselves to analyzing the effect of these additional variables on deaths from all causes, or in one case (157) from cardiovascular diseases. The current Hammond study is concerned with inhalation practices, but here also the total number of lung cancer deaths analyzed to date does not permit extensive classification by age, type of smoking, amount smoked daily, present smoking status, and age when smoking was begun. In the studies of total mortality ratios, duration of smoking, obviously immediately dependent upon the age of the individual, was in turn dependent upon age when smoking (cigarettes) was begun. Age when smoking began was also a determinant, not only of the number of cigarettes smoked daily, but of the degree of inhalation, with smokers starting at earlier ages very distinctly tending to smoke more and inhale more deeply than those starting to smoke at older ages (157). According to Hammond, men who smoke more per day also tended to inhale more deeply than those who smoke fewer cigarettes per day. When inhalation and quantity smoked were held constant, the total mortality ratios also increased as age at start of smoking decreased.

The stability of the lung cancer mortality ratios referred to in Table 5 is to a great extent dependent upon the number of observed lung cancer deaths among non-smokers from which the expected values for the several smoker classes are calculated. Referring again to Table 5, in at least two of the studies (83, 96), calculation of the expected deaths among smoker classes had to be based on extremely small numbers of non-smokers. However,

TABLE 5.—*Mortality ratios for lung cancer by smoking status, type of smoking, and amount smoked, from seven prospective studies*

Study	Doll and Hill	Hammond and Horn	Dorn	Dunn, Linden and Breslow—Occupational	Dunn, Buell and Breslow—Legion	Best, Josie and Walker	Hammond
Lung cancer deaths in Study	129	448	535	139	98	221	414
Lung cancer deaths Non-smokers	†3	†25	†56	†3	†12	†8	†16
(Reference number)	(83)	(163)	(88)	(96)	(97)	(25)	(157)
MORTALITY RATIOS:							
All Smokers	12.8	10.7	6.0	–	–	*25.2	†8.1
1–14 gm. tobacco	6.7	–	–	–	–	–	–
15–24 gm. tobacco	12.3	–	–	–	–	–	–
25 gm. tobacco	23.7	–	–	–	–	–	–
Current: **							
Cigarettes only	†20.2	†10.0	†12.0	†15.9	†4.9	†11.7	†9.6
<10	4.4	†5.8	†5.2	(5)– 8.3	–	†8.4	–
10–20	10.8	†7.3	†9.4	(10)– 9.0	–	†13.5	–
21–39	43.7	†15.9	†18.1	(20)–19.4	–	†15.1	–
40+		†21.7	†23.3	(30)–25.1	–		–
				(40)–28.7			
≦1 pack †	8.1	6.9	8.1	13.6	4.2	11.8	–
>1 pack †	43.8	16.9	18.0	24.1	7.4	15.1	–
Pipes only	5.4	2.6	1.3	–	–	†1.1	†1.5
Cigars only	†4.6	1.0 †1.3	1.5 †1.6	–	–		
Pipes and cigars		–	–	–	–		
Cigarettes, pipes and cigars	9.7	10.7	6.2	–	–	†24.4	–
Occasional	–	1.3	–	–	–	–	–
Ex-Smokers:							
>10 yrs. since stopped	5.0	–	–	–	–	–	–
<20 cigarettes	–	2.4	–	–	–	–	–
>20 cigarettes	–	17.8	–	–	–	–	–
<10 yrs. since stopped	8.4	–	–	–	–	–	–
<20 cigarettes	–	10.4	–	–	–	–	–
>20 cigarettes	–	22.8	–	–	–	–	–
<20 cigarettes (irrespective of when stopped)	–	–	†1.3	–	–	–	–
>20 cigarettes (irrespective of when stopped)	–	–	†1.6	–	–	–	–

*Current and ex-smokers combined.
†Most recent information.
–Data not available or not available for designated classes.
**Two California studies and current Hammond study include all cigarette smokers (cigarettes and other and current and ex-cigarette smokers).

the other studies have now yielded significantly greater numbers of non-smoker lung cancer deaths and in at least three of them (88, 157, 163) these are now appreciable.

Experimental Pulmonary Carcinogenesis

ATTEMPTS TO INDUCE LUNG CANCER WITH TOBACCO AND TOBACCO SMOKE

Few attempts have been made to produce bronchogenic carcinoma in experimental animals with tobacco extracts, smoke, or smoke condensates. With one possible exception (289), none has been successful (331).

Mice rarely develop spontaneous bronchogenic, oral, esophageal, gastric, prostatic, laryngeal, or vesical carcinomas, but certain inbred strains have a high incidence of spontaneous pulmonary adenomas (6). The administration, by any route, of carcinogenic polycyclic hydrocarbons, including some found in tobacco tar, increases the incidence and decreases the time of occurrence of pulmonary adenomas. These tumors are usually regarded as benign, and probably arise from the alveolar epithelium (4, 5, 6, 131, 330) rather than the bronchial wall. They have no resemblance to most human bronchogenic carcinomas.

Essenberg (106) and Mühlbock (248) exposed mice to cigarette smoke, but their reported results are equivocal. Lorenz et al. (224) and Leuchtenberger et al. (206) did not observe an increase in pulmonary adenomas in mice that inhaled cigarette smoke.

Leuchtenberger et al. (205a.) described a sequence of microscopic changes in lungs of mice exposed to cigarette smoke resembling somewhat those found by Auerbach et al. in the lungs of human smokers. No dose-response effect was reported. The morphologic findings consisted of bronchitis with proliferation of the epithelium. Some areas of hyperplasia showed atypical changes. However, the changes were reversible when exposure to smoke was stopped. The production of bronchogenic carcinomas has not been reported by any investigator exposing experimental animals to tobacco smoke.

Most experiments in which tobacco tars were brought into direct contact with the lung and tracheobronchial tree of experimental animals have yielded negative results (273, 274, 275). Blacklock (29) found one carcinoma when tar from cigarette filters was placed in olive oil together with killed tubercle bacilli and injected into the hilum of a small number of rats. Rockey et al. (289) painted tobacco tar three to five times each week on the trachea of dogs with a tracheocutaneous fistula. Hyperplastic changes with squamous metaplasia of the bronchial epithelium were seen in seven dogs that survived 178 to 320 days. Carcinoma-in-situ was reported to occur in three, and invasive carcinoma in one out of 137 dogs, but this work has not yet been confirmed.

SUMMARY.—Bronchogenic carcinoma has not been produced by the application of tobacco extracts, smoke, or condensates to the lung or the tracheobronchial tree of experimental animals with the possible exception of dogs.

SUSCEPTIBILITY OF LUNG OF LABORATORY ANIMALS TO CARCINOGENS

POLYCYCLIC AROMATIC HYDROCARBONS.—Epidermoid carcinoma has been induced in mice by Andervont by the transfixion of the lungs or bronchi with a thread coated with a carcinogen (5) and by Kotin and Wiseley (191) by treatment with an aerosol of ozonized gasoline plus mouse-adapted influenza viruses.

Kuschner et al. (197, 197a) induced epidermoid carcinomas in the lungs of rats by the local application of polycyclic aromatic hydrocarbons, either by thread transfixation or pellet implantation. Distant metastases occurred from some of the carcinomas. The changes in the bronchial tree at different times prior to the appearance of cancer included hyperplasia, metaplasia and anaplasia of the surface epithelium as well as of the subjacent glands. These changes resembled those described by Auerbach in the tracheobronchial tree of human smokers (9).

Stanton and Blackwell (324) induced epidermoid carcinoma in the lungs of rats that had received 3-methylcholanthrene intravenously. The carcinogen was deposited in areas of pulmonary infarction.

Saffiotti et al. (302) produced squamous cell bronchogenic carcinomas in hamsters by weekly intubation and insufflation of benzo(a)pyrene (4 percent) ground with iron oxide (96 percent) resulting in a dust with particles smaller than 1.0 micron. A proliferative response followed by metaplasia preceded the appearance of the carcinomas, but was not an invariable antecedent.

VIRUSES.—Bronchogenic carcinoma has been induced in animals inoculated with polyoma virus by Rabson et al. (282). Carcinogens enhance the effect of viruses known to cause cancer in animals (99) and localize the neoplastic lesions at the site of inoculation of the virus (98). However, no evidence has been forthcoming to date implicating a virus in the etiology of cancer in man.

POSSIBLE INDUSTRIAL CARCINOGENS.—Vorwald reported that exposure of rats to beryllium sulfate aerosol resulted in carcinomas of the lung; 12 percent were epidermoid but most were adenocarcinomas. The tumors usually arose from the alveolar or bronchiolar epithelium. He also produced bronchogenic carcinomas in two out of ten rhesus monkeys injected with beryllium oxide and in three out of ten exposed to beryllium oxide by inhalation (357).

Lisco and Finkel in 1949 (217) reported the production of epidermoid cancer of the lung in rats with radioactive cerium. Subsequently many other investigators have succeeded in producing carcinomas of the lung, predominantly of the epidermoid type, in a high percentage of rats and mice with other radioactive substances. The various modes of exposure included inhalation, intratracheal injection, or insufflation and implantation of wire or cylinder. These experiments were reviewed by Gates and Warren in 1961 (125).

Hueper exposed rats and guinea pigs to nickel dust and found metaplastic and anaplastic changes in the bronchi (180). Following up earlier work in which squamous metaplasia of the bronchial epithelium was found in rats exposed to nickel carbonyl (341), Sunderman and Sunderman (342) induced bronchogenic carcinoma in rats by exposure to this compound. This

group also found 1.59 to 3.07 μg. of nickel per cigarette in the ash and in the smoke in several different brands. About three-fourths was contained in the ash. Although Hueper and Payne (182, 183) and Payne (270) have demonstrated that pure chromium compounds will produce both sarcomas and carcinomas in several tissues in rats and mice, bronchogenic carcinomas have not been produced by inhalation of chromium compounds in experimental animals. Experiments designed to test the carcinogenicity of arsenical compounds have been either negative or inconclusive.

Asbestosis can be produced without difficulty in experimental animals by inhalation of asbestos fibers (359), but efforts to produce bronchogenic carcinoma have been unsuccessful (129, 181, 227, 358).

SUMMARY.—The lungs of mice, rats, hamsters, and primates have been found to be susceptible to the induction of bronchogenic carcinoma by the administration of polycyclic aromatic hydrocarbons, certain metals, radioactive substances, and oncogenic viruses. The histopathologic characteristics of the tumors produced are similar to those observed in man and are frequently of the squamous variety.

ROLE OF GENETIC FACTORS IN PULMONARY ADENOMAS IN MICE

Genetic factors exert a determining influence on the spontaneous development and induction of lung tumors in mice. Early studies of Murphy and Sturm (251) and of Lynch (225, 226) demonstrated the development of pulmonary tumors in mice after the skin was painted with coal tar, and Lynch (225) indicated the existence of genetic factors in the development of these tumors. Later investigations of Heston (169, 170) on the effect of intravenous injection of dibenzanthracene and the studies of several other investigators (3, 4, 27, 47, 320) utilizing different techniques gave additional evidence of the operation of genetic factors in induced tumors. Linkage between multiple genes for susceptibility to spontaneous and induced tumors in mice and specific chromosomes has also been established (47, 168) and transplantation experiments (171, 173) indicate that the genetic susceptibility resides within the pulmonary parenchyma. A number of investigators (36, 47, 124, 131) demonstrated conclusively that these tumors usually arise distal to the bronchus and are probably alveogenic. Metastases rarely occur. The relative importance of genes for susceptibility to these tumors of the lung is indicated by an incidence ranging from a few tumors to over 90 percent, depending on the inbred strain examined.

Spontaneous tumors of the lungs are rare in species of laboratory animals other than mice, and the genetics of these neoplasms in other species has been investigated only superficially.

SUMMARY.—Genetic susceptibility plays a significant role in the development of pulmonary adenomas in mice.

Pathology—Morphology

RELATIONSHIP OF SMOKING TO HISTOPATHOLOGICAL CHANGES IN THE TRACHEOBRONCHIAL TREE

In an extensive and controlled blind study of the tracheobronchial tree of 402 male patients, Auerbach et al. (11, 13, 15) observed that several

kinds of changes of the epithelium were much more common in the trachea and bronchi of cigarette smokers and subjects with lung cancer than of non-smokers and of patients without lung cancer (Table 6). The epithelial changes observed were (a) loss of cilia, (b) basal cell hyperplasia (more than two layers of basal cells), and (c) presence of atypical cells. The atypical cells had hyperchromatic nuclei which varied in size and shape. The arrangement of such cells was frequently disorderly (see illustrations below). Hyperplastic changes were also seen in the bronchial glands.

TABLE 6.—*Percent of slides with selected lesions,*[1] *by smoking status and presence of lung cancer*

Group	Number cases	Number slides	Percent of slides with cilia absent and averaging 4 or more cell rows in depth			
			No cells atypical	Some cells atypical	All cells atypical [2]	Total
Cases without lung cancer						
Never smoked regularly	65	3,324	1.0	0.03	----	1.1
Ex-cigarette smokers	72	3,436	3.5	0.4	0.2	4.1
Cigarettes—½ pk. a day	36	1,824	0.2	4.2	0.3	4.7
Cigarettes—½–1 pk. a day	59	3,016	----	7.1	0.8	7.9
Cigarettes—1–2 pks. a day	143	7,062	----	12.6	4.3	16.9
Cigarettes—2+ pks. a day	36	1,787	----	26.2	11.4	37.5
Lung cancer cases [3]	63	2,784	----	12.5	14.3	26.8

[1] In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included in both individual columns and in the total column of the table. Lesions found at the edge of an ulcer were excluded.

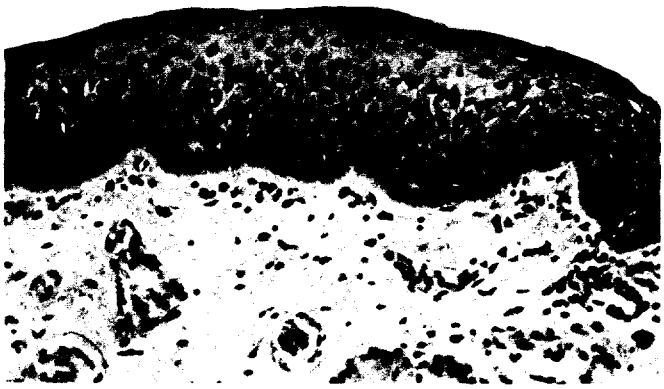
[2] These lesions may be called carcinoma-in-situ.

[3] Of the 63 who died of lung cancer, 55 regularly smoked cigarettes up to the time of diagnosis, 5 regularly smoked cigarettes but stopped before diagnosis, 1 smoked cigars, 1 smoked pipe and cigars, 1 was an occasional cigar smoker.

Each of the three kinds of epithelial changes was found to increase with the number of cigarettes smoked (Table 6). In smokers who had no cancers, frequency and intensity of these changes correlated with the number of

EXAMPLES OF NORMAL AND ABNORMAL BRONCHIAL EPITHELIUM

1. *Normal*



2. *Basal-cell hyperplasia—replacement of ciliary epithelium with a thick layer of cells resembling stratified squamous epithelium.*

3. *Extensive basal-cell hyperplasia with numerous atypical cells.*

Source: Auerbach, Oscar. Special communication to the Surgeon General's Advisory Committee on Smoking and Health.

cigarettes smoked. Among non-smokers, lesions composed entirely of atypical cells with loss of cilia were uniformly absent, although a few could be seen with more than two rows of basal cells containing some atypical cells. In contrast, atypical cells were found in all lesions seen in the tracheobronchial tree of patients who smoked two or more packs of cigarettes a day, irrespective of the presence of hyperplasia and/or cilia loss or whether the patients died of lung cancer. The most severe lesion, aside from invasive carcinoma, consisted of loss of cilia, and hyperplasia up to five or more cell rows composed entirely of atypical cells. This lesion was never found among men who did not smoke regularly and was found only rarely among light smokers. However, it was found in 4.3 percent of sections from men

who smoked one to two packs a day, in 11.4 percent of sections from those who smoked two or more packs a day, and in 14.3 percent of sections from smokers who died of lung cancer (15).

While epithelial changes were found in all portions of the tracheobronchial tree, quantitative differences were found between the changes in the trachea and those in the bronchi; hyperplastic lesions consisting entirely of atypical cells without cilia were found in all regions of the bronchial mucosa but only rarely in the trachea. It is notable that cancer rarely occurs in the trachea.

In 35 children less than 15 years of age, Auerbach et al. (16) found the same percent of epithelial changes in the tracheobronchial tree as in the same number of adults who had never smoked regularly (16.6 percent of children and 16.8 percent of adults). No hyperplasia with atypical cells was seen in any section.

Later, Auerbach et al. (15a.) studied the morphology of the tracheobronchial tree from 302 women and 456 men with respect to additional variables—sex, age, pneumonia, and amount smoked. One or more epithelial lesions were found in 68.2 percent of sections from men smokers and 68.6 percent from women smokers when matched groups were examined. However, on further study, hyperplastic lesions composed entirely of atypical cells were found in 6.9 percent of the sections from the male group and in 2.5 percent of those from females.

Matched groups of male cigarette smokers of two age groups (averages of 37 and 67 years) were compared. Many more lesions, characterized by a large number of cells with atypical nuclei, were observed in the older than in the younger group. In a parallel study of women who did not smoke (average ages of 46 and 76 years), no difference in the number or type of lesions was noted. Few changes in the bronchial epithelium were found in sections from 27 women non-smokers over 85 years of age.

Occasional atypical changes were found in women non-smokers (a) who died of pneumonia, (b) who died of various other causes but had pneumonia at the time of death, and (c) who died with no evidence of pneumonia. However, basal cell hyperplasia, loss of cilia, and ulceration were found more frequently in sections from women who died with pneumonia than from women who had no evidence of pneumonia. These observations are in agreement with those of other investigators who found metaplasia of the bronchial epithelium to be more frequent in patients with various non-neoplastic pulmonary diseases than in controls without such disease (256, 305, 352, 366).

Far fewer epithelial lesions were found in non-smokers than in pipe, cigar, or cigarette smokers (15a.), the difference being particularly evident in the occurrence of atypical cells. However, sections from pipe and cigar smokers showed fewer epithelial lesions than did sections from cigarette smokers. Cells with atypical nuclei were found far more frequently in cigarette smokers than in cigar or pipe smokers (Table 7).

In 72 male ex-cigarette smokers who had smoked for at least ten years and had not smoked for at least five years prior to the time of death, there were less hyperplasia, less loss of cilia, and fewer atypical cells than in sections from current cigarette smokers (14). An interesting by-product of this study was the finding of "cells with disintegrating nuclei" in the

TABLE 7.—*Changes in bronchial epithelium in matched triads of male non-smokers and smokers of different types of tobacco.*[1]

Group	Number of subjects	Total sections with epithelium	Sections with 1 or more epithelial lesions		3+cell rows with cilia present		Cilia absent		Atypical cells present		Atypical cells present with cilia absent		Entirely atypical cells with cilia absent [2]	
			Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
7th set (none vs. pipe vs. cigarette)[3]														
Non-smokers	20	985	214	21.7	110	11.2	101	10.3	26	2.6	3	0.3	0	----------
Pipe smokers	20	924	605	65.5	352	38.1	117	12.7	342	37.0	29	3.1	0	----------
Cigarette smokers	20	914	885	96.8	810	88.6	116	12.7	870	95.2	111	12.1	35	3.8
8th set (none vs. pipe vs. cigarette)														
Non-smokers	25	1,246	285	22.9	167	13.4	132	10.6	9	0.7	1	0.1	0	----------
Pipe smokers	25	1,164	800	68.7	451	38.7	172	14.8	445	38.2	38	3.3	0	----------
Cigarette smokers	25	1,126	1,084	96.3	999	88.7	238	21.1	1,008	89.5	205	18.2	70	6.2
9th set (none vs. cigar vs. cigarette)														
Non-smokers	35	1,706	467	27.4	216	12.7	281	16.5	14	0.8	3	0.2	0	----------
Pipe smokers	35	1,733	1,573	90.8	694	40.0	247	14.3	1,275	73.6	173	10.0	5	0.3
Cigarette smokers	35	1,526	1,511	99.0	1,414	92.7	428	28.0	1,493	97.8	417	27.3	196	12.8

[1] Modified table from Auerbach et al. (15a).
[2] Carcinoma in situ.
[3] Triads were matched for age, occupation, residency and (for smokers) by amount of tobacco used.

bronchial epithelium of 43 out of 72 ex-smokers. These cells were not found in the bronchial epithelium of current cigarette smokers or non-smokers. They were considered by Auerbach et al. to be pathognomonic of the ex-smoker.

Many of the histopathologic findings observed by Auerbach et al. in the bronchial epithelium of smokers have been confirmed by other investigators (64, 155, 189, 304).

The significance of the hyperplastic changes in the bronchial epithelium for the pathogenesis of lung cancer in smokers is not fully understood. The establishment of a link between the hyperplastic changes and the subsequent development of lung cancer would relate smoking causally to lung cancer. However, the non-specificity of hyperplasia of the bronchial epithelium is universally recognized. Furthermore, similar changes are known to be reversible.

On the other hand, evidence from both human and experimental observations points strongly to the conclusion that some hyperplastic changes of the bronchial epithelium, especially those with many atypical alterations, are probably premalignant.

It is well documented that the bronchial trees of patients with lung cancer have areas, sometimes very widespread, of epithelial hyperplasia containing many atypical and bizarre cells. This was reported by Lindberg in 1935 (216) and by many other investigators (10, 12, 28, 52, 134, 265, 285, 349, 370). Black and Ackerman (28) have carried out an extensive study of the relationship between metaplasia and anaplasia and lung cancer in human lungs and have presented strong circumstantial evidence for the opinion that the basal cell hyperplasia with advanced atypical changes and loss of cilia (the so-called carcinoma in-situ) represent a stage in the development of lung cancer. They also emphasized, as has Auerbach et al. (12), the frequent occurrence of atypical basal cell hyperplasia at multiple sites in the bronchial tree considerably removed from the site of the lung cancer. They have pointed out the similarities between the atypical hyperplasias in the tracheobronchial tree and carcinoma in-situ in other sites, such as the cervix, skin, and larynx.

Lung cancer was induced in animals by radioactive substances (198, 217), chemical carcinogens (198, 340), and air pollutants plus influenza virus (191). These studies have demonstrated the occurrence of extensive atypical hyperplastic changes in the bronchial epithelium of experimental animals preceding the appearance of lung cancer. The changes described are, on the whole, similar to those seen by Auerbach et al. in the bronchial epithelium of heavy cigarette smokers and by others in patients with lung cancer. The hyperplastic lesions in animals do not invariably develop into cancer. This appears to be the case also in man (14).

In view of these observations, it seems probable that some of the lesions found in the tracheobronchial tree in cigarette smokers are capable of developing into lung cancer. Thus, these lesions may be a link in the pathogenesis of lung cancer in smokers.

SUMMARY.—Several types of epithelial changes are much more common in the trachea and bronchi of cigarette smokers, with or without lung cancer, than of non-smokers and of patients without lung cancer. These epithelial

changes are (a) loss of cilia, (b) basal cell hyperplasia, and (c) appearance of atypical cells with irregular hyperchromatic nuclei. The degree of each of the epithelial changes in general increases with the number of cigarettes smoked. Extensive atypical changes have been seen most frequently in men who smoked two or more packs of cigarettes a day. Hyperplasia without atypical changes was seen in the bronchial tree of children under 15 years of age and in women non-smokers at all ages who died with pneumonia. Women cigarette smokers, in general, have the same epithelial changes as do men smokers. However, at given levels of cigarette use, women appear to show fewer atypical cells than do men. Older men smokers have many more atypical cells than do younger men smokers. Men who smoke pipes or cigars have more epithelial changes than do non-smokers, but have fewer changes than do cigarette smokers consuming approximately the same amount of tobacco. Male ex-cigarette smokers have less hyperplasia and fewer atypical cells than do current cigarette smokers.

CONCLUSION.—It may be concluded on the basis of human and experimental evidence that some of the advanced epithelial hyperplastic lesions with many atypical cells, seen in the bronchi of some cigarette smokers, are probably premalignant.

TYPING OF LUNG TUMORS

Historical aspects of the typing of lung tumors in relation to possible etiological agents are reviewed in the section on Retrospective Studies, Histologic Types.

Kreyberg (195, 196) noted that the increase of lung cancer in recent decades seemed to occur for only certain types of lung cancers (his Group I), and that other types did not increase (his Group II). Kreyberg's classification is compared with the World Health Organization classification in Table 8. His Group I includes epidermoid carcinomas and small-cell anaplastic carcinomas. His Group II includes adenocarcinomas and a few rare types. He postulated that a determination of the ratio between Groups I and II is a good index of the occurrence and magnitude of an increase in lung cancer in a given locality and his epidemiologic studies linked the increase almost entirely to the use of cigarettes. His thesis has been accepted by many while disputed by others.

The results of the study of lung cancer at Los Angeles County General Hospital (LACGH) by Herman and Crittenden (167) did not confirm Kreyberg's conclusions. These investigators, analyzing the autopsy data on lung cancer from 1927 to 1957 at LACGH, observed a marked increase in the number of lung cancer cases as had been noted by many other investigators. However, the ratio of Kreyberg's Group I to Group II had not changed perceptibly over this period and was notably lower than in other series studied.

The Committee on Smoking and Health sponsored a workshop in which slides from coded cases of lung cancer from four different institutions in three areas of the United States were typed "blind" by Dr. Kreyberg and pathologists from the cooperating institutions.[1] There was good agreement as to typing. The low ratio of Group I to Group II cancers at LACGH was confirmed. When typing of the reviewed cases was compared with smoking

[1] Workshop on typing of lung tumors held in Washington, D.C., April 11, 1963.

TABLE 8.—*Relation between WHO and Kreyberg classifications of lung tumors*

WHO classification [1]	Kreyberg classification [2]
A. *Epithelial Tumors*	
1. Epidermoid carcinomas	Group I
a. highly differentiated	
b. moderately differentiated	
c. slightly differentiated	
2. Small-cell anaplastic carcinomas	Group I
a. with oval-cell structure ("oat-cell" carcinoma)	
3. Adenocarcinomas	Group II
a. acinar (with or without formation of mucus)	
b. papillary (with or without formation of mucus)	
c. tumors with a predominance of "large cells" some of which show formation of glands and/or production of mucus.	
4. Large-cell undifferentiated carcinomas	Other [3]
5. Combined epidermoid and adenocarcinomas	Other
6. Bronchiolo-alveolar cell carcinomas	Group II
7. Carcinoid tumors (solid, trabecular, alveolar)	Group II
8. Tumors of mucous glands	Group II
a. cylindroma	
b. muco-epidermoid tumors	
9. Papillomas of the surface epithelium	Other
a. epidermoid	
b. epidermoid with goblet cells	
B. *Sarcomas*	Other
C. *Combined Tumors of Epithelial and Mesenchymal Cells*	Other
D. *Mesotheliomas of the Pleura*	Other
1. Localized	
2. Diffuse	
E. *Tumors Unclassified*	

[1] Committee on Cancer of the Lung, World Health Organization.
[2] Kreyberg, L. Histological Lung Cancer Types. A Morphological and Biological Correlation. Norwegian Universities Press, 1962.
[3] Types marked "other" are not included in either of Kreyberg groups.

histories, moreover, it became evident that both Group I and Group II were increased among heavy smokers.

Several factors were recognized to influence Group I/Group II ratios: (a) source of material (for example, significant differences in the ratio were found between autopsy and surgical materials, and between surgical materials obtained by biopsy and by resection during operation for lung cancer); (b) failure to autopsy certain cases which were judged to be inoperable (the patient being sent home as incurable); (c) the fact that Group I (squamous and oval-cell) carcinomas are more likely to be among the operable cases and among those accessible to bronchoscopy, and (d) variations in selection of patients in different institutions.

An independent review of the histopathology of 1,146 lung cancer cases from the U.S. veterans study (policyholders) by Dorn, Herrold and Haenszel (Table 9) (89) showed high mortality ratios for both Group I and Group II cancers in current heavy smokers (over 20 cigarettes/day), although Group I had a higher mortality ratio (31.2) than Group II (7.2).

Another study of Haenszel on white females (152), as well as studies of female patients at Massachusetts General Hospital (54), Roswell Park Memorial Institute (133), Presbyterian Hospital (323), and Washington University (260), indicated that adenocarcinoma is also contributing to the increment of lung cancer in women.

CONCLUSIONS—(a) The histological typing of lung cancer is reliable. However, the use of the ratio of Group I and Group II is an index to the magnitude of increase in lung cancer is of limited value.

TABLE 9.—*Mortality ratios for cancer of the lung by smoking class and by type of tumor, U.S. veterans study*

	All Deaths	Group I	Group II
Nonsmokers [1]	1.0	1.0	1.0
Pipe and/or cigar smokers	1.5	2.2	0.6
Cigarette smokers, total [2]	8.2	15.4	5.1
Current			
Total	10.0	18.9	5.8
≤20 cigarettes/day	7.1	12.9	5.1
>20 cigarettes/day	16.0	31.2	7.2
Discontinued (By Maximum Amt. Ever Smoked)			
Total	4.7	8.4	3.7
≤20 cigarettes/day	3.5	6.6	2.7
>20 cigarettes/day	7.4	12.1	5.6

[1] Includes occasional smokers.
[2] Includes men who were using pipe and/or cigars in addition to cigarettes.

Source: Dorn, H. F., Haenszel, W. and Herrold, K. (89) (see Chapter 8 also).

(b) Squamous and oval-cell carcinomas (Group I) comprise the predominant types associated with the increase of lung cancer in both males and females. In several studies, adenocarcinomas (Group II) have also increased in both sexes although to a lesser degree.

Evaluation of the Association between Smoking and Lung Cancer

It is not practical to attempt an experiment in man to test whether a causal relationship exists between smoking of tobacco and lung cancer. Such an experiment would imply the random selection of very young subjects living under environmental conditions as nearly identical as possible, and random selection of those who were to be smokers and those who were to be the non-smoker controls. Their smoking and other habits would need to be held constant for many years. Because of the relatively low incidence of lung cancer in the human population, both the test and the control groups would have to be very large.

As such an experiment in man is not feasible, the judgment of causality must be made on other grounds. The epidemiologic method, when coupled with clinical or laboratory observations, can provide the basis from which judgments of causality may be derived.

INDIRECT MEASURE OF THE ASSOCIATION

The crudest indicators of an association between lung cancer and smoking are certain indirect measures: (a) a correlative increase in lung cancer mortality rates and in per capita tobacco consumption in a number of countries (76, 138, 211, 239, 255), and (b) disparities between male and female lung cancer mortality rates correlated with corresponding differences in smoking habits of men and women, both by amounts smoked and duration of smoking (65, 151, 344).

Figure 9 shows a correlation of crude male death rates from lung cancer in 11 countries in 1950 with the per capita consumption of cigarettes in these countries in 1930 as presented by Doll (76). Assuming a 20-year induction period for the appearance of lung cancer, Doll found a significant correlation (0.73 ± 0.30) between the death rates and cigarette consumption. Since virtually all the tobacco consumption in 1930 was among men in the countries