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Some Aspects of Carcinogenesis

By P. Rondoni, *Cancer Institute, Milan, Italy*

Pulmonary Tumors in Experimental Animals

By Michael B. Shimkin, *National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

Oxidative Metabolism of Neoplastic Tissues

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Etiology of Lung Cancer

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I. Introduction

1. Conclusions of Louvain Symposium

Knowledge of the causes of lung cancer was reviewed at an international symposium on the "Endemiology of Lung Cancer" held at Louvain in 1952 (Council for International Organizations of Medical Sciences, 1953). The members of the symposium were unable to decide what factors were responsible for the majority of cases, but important conclusions

were reached on more limited problems. Firstly, it was agreed that "a significant part" of the increase in mortality which had been reported from many countries "is absolute and represents a real increase in the number of people suffering from primary cancer of the lung"; secondly, "that there is now evidence of an association between cigarette smoking and cancer of the lung, and that this association is in general proportional to the total consumption"; and thirdly, that "occupational hazards giving rise to lung carcinoma have been demonstrated in a number of industries, in particular, in the handling of asbestos and chromates, in gas-works, in a factory refining nickel and in certain mines bearing radio-active ores."

Other possible etiological factors were considered—in particular, atmospheric pollution by effluvia and smoke from factories and domestic chimneys and by exhaust fumes from petrol and diesel engines. The possibility that carcinogenic agents might be absorbed through ingestion or skin contact was reviewed, as was the possibility that individuals might vary in their susceptibility to the environmental influences to which they were exposed. No positive conclusions were reached with regard to these latter problems.

In the last two years, however, much new evidence has been obtained, and it is now possible to give a more complete picture of the etiology of the disease.

II. Increase in Incidence

1. Extent of Increase

The highest death rate from lung cancer is recorded in Britain, where, in 1953, it was 342 per million persons. For both sexes taken together, lung cancer was the commonest type of fatal cancer, accounting for 17% of all cancer deaths; it accounted for 5% of male deaths from all causes at all ages and, in the age group 45 to 64 years, for 10% of all male deaths. In other countries for which detailed statistics are available the rate varies from a seventh to approximately two-thirds the British rate (Table I).* The disparity between the rates is mainly due to a disparity between the rates for men; with the exception of England and Wales, Scotland, and Finland the female rates are similar, varying only between 34 and 47 per million women. Each of the countries listed has experienced an increase in the mortality attributed to lung cancer in the last half century, and the increase appears to be still continuing (Fig. 1).

*In Table I, the figures for England and Wales and for Scotland are shown separately. The Scottish rate for all persons has usually been lower than the English and Welsh rate, but in 1953 the rate was slightly higher—346 per million against 342 per million.

In England and Wales the rate of increase has slackened in the last five years, and the death rate among men under the age of 50 years is now steady. On the assumption that the rates at the younger ages remain steady and that the rates at the older ages continue to increase until the age distribution of deaths from lung cancer resembles that of other extra-genital epithelial cancers, Mackenzie (personal communication) estimates that the male death rate may increase to approximately 1350 per million men, *i.e.*, to more than twice its present level of 602 per million, before it stabilizes. By a similar method, Clemmesen, Nielsen, and Jensen (1953) estimate that the death rate among men in Copenhagen may become even greater (*i.e.*, 2200 per million).

TABLE I

Crude Death Rate from Lung Cancer in Various Countries

Country	Year	Crude Death Rate per 1,000,000		
		Men	Women	Persons
England and Wales	1951	530	91	303
Scotland	1951	470	104	279
Finland	1950	353	61	201
Holland	1951	271	45	158
Switzerland	1950	252	38	136
U.S.A.	1951	214	45	129
Denmark	1951	185	46	115
Australia	1951–52	173	37	106
Canada	1951	154	34	95
France	1950	161	47	87
Sweden	1951	111	43	77
Norway	1951	81	39	60
Iceland	1950	—	—	42

Rates have been shown for 1951, whenever possible, as data were available for the greatest number of countries around that year.

Much of the recorded increase is due to the advancing average age of the population. This factor can, however, be allowed for. In England and Wales, for example, the recorded death rate from lung cancer rose from 8 per million in 1900 to 342 per million in 1953; *i.e.*, 43 times. But if the sex and age-specific death rates of 1953 had occurred in a population with the sex and age distribution characteristic of the population at the beginning of the century, the total death rate would have been only 188 per million. The extent of the recorded increase after allowing for demographic changes is, therefore, 24 times, or little more than half the figure given by the comparison of the crude rates. Similar conclusions apply to the increases recorded in other countries.

How much of the increase "is absolute and represents a real increase in the number of people suffering from primary cancer of the lung" and how much is merely due to better diagnosis is uncertain. It is doubtful if the nature of the data concerned will ever permit a precise answer to be given. Rigdon and Kirchoff (1953) still maintain that the whole increase may be spurious, but in this opinion they are almost alone.

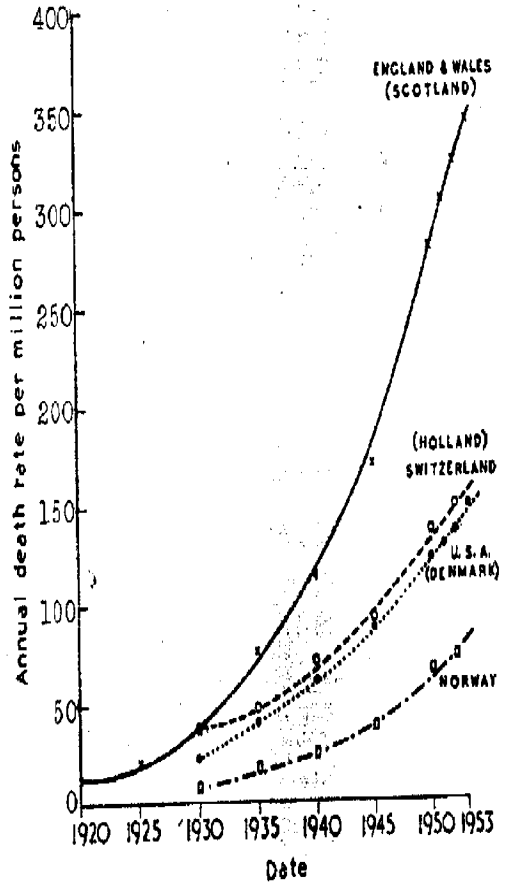

FIG. 1. Increase in crude death rate from lung cancer in various countries, 1920–1953. The trend of the death rate in those countries shown in parentheses has been similar to that in the countries against which they are placed.

Clemmesen, Nielsen, and Jensen (1953) in Denmark; Doll (1953a) and Stocks (1953a) in England; Kreyberg (1954b) in Norway; and Dorn (1954) in the United States have recently cited the reasons for believing that part of the increase is real. Three of the reasons are based on observations which are of special significance for the etiology of the disease. The observations are that the increase has fallen unevenly on:

1. The two sexes.
2. Different age groups.
3. Different histological types.

2. *Changes in Sex Distribution*

National mortality statistics and autopsy series both agree that the change in incidence of the disease has been accompanied by an increasing preponderance of male cases. Figure 2 shows how in different countries

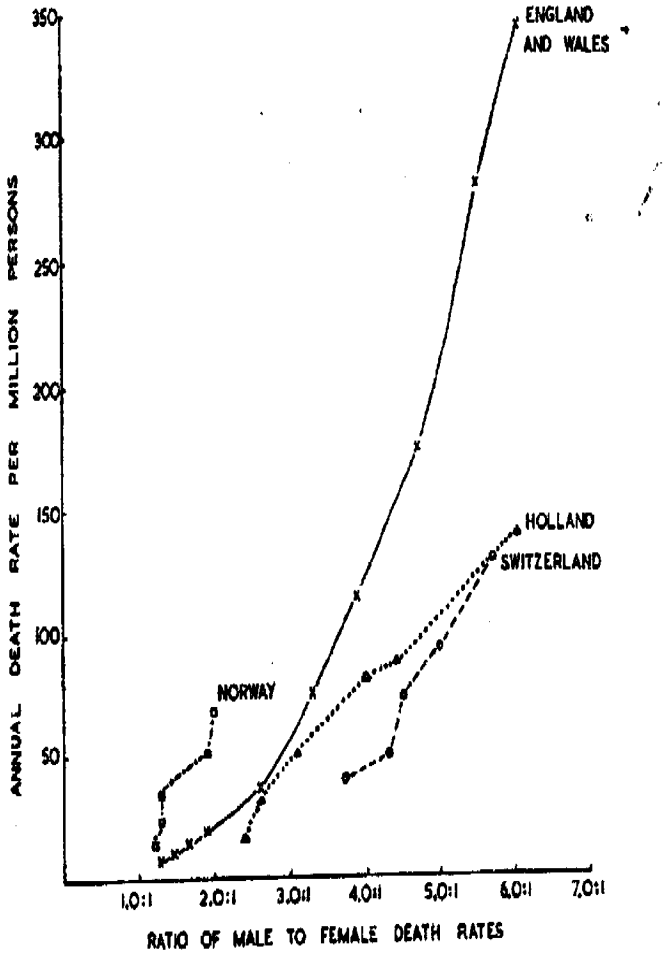

FIG. 2. Increase in ratio of male to female death rates with the increase in the crude lung cancer mortality in various countries.

the proportion of male to female deaths has become progressively greater as the total mortality has arisen. The reality and implication of this change are too well recognized to warrant further comment.

3. *Changes in Age Distribution*

It has long been noted that the age distribution of lung cancer in men differs from that in women and from that of other extragenital epithelial tumors, in that, in countries with a high incidence, the male mortality rises to a maximum comparatively early and falls off rapidly in the later age groups. The increase in mortality over the last 50 years did not affect all ages equally; at first the younger age groups were principally affected

and the maximum mortality came to be between the ages of 60 and 64 years; recently the increase has been most marked in the older age groups and the age of maximum mortality has risen. Korteweg (1951) has pointed out that these trends can be understood if comparisons are made between the age-specific death rates of groups of men all of whom were born at a given period, rather than between groups of men living at a given date, as is the normal custom. By this method of "cohort analysis" similar results have been obtained in Australia (Lancaster, personal communication), Denmark (Clemmesen, Nielsen, and Jensen, 1953), England and

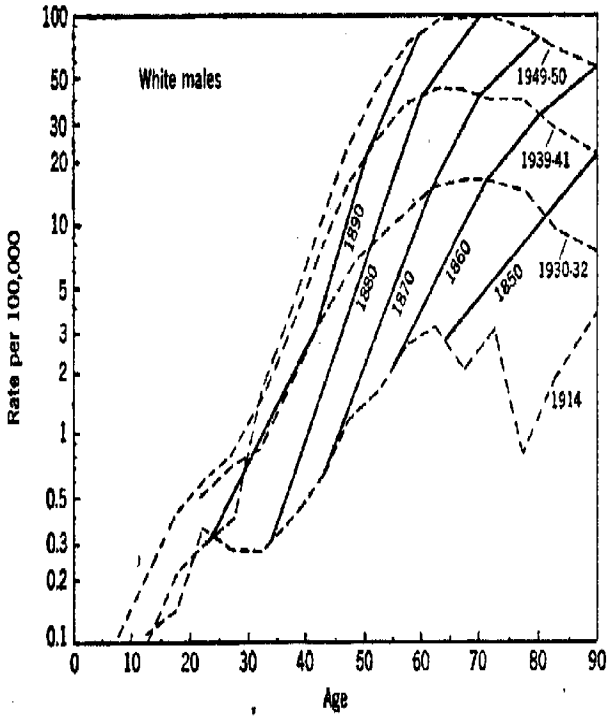

FIG. 3. Male death rates from lung cancer in the U.S.A. by age in 1914, 1930–32, 1939–41, and 1949–50, showing (heavy lines) the increase in mortality with age for men born in 1850, 1860, 1870, 1880, and 1890. (Reproduced from a paper by Dr. H. F. Dorn in *Industrial Medicine and Surgery* **23**, 253–257, 1954.)

Wales (Korteweg, 1951, and—in a modified form—Stocks, 1953a), and the United States (Dorn, 1954). Dorn's data are reproduced in Fig. 3. The dotted lines indicate the pattern of age-specific death rates when studied at different dates (1914, 1930–32, etc.); the solid lines indicate the pattern when men who were born at a given period (1850–59, 1860–69, etc.) are followed throughout their lifetime. It is seen that for each "cohort" the mortality increases continuously with age, but that the later "cohorts" have a progressively higher mortality at each age than the earlier ones. The changes in the shape of the customary age distribution curve for lung cancer can, therefore, be understood if it is postulated (1) that groups of men born at each period suffer a mortality which

increases in a way similar to that observed for other forms of extragenital epithelial cancer and (2) that men born at successive periods were increasingly exposed to an environmental carcinogen. On the other hand, the observed changes cannot be explained, as Clemmesen (1954) has pointed out, if men of all age groups were equally exposed to a new agent at the same time.

4. Changes in Histological Distribution

With the increase in lung cancer the proportions recorded as belonging to the various histological types have altered; adenocarcinoma has become relatively less common, and its incidence must, therefore, be presumed to have increased less than that of other types. In conformity with this and with the comparatively small increase of lung cancer in women, the sex ratio for adenocarcinoma has remained close to equality, whereas that for other types has shown a marked male predominance. Moreover, adenocarcinoma was not observed among the industrial tumors from which the Schneeberg and Joachimstal miners suffered (Schmorl, 1928; Hueper, 1942; Šikl, 1950). For these and other reasons, Womack and Graham (1938, 1941), Lickint (1953), and Kreyberg (1954a,b,c,d) have concluded that lung cancer may be divided into two essentially different types—endogenous and exogenous in origin.

Kreyberg's papers are particularly important because the data have been collected in a country where the total lung cancer mortality is low and during a period when changes similar to those which took place in Britain and the United States 20 to 30 years ago are only beginning to appear. Kreyberg classified his cases into two main groups: group I consisting of squamous and large- and small-cell carcinomas, and group II of adenocarcinomas, bronchiolar cell carcinomas, and benign and malignant adenomas and salivary gland type tumors. The group I tumors were predominantly male (273 M to 31 F) and, when related to the size of the Norwegian population in 1950, showed an age distribution similar to that observed for all lung cancer in countries with a high incidence—save only that the characteristics of the distribution were more pronounced, *i.e.*, the "incidence" had an earlier peak (50 to 59 years) and fell off more sharply in the older age groups. The group II tumors were found almost equally often in each sex (81 M to 76 F) and showed an "incidence" which increased steadily with age in the case of adenocarcinoma and was approximately evenly distributed throughout the range of adult ages in the case of the adenomas and the salivary gland type tumors. When the cases were subdivided according to their date of occurrence, Kreyberg found that there had been no increase in the proportion of group I to group II cases among women over the whole period 1925

to 1953, despite the fact that the standardized mortality rate for women increased four and a half times. On the other hand, group I tumors became relatively much more frequent among men compared with group II tumors, while the standardized male mortality rate increased sevenfold. Despite the considerable difference in the total mortality experience of the two sexes, the sex ratio for the group II tumors remained close to equality.

It is easy to criticize Kreyberg's material on the grounds that it was heterogeneous in origin (part collected from clinical and part from autopsy series) and that the relative amounts collected in the different ways varied over the period studied. Moreover, it is likely that his cases provided a larger sample of those occurring in the younger age groups than in the older groups. Nevertheless, the characteristics of the histological types varied so markedly and the observations agree so well with the trend of the data obtained in other countries, that it would be unreasonable to dismiss the material because it falls short of perfection. Kreyberg interpreted his findings to mean that the group I tumors were largely the result of the introduction of some new carcinogenic agent into the environment, to which men were more exposed than women, whereas the adenocarcinomas "are probably caused by comparatively weak carcinogenic influences, evenly distributed over large areas, well established in the society and striking both sexes with equal force." The recorded increase in mortality in women in Norway may, he suggests, indicate the extent of the increase due to better diagnosis, and the total mortality in women (including a small proportion due to group I tumors) may, with present knowledge, be regarded as "unavoidable" cancer. In contrast, the increased mortality in men additional to that recorded in women and attributed solely to group I tumors can be regarded as "avoidable" cancer. It may well prove that these conclusions are of general significance and also apply to many countries other than the one in which the data were collected.

III. Etiological Factors

1. *Tobacco*

A. *Retrospective Inquiries.* When the Louvain symposium concluded "that there is now evidence of an association between cigarette smoking and cancer of the lung," it did so on the basis of evidence which was derived entirely from retrospective studies of patient's histories. In these studies the histories given by patients with lung cancer had been compared with the histories given by patients without lung cancer who, in one or other way, had been selected as "controls." Many studies of this general type have been reported, and the principal results obtained from

them are summarized in Table II. All agree in showing that there are more heavy smokers and fewer nonsmokers among patients with lung cancer than among patients with other diseases. With one exception (the difference between the proportions of nonsmokers found by McConnell, Gordon, and Jones), the differences are large enough to be important. More detailed results of two of the investigations are shown in Tables III and IV. From these it is seen (1) that there is a steady increase in the relative proportions of lung cancer to control patients as the amount smoked daily increases, and (2) that the difference in smoking habits between persons with and without the disease is more marked for men than for women.

TABLE II

Principal Characteristics of Smoking Histories of Men with and without Lung Cancer, Reported by Various Authors

Author	Date	Number of Men		Percentage of "Nonsmokers" among Men		Percentage of "Heavy Smokers" among Men	
		With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer
Müller	1939	86	86	3.5	16.3	65	36
Schairer and Schöniger	1943	93	270	3.2	15.9	52	27
Wassink	1948	134	100	4.5	19.0	55	19
Schrek *et al.*	1950	82	522	14.6	23.9	18	9
Mills and Porter	1950	444	430	7	31	—	—
Levin *et al.*	1950	236	481	15.3	21.7	—	—
Wynder and Graham	1950	605	780	1.3	14.6	51	19
McConnell *et al.*	1952	93	186	5.4	6.5	35	22
Doll and Hill	1952	1357	1357	0.5	4.5	25	13
Sadowsky *et al.*	1953	477	615	3.8	13.2	—	—
Wynder and Cornfield	1953	63	133	4.1	20.6	68	29
Koulumies	1953	812	300	0.6	18.0	66	31
Lickint	1953	224	1000	1.8	16.0	74	29
Breslow *et al.*	1954	518	518	3.7	10.8	74	42
Watson and Conte	1954	265	277	1.9	9.7	73	57
Gsell	1954	135	135	0.7	16.7	86	33
Randig	1954	415	381	1.2	5.8	34	18

Note. It has not been possible to make all the figures in this Table completely comparable. Some series include, for example, a few women; in others the proportions of heavy smokers are based on totals which are different from those used to calculate the proportion of nonsmokers. One series excludes adenocarcinoma. The individual papers should be referred to before any detailed use is made of the figures.

TABLE III

Average Amount of Tobacco Smoked Daily: Lung Carcinoma Patients and Control Patients with Other Diseases*

Sex	Disease Group	No. of Patients	% Non-smokers†	% Smoking a Daily Average for 20 Years of: 1 g.-	10 g.-	16 g.-	21 g.-	35 g.+
M	Lung Carcinoma (squamous or undifferentiated)	605 (100.1%)	1.3	2.3	10.1	35.2	30.9	20.3
M	Other Diseases‡	780 (99.8%)	14.6	11.5	19.0	35.6	11.5	7.6
F	Lung Carcinoma (squamous or undifferentiated)	25 (100.0%)	40.0	4.0	16.0	24.0	8.0	8.0
F	Other Diseases‡	522 (100.1%)	79.6	9.2	6.9	3.2	0.6	0.6

* After Wynder and Graham, 1950.

† Nonsmokers defined as persons smoking an average of less than 1 cigarette a day (or its equivalent in pipe tobacco or cigars) over the previous 20 years.

‡ The age distributions of the control patients were different from those of the lung carcinoma patients; the percentages quoted were therefore obtained by weighting the age groups so as to make them have the same relative importance as they had in the group of 605 men with squamous cancer.

TABLE IV

Average Amount of Tobacco Smoked Daily: Lung Carcinoma Patients and Control Patients with Other Diseases*

Sex	Disease Group	No. of Patients	% Non-smokers†	% Smoking a Daily Average for 10 Years of: <5 g.	5 g.-	15 g.-	25 g.-	50 g.+
M	Lung Carcinoma	1357 (99.9%)	0.5	4.0	36.0	35.0	21.6	2.8
M	Other Diseases‡	1357 (100.0%)	4.5	9.5	42.0	31.8	11.3	0.9
F	Lung Carcinoma	108 (100.0%)	37.0	14.8	22.2	13.0	13.0	0.0
F	Other Diseases‡	108 (100.0%)	54.6	23.1	16.7	5.6	0.0	0.0

* After Doll and Hill, 1952.

† Nonsmokers defined as persons who had never consistently smoked as much as 1 g. of tobacco a day for as long as one year.

‡ Patients with other diseases matched to be within the same five-year age group and to be in hospitals of the same type and in the same region at approximately the same time as the lung carcinoma patients.

The conclusions to be drawn from these investigations depend on whether the comparisons between the smoking histories of the various groups of lung cancer and control patients are valid and on the extent to which the control patients were representative of the populations from which the lung cancer patients were drawn. In some of the earlier investigations there were reasons for doubting whether the comparisons were valid—for example, when the histories of the two groups of patients were recorded by different methods. Other investigations, in which the patients were interviewed by the same persons and by the same methods throughout and in which the control patients were chosen to "match" the lung cancer patients with regard to sex and age, the date of interview, and the hospital in which they were treated, were not open to objection on this score. Nevertheless, there was the possibility that bias of one or another sort could have entered into the selection of the patients or the recording of the results. The various types of bias which might have occurred were considered in detail by Doll and Hill (1950, 1952). They concluded that bias could not be responsible for their results and that the only logical explanation was that the observed association between the smoking of tobacco and the development of lung cancer was real.

Further important evidence has been obtained from the preliminary results of two "prospective" inquiries. These inquiries have been conducted on a different principle and are not subjected to the types of bias which might theoretically have occurred in the retrospective studies. Since they lead to the same conclusion, it is not now necessary to give further detailed consideration to the evidence from which it was deduced that the association shown by the retrospective studies was real.

B. *Prospective Inquiries.* In the prospective inquiries, the smoking habits of large numbers of "normal" persons have been recorded, and the subjects have subsequently been watched to see what diseases they developed. Preliminary results of studies of this type have been reported by Doll and Hill (1954a) and by Hammond and Horn (1954).

In Hammond and Horn's inquiry, a large number of people who volunteered to help the American Cancer Society were each asked to interview approximately 10 white men, aged between 50 and 69 years, to be chosen from among acquaintances with whom they expected to remain in contact for several years. The smoking histories obtained at the interview were recorded on a standard questionnaire. Subsequently, on the 1st of November each year, the interviewers filled in a follow-up form stating whether the men were alive or dead or had been lost sight of. The State Health Department was then asked to supply an abstract of the death certificate of each man reported to have died. When cancer was certified as the cause of death, an attempt was made to obtain further

details from the certifying physician. A total of 204,547 questionnaires was collected, of which 14,413 were eliminated because they referred to inappropriate subjects or to subjects who were interviewed outside the specified period 1.1.52 to 31.5.52, or because they were inadequately completed. Of the subjects corresponding to the remaining questionnaires, 187,766 (98.8%) were successfully traced at 1.11.53. Altogether, 4854

TABLE V

Lung Cancer Death Rates among Men by Type of Smoking and by Amount Smoked*

Type of Smoking	Population	All Cases Reported as Primary Lung Cancer		Microscopically Proved Lung Cancer (Excluding Adenocarcinoma)	
		No. of Deaths	Death Rates	No. of Deaths	Death Rates
Never smoked or occasional only	44,091	12	27.2	4	9.1
Cigar and/or pipe smoking but never smoked cigarettes regularly	35,853	12	35.5	3	8.4
History of regular cigarette smoking	107,822	143	132.6	45	41.7
Total	187,766	167	88.9	52	27.7
Regular cigarette smoking; less than 1 pack a day at time of questioning	54,799	62	113.1	17	31.0
Regular cigarette smoking; 1 pack or more a day at time of questioning	25,497	61	239.2	24	94.1

* Reproduced from the *Journal of the American Medical Association* (Hammond and Horn, 1954).

men were reported to have died, and the certified cause of death was obtained for 4710 (*i.e.*, in 97%). Cancer of the lung was certified as the cause in 167 instances. According to the authors, "The evidence at present at hand does not warrant presenting the findings in any greater detail than is shown in Table 13 (reproduced above as Table V). The lung cancer death rate was higher among men with a history of regular cigarette smoking than among men who had never smoked regularly and even higher among men who currently smoked one pack or more of cigarettes a day at the time of questioning. The differences are statistically

significant ($P = 0.002$ or less). In fact, even the men smoking less than one pack of cigarettes daily have significantly higher death rates from lung cancer than those who have never smoked regularly ($P = 0.03$ or less). The best estimate that can be made at the present time (at the 5% level of confidence) is that lung cancer deaths are from 3 to 9 times as common among men with a history of cigarette smoking as among men who have never smoked regularly and that lung cancer deaths are from 5 to 16 times as common among men who smoke one pack or more per day."

Differences in the age distributions of the men in the different categories have not been allowed for in Table V. Such differences cannot, however, be responsible for the results, because Hammond and Horn have also shown that the proportion of nonsmokers is greater and the proportion of cigarette smokers is smaller in the older age groups in which lung cancer is more common. If, therefore, an allowance for age differences is made it will be found that the real difference in mortality between cigarette smokers and nonsmokers is, in fact, even greater than would appear from the above data.

The investigation reported by Doll and Hill (1954a) was on a smaller scale and was organized differently, but the trend of the results is similar. A postal questionnaire was sent to nearly 60,000 men and women on the British Medical Register. Just over 40,000 replied, giving details of their smoking habits. Subsequently the national offices for the registration of deaths notified the causes of death of all doctors, and clinical details of the deaths attributed to lung cancer were obtained through the physicians who had signed the death certificates. In the first 29 months following the date when the questionnaires were sent out, 789 deaths occurred among the 24,389 male doctors, aged 35 years and above, whose smoking habits had previously been recorded and classified. The numbers of deaths from lung cancer which occurred among men in the different smoking categories are shown in Table VI, in comparison with the numbers which would

TABLE VI

Number of Deaths from Lung Cancer, Observed and Expected, among Doctors Smoking Different Amounts of Tobacco*

Most Recent Amount Smoked Daily†	0	1–14 g.	15–24 g.	25 g.+
No. of Observed Deaths	0	12	14	13
No. of Expected Deaths	3.77	14.20	10.73	7.33
Observed as Percentage of Expected	0	85	130	177

* After Doll and Hill, 1954a.

† Defined as the amount smoked at the time of completing the questionnaire or, if smoking had been stopped, immediately before stopping.

have been expected to occur if smoking had been unrelated to the disease. (As in the American investigation, the proportions of nonsmokers, of pipe smokers, and of light cigarette smokers were greatest in the oldest age groups, so that the expected numbers had to be calculated separately for each age group and added for all ages.) The number of cases so far studied is small, but there is a steady and striking increase in the ratio between the numbers of cases observed and expected in each smoking category as the amount smoked increases. When this biologically important trend is taken into account, the differences are statistically highly significant ($P < 0.01$). The similarity of the quantitative relationships between smoking and mortality which have been estimated from the retrospective and the prospective inquiries is also striking (Doll and Hill, 1952, 1954a). The mortality rates estimated by the two methods for each of the smoking categories have been expressed as percentages of the unweighted averages of the four rates, and a comparison of the relationships between them is shown in Fig. 4. The slopes of the two graphs are almost identical.

Four explanations are theoretically possible.

1. Doll and Hill's results might have been produced if heavy smokers who suspected that they had lung cancer had replied to the questionnaire more readily than nonsmokers or lighter smokers in a similar situation. If this had been so, the effect would necessarily wear off as the duration of time increased between the completion of the questionnaire and death. In fact, no such diminution in the strength of the relationship occurred over the first 29 months of the inquiry. It is, in any case, unlikely that a similar form of selection could have entered into the choice of subjects for interview in Hammond and Horn's inquiry.

2. Certification of the cause of death may have been biased by knowledge of the subject's smoking history. If, however, there was a tendency to diagnose lung cancer more readily in heavy smokers, the death rate attributed to other causes among men in this category would be expected to be proportionately less than average, and this was not so in either investigation. In fact, by no means all doctors are convinced of the reality of the association—as was shown, for example, in response to a questionnaire sent to Massachusetts physicians by Snegireff and Lombard (1954); bias in diagnosis, if it existed at all, may well have operated in the opposite direction.

3. Smoking may be associated with lung cancer only indirectly, being linked with another factor which is associated with it directly. Such an indirect link may, perhaps, account for some of the association found by Hammond and Horn, since both smoking and the disease may be commoner in certain social and occupational groups within the population.

Such factors are unlikely to have contributed to Doll and Hill's results, since the population studied was entirely composed of doctors and was, therefore, comparatively homogeneous. In both inquiries an indirect link may have arisen because cigarette smoking and lung cancer are both commoner in towns than in the countryside. But this cannot account for

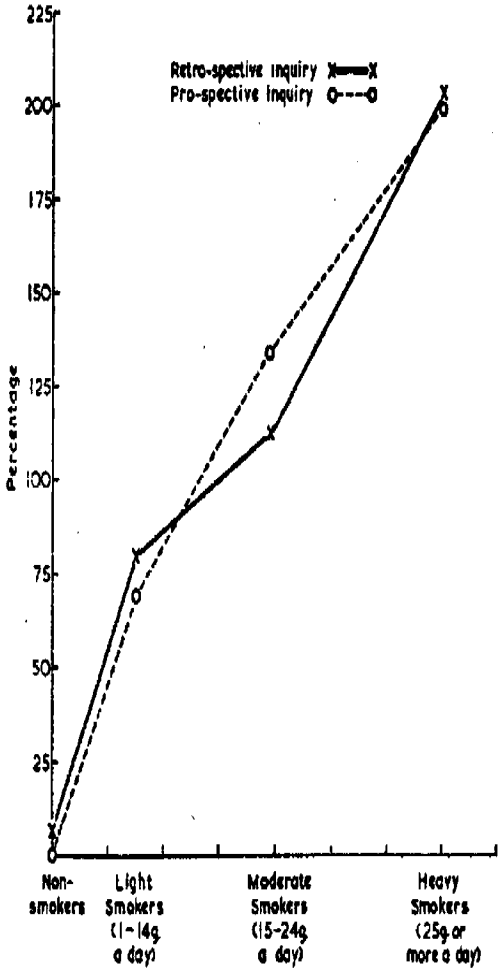

FIG. 4. Standardized death rate from lung cancer among men smoking four different amounts of tobacco, expressed as a percentage of the unweighted average of the four rates: (1) estimated from a retrospective inquiry into patients smoking histories (Doll and Hill, 1952), and (2) observed during a prospective inquiry into the mortality of doctors (Doll and Hill, 1954a).

much of the observed differences, since the association between smoking habits and place of residence (Doll and Hill, 1952; Hammond and Horn, 1954) is much weaker than the association between smoking and the disease.

4. There remains, therefore, the possibility that the association is real and direct.

C. *Method of Smoking.* The evidence suggests that all forms of smoking are not equally associated with the disease. Pipe smoking and cigar smok-

ing are less closely associated with it than cigarette smoking (Wynder and Graham, 1950; Levin *et al.*, 1950; Schrek *et al.*, 1950; Doll and Hill, 1952, 1954a; Sadowsky, Gilliam, and Cornfield, 1953; Breslow *et al.*, 1954; Watson and Conte, 1954; and Hammond and Horn, 1954). Only McConnell, Gordon, and Jones (1952) and Randig (1954) failed to find any distinction between the various methods of consumption of tobacco. From the mortality rates estimated by Doll and Hill (1952) it would appear that the risk among "pure pipe smokers" may be as much as two-thirds the risk among "pure cigarette smokers," but they hesitated to draw any precise conclusion because of the variation in the average amounts of tobacco smoked by the different types of smoker and because of the difficulty of separating with certainty a group of smokers who had never smoked cigarettes at all. Sadowsky, Gilliam, and Cornfield (1953) found a greater difference between pipe and cigarette smokers, and Hammond and Horn (1954) found that the mortality among smokers who had never smoked cigarettes was practically identical with that among nonsmokers (see Table V). Hammond and Horn's evidence is particularly important because it was obtained from a prospective inquiry in which great care had been taken to eliminate from the pipe and cigar group all men who had ever smoked as much as ten packs of cigarettes in their entire lives. The investigation was on such a scale that even with this definition it was still possible to secure a large group for study, and these results are likely to be more reliable than those of other workers who defined the categories of smokers less strictly.

Few people (outside South Africa) have smoked filter-tipped cigarettes or used cigarette holders regularly for any length of time, and it has, therefore, been difficult to obtain evidence regarding the possible protective effect of these methods of smoking. The data obtained by Doll and Hill (1952) are shown in Table VII. A smaller proportion of the lung cancer patients than of the control patients had used holders and a smaller proportion had smoked filter-tipped cigarettes, but the numbers are small and it would be unwise to draw any positive conclusions from this very limited evidence. It might be that the use of cigarette holders and of filter-tipped cigarettes are both associated with light smoking, but this did not appear to be the explanation among the patients referred to above.

D. *Extent of Risk.* The results of the two prospective inquiries which have been reported do not as yet permit direct measurements to be made of the full extent of the lung cancer mortality among smokers of different quantities of tobacco. Persons who were seriously ill when the inquiries were started are relatively unlikely to have been included in the initial population, and consequently the mortality rates recorded in the first year

or two of follow-up are almost certainly too low. Until a few more years have elapsed, estimates of the risks to which the different categories of smokers are exposed must, therefore, still be based on the data derived from the retrospective studies.

Estimates have been made by Doll and Hill (1952), Heady and Barley (1953), Sadowsky, Gilliam, and Cornfield (1953), and Wynder and Cornfield (1953). The results obtained in Britain and the United States have

TABLE VII

Use of Cigarette Holders and of Filter-Tipped Cigarettes: Male Lung Cancer Patients and Matched Control Patients*

Type of Smoker	Male Lung Cancer Patients		Male Control Patients	
	No.	%	No.	%
Use of Cigarette Holders				
Regularly	10	2.0	27	5.8
Occasionally	15	3.0	27	5.8
Never	479	95.0	413	88.4
Total Cigarette Smokers	504	100.0	467	100.0
Use of Filter-Tipped Cigarettes				
Ever regularly	3	0.6	15	3.2
Never regularly	501	99.4	452	96.8
Total Cigarette Smokers	504	100.0	467	100.0
Smokers Who Had Never Smoked Cigarettes	15		30	
Nonsmokers	4		26	
Total men	523†		523†	

* After Doll and Hill, 1952.

† The total numbers of men are different from the numbers shown in Table IV, because questions about the use of cigarette holders and filter-tipped cigarettes were only introduced in the last part of the inquiry.

been compared by the two latter groups of authors and, in a more detailed fashion, by Cutler and Loveland (1954). Cutler and Loveland's estimates are summarized in Table VIII. From the table it appears that for a man aged 40 years who smokes 20 or more cigarettes a day (1) the risk of dying of lung cancer before the age of 80 years is of the order of 8% and that (2) this risk is some $6\frac{1}{2}$ to 30 times as high as that among nonsmokers.

The reliability of these estimates depends on the validity of certain

assumptions which had to be made before the rates could be calculated. These are:

1. That the deaths recorded nationally as being due to lung cancer provide a fair estimate of the actual number of deaths due to the disease.

2. That the smoking habits recorded by patients with lung cancer were, at each age and in each sex, typical of all those persons who died of the disease during the period of the survey.

3. That the smoking habits recorded by the "control" patients without lung cancer were similarly representative of those of all members of the population from which the lung cancer patients were drawn.

TABLE VIII

Risk of Developing Lung Cancer among Men Smoking Different Amounts of Tobacco, Estimated from the Results of Three Groups of Investigators*

Amount Smoked	Estimated Risk of Developing Lung Cancer by the Age of 80 Years, per 1000 Men Aged 40 Years			
	Sadowsky, Gilliam, and Cornfield (1953)	Wynder and Graham (1950)	Doll and Hill (1952)	Combined Results
Nonsmokers	10	3	5	6
Smokers of under 10 g. a day	22	19	34	25
Smokers of 10–20 g. a day	46	52	48	49
Smokers of more than 20 g. a day	65	90	86	80

* After Cutler and Loveland, 1954.

Further assumptions are also required about the trend of future changes in mortality in order to present the risks in the form chosen by Heady and Barley (1953) and by Cutler and Loveland (1954), but these are of minor importance in that they have little effect on the relative sizes of the risks for the different smoking categories.

Whether the assumptions are justified is impossible to say with certainty, and the rates must be regarded as provisional. In view, however, of the conformity of the estimates calculated from data from independent investigations in different countries and the further confirmation of the relative sizes of the risks by the preliminary results of the prospective inquiries, it is unlikely that the estimated rates are seriously in error. The correspondence between the results of Doll and Hill's two investigations has been shown previously in Fig. 4, and Hammond and Horn's

"best estimate . . . that lung cancer deaths are from 5 to 16 times as common among men who smoke one pack or more per day" as among nonsmokers largely overlaps the estimates made by Cutler and Loveland (Table VIII). On the other hand, the fact that smoking habits are not invariable and that the amounts which have been related to mortality have been recorded only at one point in time must have blurred the differences between the smoking categories, so that the estimated rates for light smokers are probably somewhat overestimated, whereas the rates for heavy smokers are likely to have been underestimated.

The estimated rate for nonsmokers is low but it is not intrinsically unreasonable. At ages 45 to 74 the rates calculated from the English data are slightly lower than the rates which actually occurred among women in rural areas in England (Doll, 1953b), and they are similar to the rates now recorded among women in Denmark and several other countries (see Table I). If these rates represent the mortality risk in the absence of smoking, then the number of deaths from lung cancer attributable to causes other than smoking among persons aged 25 to 74 years in England and Wales in 1950 would have been about one-fifth of the total number actually recorded.

E. *Difference between Histological Types.* In the foregoing discussion no consideration has been given to the possibility that the different histological types of carcinoma of the lung may have different etiological relationships to smoking. It has, however, been suggested that the relationship with smoking holds only for squamous, oat-cell, and anaplastic carcinomas. This qualification makes little difference to the conclusions which have already been drawn, because, wherever lung cancer is common, the great majority of cases are of the squamous, oat-cell, or anaplastic types. The distinction is, however, of considerable theoretical interest.

Three reports have paid special attention to histological differences. Wynder and Graham (1950) found that the smoking habits of 39 men and 15 women with adenocarcinoma were closely similar to those of control patients with diseases other than lung cancer. Doll and Hill (1952) reported that there was "no statistically significant difference between the amounts smoked by patients in the different histological groups in either sex. The number of cases of adenocarcinoma is, however, too small (33 male and 10 female) to conclude that no difference exists. There were, in fact, relatively more non-smokers and very light smokers . . . among the patients with adenocarcinoma in both sexes." Breslow *et al.* (1954) noted that "Six out of 46 (13 per cent) of the cases of adenocarcinoma did not smoke cigarettes; whereas only 28 out of 472 (6 per cent) of the patients with other types of carcinoma . . . did not smoke ciga-

rettes." The interpretation of these data is complicated by the inclusion of men and women in a single series. When, however, the sexes are separated, the distinction still persists (Breslow, personal communication).

The most striking evidence has, however, been obtained by Kreyberg (personal communication), and the author is indebted to him for permission to cite his results obtained up to the end of 1954. Smoking histories were taken from patients in the wards of the Rikshospitalet, Oslo, before operation, and the histological typing of the tumors was made independently without knowledge of the patient's history, sex, or age. The most recent amount of tobacco smoked daily by men whose tumors were classified as belonging to the two main histological groups (see page 7) was as follows:

Type of Tumor	No. of Nonsmokers	No. of Men Smoking Daily: 1-9 g.	10-19 g.	20 g.+	Total No. of Men
Group 1	3	40	98	52	193
Group 2	2	11	14	5	32
Ratio of group 1 to group 2 tumors	1.5/1	3.6/1	7.0/1	10.4/1	6.0/1

Finally, Wynder (1954) has studied the problem by collecting details of the histology of the cases of lung cancer which are reported to have occurred among male nonsmokers. Twenty nine per cent (*i.e.*, 14 out of 48) were adenocarcinomatous, whereas only 5% (*i.e.*, 54 out of 1019) were adenocarcinomatous among male smokers with lung cancer in his personal series.

It must, therefore, be concluded that adenocarcinoma of the lung is less closely related to smoking habits than are the squamous, oat-cell, and undifferentiated types of cancer, and it may well prove that smoking plays no part at all in its production.

F. *Vital Statistics and Tobacco Consumption.* The sharp increase in the number of deaths attributed to lung cancer during a period when tobacco consumption was also increasing has been cited as one reason for believing that tobacco is a cause of the disease. In fact, correlations in time may be—and often are—entirely irrelevant, so that they are of no value in proving the existence of a causal relationship. On the other hand, if a relationship can be demonstrated by other means, it is reasonable to test its significance by seeing if it is consistent with such temporal changes as are observed to occur.

The changes which have taken place in tobacco and cigarette consumption and in lung cancer mortality in England and Wales in the last 70 years are illustrated in Fig. 5 and Table IX. Whether the correlation between cigarette consumption and mortality is as close as would be expected if cigarettes were one of the principal causes of the disease is

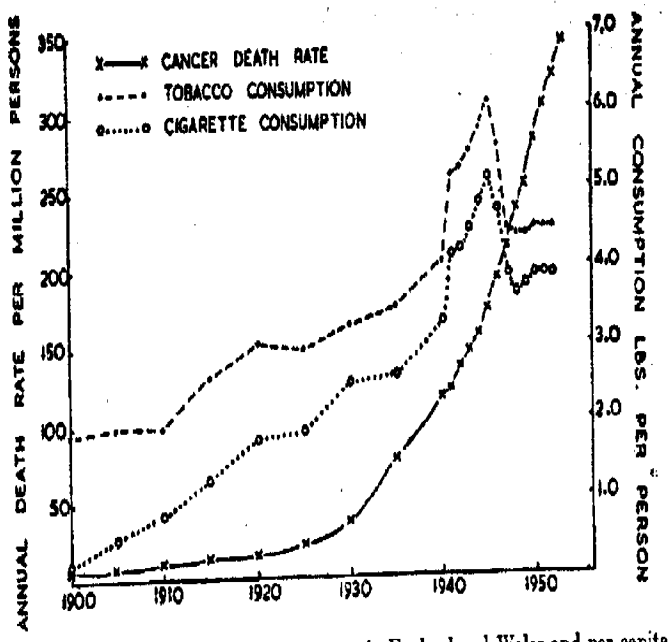

FIG. 5. Crude death rate from lung cancer in England and Wales and per capita consumption of cigarettes and of all tobacco products in Great Britain, 1900–1953.

TABLE IX

Crude Lung Cancer Death Rate and Consumption of Cigarettes and Other Tobacco Products for Men and Women Separately in England and Wales, 1881–1950

	Annual Consumption, Lbs. per Adult (aged 15 years +)				Lung Cancer Death Rate per 1,000,000 Persons (aged 15 years +)	
	Men		Women			
Period	Cigarettes	Other Tobacco	Cigarettes	Date	Men	Women
1881-90	0.006	6.1	0.0			
1891-1900	0.4	6.2	0.0			
1901-10	1.8	4.9	0.0			
1911-20	3.8	4.3	0.0	1920	25	13
1921-30	5.1	3.7	0.2	1930	74	27
1931-40	6.9	2.7	0.8	1940	256	68
1941-50	8.3	2.4	2.4	1950	624	111

Note. The figures shown in this table are derived from a different source from those shown in Fig. 5 and differ in that the estimates of tobacco consumption exclude the amounts consumed duty-free in the Merchant Navy and in the Armed Forces abroad. Except in wartime these amounts are negligible. The figures also differ in that the table shows rates per adult (or per 1,000,000 adults) and the figure shows rates per person (or per million persons).

uncertain, because many of the relevant facts are unknown. It is, for example, not known:

1. What proportion of the increase in recorded mortality is real.
2. What are the relative risks attached to the smoking of tobacco in cigarettes and in other forms.
3. What is the biological relationship between the dose of cigarette smoke and the development of the disease.

On the basis of present knowledge one may, perhaps, suggest more or less reasonable solutions to the first two problems; although it must be admitted that no estimate of the extent of the real increase in mortality can be more than an intelligent guess. Save, however, that the evidence indicates that mortality varies in direct arithmetical proportion with the amount smoked at a given time, we are completely ignorant of the third. We neither know the induction time of the tumor nor the relative effects of the same dose at different periods of life; and different hypotheses about either of these must lead to gross differences in the temporal relationship between consumption and mortality. If, for example, it is postulated that the mechanism of carcinogenesis is of the type suggested by Nordling (1953), Stocks (1953b), and Ambrose (1954), it might well be that the effect of a dose of cigarette smoke at a given time is proportional to the fourth or fifth power of the time elapsing after its administration (Armitage and Doll, 1954). On such a hypothesis a reasonable agreement between the figures in Table IX can be demonstrated. In the present state of ignorance, however, it is probably better not to attempt any exact correlation; but to note only that if smoking is a major cause of lung cancer it will be difficult to account for the figures unless there is also a considerable difference in the relative effects of smoking cigarettes and pipes.

It is almost equally difficult to decide whether differences in smoking habits are adequate to account for the difference in mortality observed in men and women. At first sight it would seem unlikely that they were, since women have been responsible for an increasing proportion of the total amount smoked and, in all countries, the preponderance of men among subjects of the disease has become more marked. The difficulty, however, is the same as was encountered previously; that is, we do not know the induction time of the disease nor the relative importance of smoking at different periods of life. From the figures which are available for Britain (Table IX) it would seem that so long as the effect of smoking does not reach its maximum till after 20 years, differences in smoking habits could readily account for a large and still increasing difference in the mortality of men and women. In fact, it may well be that the cases of

lung cancer among women still include only a small proportion specifically related to tobacco and that the major increase in female mortality is to come.

An alternative approach is to estimate the mortality among male and female nonsmokers. According to Doll (1953b) the proportions of men and women found among the nonsmokers with lung cancer in Doll and Hill's (1952) series are consistent with the hypothesis that in the absence of smoking (and exposure to certain industrial carcinogens) the death rates are equal in the two sexes.

The attempt to compare mortality and tobacco consumption in different countries is even more hazardous, for not only do standards of death certification vary but so do methods of smoking. It is said, for example, that few Europeans throw away as large an unsmoked butt as is commonly discarded in the United States. It is, however, of interest to make the comparisons, provided that the deficiencies of the data are recognized. Statistics for 8 countries have been collected by Nielsen and Clemmesen (1955), and these have largely been drawn on, in the preparation of Figs. 6 and 7. In Fig. 6, the male death rate from lung cancer in 11 countries in 1950 (or in the nearest year for which the information is available) has been plotted against the annual consumption of all tobacco products per head of the population 20 years earlier; in Fig. 7 it has been plotted against the annual consumption of cigarettes per head 20 years earlier. In fact, nearly all the tobacco consumed in 1930 was consumed by men (even in the Scandinavian countries the amount of tobacco smoked by women at that period was small) so that it is not unreasonable to compare the male death rate with the per capita consumption. In nearly all the countries the consumption per man in 1930 is likely to have been approximately double the consumption per person. Figure 6 fails to show any relationship between lung cancer mortality and total tobacco consumption in the various countries, but from Fig. 7 it would appear that the data (with the exception of those from the United States) are not inconsistent with the existence of a relationship with cigarette consumption. To a small extent the anomalous position of the United States can be explained by the high proportion of young people in its population; whether the sort of consideration which has been referred to above can account for the rest is a matter for conjecture. What is certain is that the observed facts fit the hypothesis of a relationship between the disease and cigarettes much better than the hypothesis of a relationship with tobacco generally.

G. *Identification of Carcinogenic Agent.* Numerous attempts have been made to induce cancer with tobacco products in animals. A significantly increased incidence of the common pulmonary adenoma of mice was ob-

served on one occasion by exposing animals with a high spontaneous incidence of the tumor to strong concentrations of cigarette smoke (Essenberg, 1952), but no change, or very little change, in incidence has been observed by others (Passey, 1929; Campbell, 1936; Lorenz *et al.*, 1943).

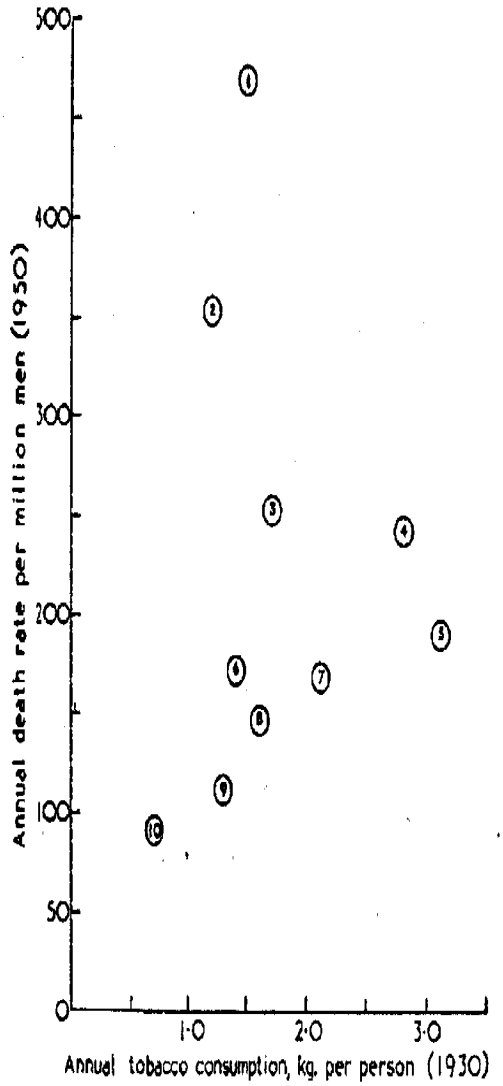

FIG. 6. Crude male death rate from lung cancer in 1950 and per capita consumption of all tobacco products in 1930 in various countries: (1) Great Britain, (2) Finland, (3) Switzerland (tobacco consumption estimated from data published by Gsell, 1951, and Nielsen and Clemmesen, 1954), (4) Holland, (5) U.S.A., (6) Australia (death rate for 1951-52), (7) Denmark, (8) Canada, (9) Sweden, and (10) Norway. *Coefficient of correlation between death rate and tobacco consumption*, 0.10 ± 0.31.

Wright (1955), in particular, exposed 80 mice of the "Strong A" strain to an average concentration of 0.08 mg. of smoke per liter for 20 hours a day for 5 days a week. There were many deaths in the early weeks of exposure, and Wright doubts if a stronger concentration could be used successfully. The average number of tumors in the 34 mice which survived

from 3 to 15 months exposure was higher in the experimental group than in a control group of paired litter mates killed at the same ages (1.15 against 0.76), but the number of tumor-bearing mice was less (44% against 56%). Neither difference is statistically significant. According to Moore

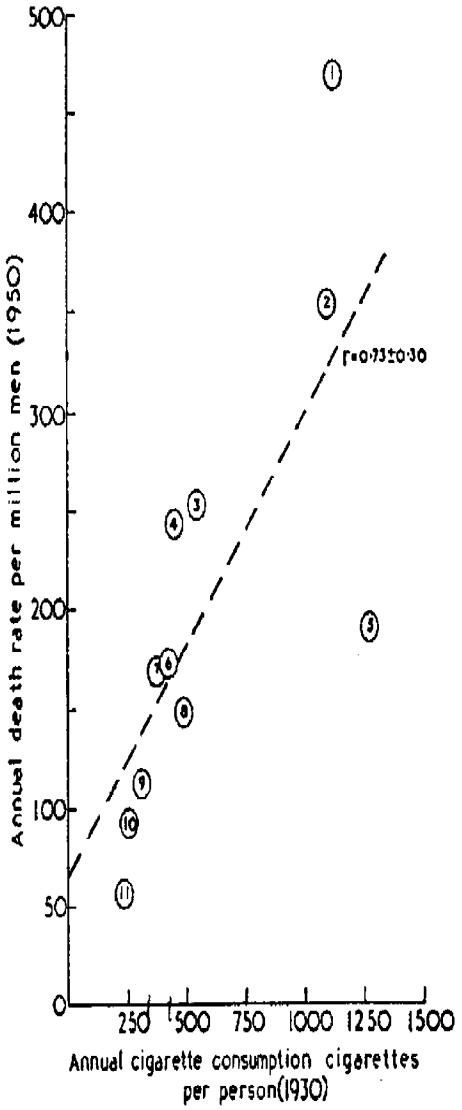

FIG. 7. Crude male death rate from lung cancer in 1950 and per capita consumption of cigarettes in 1930 in various countries: key as in Fig. 6, with the addition of (11) Iceland (death rate estimated from cancer notification rate). *Coefficient of correlation between death rate and cigarette consumption*, 0.73 ± 0.30.

(1953) Graham produced "what appeared to be one small papilloma in the bronchus of a dog" by painting tar from cigarette smoke through a fistula onto the bronchial mucosa; but the report proved to be erroneous and no tumor has appeared after three years (Graham, personal communication). Tumors comparable to bronchial carcinoma as it appears in man have not been produced by tobacco products by any method.

Occasional tumors on the skin of mice and rabbits have, on the other hand, been produced by several workers. The literature is reviewed by Wynder, Graham, and Croninger (1953), who have themselves been able to produce tumors in a high proportion of treated animals. They obtained tar from cigarettes smoked mechanically under conditions which approximated to the physical conditions of normal smoking and applied it three times a week to the skin of mice, until a carcinoma appeared or the animal died. To avoid toxic reactions from the nicotine content of the tar, the dose given initially was small and it was increased gradually over the following two months. The first papilloma appeared after eight months of painting: the first carcinoma, after one year. Of 81 mice initially included in the series, 62 survived for a year or more and 36 of them (*i.e.*, 58%) finally developed cancer. Passey (personal communication) has, however, pointed out that with the method of combustion used "Temperatures up to 966°C. were obtained" and that this is appreciably higher than the combustion temperatures in normal smoking (see page 27). Tar obtained from cigarettes burnt at temperatures not exceeding 750°C. has, in the hands of Passey *et al.* (1955) not reproduced Wynder, Graham, and Croninger's results.

Three potentially carcinogenic substances have been distinguished in tobacco smoke: arsenic, benzpyrene, and radioactive potassium. Arsenic is present in many tobaccos, probably because of its use as an insecticide. It is present in greatest amounts in tobacco of American origin and is completely, or almost completely, absent from Oriental types. Daff and Kennaway (1950) estimated that an ordinary "Virginian" cigarette as smoked in England, contains about 50 μg. expressed as As_2O_3 and that approximately 15% is volatilized in smoking. Smoking 10 cigarettes a day means, therefore, that as much arsenic as is present in one maximum official dose of Fowler's solution is volatilized in 10 weeks. Arsenic is believed to be capable of inducing bronchial carcinoma in man (see page 33) but it is unlikely to be the responsible agent in tobacco smoke, since (1) the amount to which smokers are exposed is very small compared with the amounts encountered industrially, and (2) bronchial carcinoma forms a high proportion of cancer cases found at necropsy in Istanbul (Schwartz, reported by Daff, Doll, and Kennaway, 1951) and arsenic is almost completely absent from Turkish tobacco.

The presence of polycyclic hydrocarbons in tobacco smoke has long been suspected, but no individual substances were identified until Cooper and Lindsey (1953) and Commins, Cooper, and Lindsey (1954) reported the presence of anthracene and pyrene in tar obtained from cigarette smoke. Subsequently Cooper, Lindsey, and Waller (1954) reported that they had also distinguished the presence of 3,4-benzpyrene. To obtain

the tar, the cigarettes were smoked mechanically but care was taken to make the physical conditions of combustion correspond closely to those which occur in normal smoking. The substances were detected by means of chromatography followed by absorption spectrophotometry; 10.2 μg. of anthracene, 9.0 μg. of pyrene, and 1.0 μg. of 3,4-benzpyrene were estimated to be present in the tar collected from the smoke of 100 cigarettes.

The amount of benzpyrene is small and it is necessary to smoke 200 cigarettes to obtain enough to produce, by local injection, a sarcoma in a mouse. Quantitatively it is less important than the amount in town air, since it would be necessary to smoke 50 cigarettes in order to inspire as much as is inspired from the air in one day by a "standard man" in an average English industrial town (Waller, 1952; Blacklock *et al.*, 1954). On the other hand, the benzpyrene in cigarette smoke, being dissolved in the form of a fine suspension in a solvent material, may well be more active than the atmospheric benzpyrene, which is largely adsorbed on carbon particles and is, in this state, relatively inactive (Steiner, 1954). Part of the atmospheric benzpyrene is also likely to be filtered off by the nose.

Benzpyrene has also been identified in the tar collected from the smoke of "cigarettes" made entirely of paper (Cooper and Lindsey, 1954; Lefemine, 1954). The quantity present was, however, such that the combustion of the paper could account for only about 5% of the benzpyrene present in the smoke from ordinary tobacco cigarettes. Lindsey (1954 and personal communication) has, moreover, also found that benzpyrene is present in the smoke from tobacco burnt in a pipe in the same order of quantity, weight for weight of tobacco, as was obtained from cigarette smoke.

Commins, Cooper, and Lindsey (1954) suggest that the polycyclic hydrocarbons may be formed by the pyrolysis of acetylene. Kennaway (1924, 1925) has shown that strong heating of acetylene and other unsaturated materials produces carcinogenic tars at temperatures of 700°C. and above, and Fishel and Haskins (1949) showed that acetylene was present in tobacco smoke. The temperature of combustion in ordinary cigarettes, in paper "cigarettes," in a pipe, and in a cigar, were, according to Lindsey (1954 and personal communication), as follows:

	Quiescent Combustion Temperature	Suction Combustion Temperature	Surface Temperature
Ordinary cigarette	650°C.	700°C.	900°C. +
Paper "cigarette"	Varies	655°C.	900°C. +
Pipe	Varies	470°C.	700°C. +
Cigar (Havana)	400°–500°C.	560°C.	800°C. +

Closely similar temperatures in burning cigarettes have been recorded by Wynder, Graham, and Croninger (1953) and by Hamer (1954), and a similar temperature for combustion in pipes was recorded by Cooper *et al.* (1932). If Lindsey's observations on the presence of benzpyrene in the smoke from tobacco burnt in pipes are confirmed, it would seem likely that polycyclic compounds can be formed at lower temperatures than have, hitherto, been thought to be necessary. If benzpyrene is the active agent responsible for tobacco cancer, the finding of its presence in pipe smoke will accord with the high incidence of cancer of the lip and buccal cavity, known to occur among pipe smokers. In this case it will be necessary to explain the considerable difference in the incidence of lung cancer which is found between pipe and cigarette smokers on the basis of differences in the physical dispersal of the smoke (and of particles and droplets in the smoke), associated with the two methods of smoking—for example, in the proportion of smokers who inhale.

It will, however, be recalled that although benzpyrene is a strong carcinogen to which man and animals are both susceptible, it has yet to be directly established that it has any such action on the bronchial mucosa. It is possible that the active agent is, in fact, some substance hitherto not recognized as being carcinogenic. On the other hand, the high mortality from lung cancer among gasworkers, who are specifically exposed to large quantities of benzpyrene in the course of their work (see page 34), supports the hypothesis that benzpyrene is also carcinogenic in the human bronchus.

Mulvaney (1953) suggested that radioactive potassium, present in tobacco as a naturally occurring isotope, might be an effective carcinogen. Swinbank (personal communication) found that a typical cigarette contained 24 mg. of potassium and that the radioactivity corresponded to 2 ± 1.7 mg. more. The errors of the experiment were likely to have been greater than the statistical error, so that there was probably no excess activity at all. Even if there were, and it were all due to the presence of the most dangerous substance, radium, the amount estimated would not be biologically important. Swinbank estimates that, if the whole potassium content of cigarettes were inspired and if 20 cigarettes were smoked per day for 50 years, it is unlikely that the total dose would amount to more than the maximum permissible weekly dose recommended by the International Commission on Radiological Protection. Spiers (1954) found, however, that such radioactivity as is present in cigarettes remains almost entirely in the ash, and he was able to detect only the equivalent of 6 μg. of potassium in the smoke. It is, therefore, not possible to attribute any significant carcinogenic effect to radioactivity in tobacco.

The further possibility remains that cigarette smoke is not in itself carcinogenic but that it acts as an activator or a co-carcinogen to substances already present in the air from other sources. This hypothesis is less attractive than it was, now that benzpyrene has been found to be present in appreciable quantities in cigarette smoke, but it is possible that the effect of tobacco is enhanced by the presence of solvents in the smoke such as pyridine and pyrrole which could, theoretically, elute the benzpyrene adsorbed on to carbon particles in the inspired town air and so render the atmospheric benzpyrene more active. Such a secondary effect can readily be envisaged as being responsible for some of the differences in mortality in urban and rural areas referred to below.

H. *Various Criticisms.* The conclusion that cigarette smoking is a cause of lung cancer has not been uniformly accepted. It has not, to the author's knowledge, been argued that the basic data are factually erroneous (this would hardly be possible, since all who have investigated the subject have found the same general trends) but it has been suggested that the wrong interpretation has been put on the results—an interpretation incompatible with all the known facts. At first the principal objections were (1) that the retrospective study of patients' histories provided too many opportunities of bias for the results to be relied on (Hammond and Horn, 1953; Shapiro, 1954) and (2) that no known carcinogen had been identified in tobacco smoke. In the light of the follow-up studies on men of known smoking habits and of the recent biological and chemical studies on cigarette smoke, these criticisms are now only of historical interest.

The current objections may be considered under five main heads.

1. *That the evidence is purely "statistical" and that it has not been possible to produce the disease in laboratory animals by means of tobacco smoke* (Shapiro, 1954). A similar type of objection could have been made to Snow's conclusion that cholera was a water-borne disease or to Pott's conclusion that employment as a chimney sweep in childhood led to cancer of the scrotum. It is difficult to see what can be more relevant to the etiology of human cancer than observations on the extent of human mortality under different environmental conditions and, in this instance, nature has performed the appropriate experiment, in which the amount smoked has been varied while, so far as can be seen, other variables have been kept constant. In view of the variation in animal susceptibility and the impracticability of reproducing the exact conditions of human smoking in animal experiments, the failure to reproduce the human type of bronchial carcinoma by exposing animals to tobacco smoke cannot outweigh the extensive positive evidence obtained from direct observations on men.

2. *That the data recorded in the various investigations are not wholly consistent.* Although the general trend of all the results has been consistent, there have been inconsistencies in the reports of the relative risks attached to cigarette, cigar, and pipe smoking and in regard to the significance of inhaling (Hueper, 1954). The inconsistencies reported in relation to the different methods of smoking have already been considered (see page 16), but no reference has yet been made to inhaling. It would commonly be expected that any effect of cigarette smoking would be most noticeable among persons who inhaled the smoke, and both Lickint (1953) and Breslow and his co-workers (1954) found that a higher proportion of patients with lung cancer than of control patients said they inhaled. On the other hand, Doll and Hill (1952) found no difference in the proportion of inhalers in the two groups, although there was a suggestion that inhaling might be commoner among men with peripheral growths and even less common than among the controls in men with central growths. The explanation of these conflicting reports is unknown. It may, perhaps, derive from a failure on the part of the patients to understand correctly the import of the questions.

3. *That the interpretation put on the results is incompatible with the evidence from vital statistics.* Several of the principal criticisms of this type have already been discussed and they will, therefore, only be listed here.

a. That although the consumption of tobacco has undoubtedly increased, it has not yet been shown satisfactorily that there has been any real increase in the incidence of the disease (Rigdon and Kirchoff, 1953; Shapiro, 1954). See page 4.

b. That (on the contrary) the increase in tobacco consumption has not been great enough to account for the increase in the incidence of the disease (Todd, 1954). See page 22.

c. That the correlation between mortality and cigarette consumption as recorded in a number of countries is imperfect (Hueper, 1954) and that the data from Britain and the United States are, in particular, incompatible (Russ, 1954). See page 23.

d. That the male predominance among cases of the disease persists despite the fact that the increase in cigarette smoking has been relatively greater in women (Hueper, 1954). See page 22.

Other objections which have not been referred to previously are:

e. According to Hueper (1954) the fact that the sex ratio of cases of the disease was practically equal in Norway until about 1930, and that since then an increase has begun to be recorded which is most marked in men and in towns, weighs against the view that smoking is an important cause of the disease. He considers that special factors must have influenced the epidemiological behavior of lung cancer in Norway, whereas Norwegians smoke the same type of cigarette as that smoked in the United States. He omits, however, to take into consideration the very small quantity of cigarettes which were consumed in Norway before 1930, and the Norwegian experience may, with greater justification, be cited in support of the view that cigarettes are one of the principal causes of the disease.

f. Several authors have pointed out that the mucosa of the lip, mouth, and larynx also comes into contact with cigarette smoke, and yet the mortality from cancer of these sites, in contrast with the mortality from lung cancer, has remained stationary or has fallen (Hueper, 1954; Passey, 1954; Maxwell, 1955). Many investigators have, however, shown that cancer of the lip and mouth is, if anything, associated with the smoking of cigars and pipes (Levin *et al.*, 1950; Sadowsky *et al.*, 1953), so that a reduction in mortality from cancer at these sites would have been expected to occur as smoking habits were switched from cigars and pipes to cigarettes. The evidence with regard to laryngeal cancer is more conflicting. There is no *a priori* reason to suppose that it is necessarily produced by the same factors as produce lung cancer, and, in fact, none of the known industrial causes of lung cancer are known to cause laryngeal cancer. On the other hand, there is evidence that laryngeal cancer is associated with cigarette smoking (Levin *et al.*, 1950; Sadowsky *et al.*, 1953). It is possible that the lack of any marked increase in the recorded mortality from laryngeal cancer results partly from improvements in the treatment of intrinsic cancer of the larynx and partly from confusion by the classification under one head of cancer of the extrinsic and intrinsic larnyx.

4. *That an association is not necessarily causal and that both lung cancer and smoking may be the end results of a third common factor.* It is not possible to give any conclusive answer to this type of criticism and, indeed, a similar hypothesis always provides an alternative explanation to any scientific theory. The principle of Occam's razor has, however, proved of value to the development of scientific thought in the past, and it would seem reasonable to adhere to it now, and to work on the basis of the most economical hypothesis—unless or until some conclusive reason is shown for abandoning it. The possibility that lung cancer and smoking may both be end results of a third common cause is as much applicable to the results

of the prospective studies on mortality among smokers and nonsmokers as it was to the results of the retrospective studies among patients. There is, however, no evidence to suggest that it is the explanation of them. Some of the theoretically possible common factors have been considered above (see page 14); another which has been suggested is that persons of a particular physical constitution might be prone to lung cancer and to heavy smoking (Parnell, 1951). There is no evidence of such a physical constitution characteristic of patients with lung cancer; and if one did exist, we should still have to find some environmental factor to account for the increase in the incidence of the disease.

5. *That the effect of smoking is limited to determining the site of the growth in persons previously destined to develop cancer* (Fairweather, 1954; Loxton, 1954). This objection derives from Cramer's (1936) hypothesis that the total incidence of cancer in a population is constant and that environmental and hormonal factors exert their effect by determining the site at which the cancers develop. In this general form, it can readily be demonstrated to be not true (Case, 1954). In the particular case of cigarette smoking it can also be shown to be untrue; for, if it were true, it would follow that cancer of sites other than the lung would have to be relatively more common among nonsmokers and light smokers than among heavy smokers. Several reports of the smoking habits of persons with cancer in other sites have been made. Except for a report by Gilliam (1954) none has, in fact, shown a negative association between smoking and the type of cancer investigated, though several have suggested the possibility of other positive associations, *e.g.*, between cigarette smoking and cancer of the larynx and between pipe smoking and cancer of the lip (Levin *et al.*, 1950; Doll and Hill, 1950, 1954a,b; Sadowsky *et al.*, 1953; Hammond and Horn, 1954). Gilliam added details of the data on cancer of the skin to the data previously reported in conjunction with Sadowsky and Cornfield, and these showed a greater prevalence among nonsmokers than among cigarette smokers. The excess prevalence of skin cancer among nonsmokers could conceivably result if it were found that there were fewer smokers in the South of the United States than in the North.

I. *Conclusion.* In a review of the evidence relating lung cancer to smoking, Gilliam (1954) concludes that:

"Proof in the mathematical sense is unobtainable in dealing with medical problems. Direct experimental verification in humans 'is possible to conceive but impossible to conduct.' Indirect experimental verification in humans, through country-wide discontinuance of smoking and subsequent determination of trends of the disease, could be practically accomplished only by informing the public that the disease is caused by cigarettes. If this is true, the procedure is unnecessary as an experiment. Production of the disease in experimental animals, under conditions simulating human smoking, would strengthen though not establish the hypothesis, but inability to do so could in no circumferences justify its rejection. . . .

"We are left for 'proof,' therefore, with indirect and circumstantial evidence derived largely from considerations of the pathogenesis of the disease in individuals and its observed distribution in human populations: in short, with epidemiological evidence. It is a matter of opinion how many and what facts must be consistent before this hypothesis may justifiably be accepted or rejected."

In the author's opinion, taking into consideration the philosophical principle of Occam's razor which has already been referred to, the facts are such that the hypothesis that cigarette smoking is a cause of the main histological types of lung cancer should be accepted. They also, in his opinion, justify a strong presumption that the smoking of pipes and cigars is, in this respect, relatively innocuous. The discovery that a known and powerful carcinogen is present in tobacco smoke in significant quantity strengthens the credibility of the conclusion, but it has yet to be shown experimentally that the substance concerned has a direct action on the bronchial mucosa.

The great majority of the observed facts accord with the hypothesis, but the picture is not yet complete. We need to know, in particular, why the mortality from the disease in the United States is so low relative to the past consumption of cigarettes; and why the association which appears to exist between cancer of the larynx and cigarette smoking has not been reflected in an increase in the incidence of cancer of the larynx comparable to that believed to have occurred with cancer of the lung. The data on the significance of inhaling are also conflicting, and it is uncertain whether the difference between the effects of smoking tobacco in the form of cigarettes and in a pipe can be attributed to differences in the extent to which the smoke is usually inhaled or whether it is necessary to postulate some other mechanism. These fields of uncertainty are, however, small in relation to the extent of established knowledge and do not justify throwing doubt on the main conclusion.

2. *Industrial Hazards*

When Smith (1953) presented his report to the Louvain symposium, five industrial processes (the mining of certain radioactive ores, the refining of nickel, and the manufacture of asbestos, chromates, and coal gas) had been recognized as involving a special risk of lung cancer; and there was fairly strong evidence to suggest that exposure to heavy concentrations of arsenic in the air—of up to 1000 μg. per cubic meter—might also produce the disease (Hill and Faning, 1948; Perry *et al.*, 1948). Bonser (1955) has now suggested that hematite miners should be added to the list. During the last 20 years, 17 cases of lung cancer were

observed at autopsy among 192 hematite miners (8.9%), whereas the same pathologist found only 44 lung cancers among 2378 autopsies on men over 20 years old from the same area (1.9%). The evidence is suggestive, but it is not conclusive, since it is possible that miners with chest symptoms may have been more likely to come to autopsy than men with similar symptoms in nondusty occupations.

The extent of the risk has now been defined more closely in the case of asbestos, chromates, and coal gas. Brinton, Frasier, and Koven (1952) extended the initial observations of Machle and Gregorius (1948) and compared the sickness and mortality experience of insured workers in the seven chromate-producing plants in the United States with the whole sickness data obtained by the U.S. Public Health Service and the death rates for the U.S. population. They found that, over the period 1940 to 1948, the mortality from lung cancer among white males employed by the plants was 14 times the expected; and among colored males it was 80 times the expected. In view of the small number of cases, these estimates must be liable to considerable error, but it is clear that employees of the industry were exposed to a risk which was many times the normal. The physical conditions to which the workers were exposed have been investigated by the Division of Occupational Health of the U.S. Public Health Service (Federal Security Agency, 1953), but it has not, as yet, been possible to define which of the substances involved in the manufacturing process are carcinogenic. The authors suggest that acid-soluble–water-insoluble compounds found principally in the residue from the leaching tanks may be responsible. If this were so, it might explain why the hazard has been less apparent in British factories, where the residue is discarded (Bidstrup, 1951). The British industry has, however, only recently come under observation and the possibility that a considerable risk exists has not yet been excluded.

Doll (1952) studied the causes of death among 2071 male pensioners of a London gas company and found that the number of deaths from lung cancer was approximately double that expected by comparison with male inhabitants of London of the same age distribution (25 deaths against 13.8)—that is, showed practically the same excess as had been estimated by Kennaway and Kennaway (1947) from study of the national mortality statistics. In both cases the gasworkers covered a multiplicity of occupations, and it is possible that the risk may have been greater for those most closely concerned with the production process. In a more detailed study, Sutherland (personal communication) found an incidence of respiratory cancer among the employees and pensioners of a Canadian gas company who had worked in the retort house, which was several times higher than that recorded in the general population of the district. The excess was

apparent only among men who had worked at a particular station where the gas was manufactured in horizontal retorts. No excess was observed among employees who had never worked in the retort houses. According to the earlier reports of Kuroda and Kawahata (1936) the risk experienced by men employed in generator gas plants of a Japanese steel mill is likely to have been greater still (21 cases of lung cancer occurred in a 6-year period among 100 workers who had been employed for more than 10 years).

The risk to which asbestos workers were exposed has been defined more fully by a study of the mortality among 113 men who had been exposed to the dust for 20 or more years (Doll, 1955). Eleven of the thirty-nine men who had died were found to have asbestosis and cancer of the lung at autopsy, whereas the number of deaths expected to have been due to lung cancer was estimated as less than one (0.8). Since the mortality was considerably less among men who had been employed for less than 10 years in the conditions which existed before 1932, when measures were taken to reduce the amount of dust in the atmosphere, it must be presumed that the risk had at one time been appreciably greater than the average estimated over the whole period. The occurrence of lung cancer in 14 out of 72 subjects found to have asbestosis at autopsy has been reported by Bonser (1955).

The number of men employed in all these occupations taken together constitutes only a small fraction of the total number of men employed in industry, and the number of cases of lung cancer due to these special hazards can have contributed only a very small proportion to the total number of cases. Some of the occupations are, however, of particular interest since the carcinogenic agents which are presumed to be responsible for the added risks also have a more general distribution, *i.e.*, radioactive substances and benzpyrene. It is also of interest, as was pointed out by Smith (1953), that the majority of the specific industrial risks appear to be related to inorganic substances, whereas occupational tumors of other organs have usually been traced to organic compounds.

Numerous other occupations have been suggested as possibly giving rise to specific risks. The evidence has been fully reviewed by Hueper (1951, 1952), but in no other instance is it adequate to justify a positive conclusion.* Recent studies by Wynder and Graham (1951), Doll (1953a), and Breslow *et al.* (1954) have compared the occupational histories of men with lung cancer with the histories of comparable groups of men with other diseases, and Kreyberg (1954a) has compared the occupational histories of patients with his "group I" tumors with the histories of

* Nor is the recent evidence adduced by Dunner and Hicks (1953) with regard to boiler scalers and grain dockers.

patients with "group II" tumors and with the occupational distribution of the population of Norway, as shown by the Census. The most interesting finding has been the negative one, that workers who were particularly exposed to the fumes of motor exhausts (road transport drivers, etc.) were not disproportionately represented among the lung cancer patients in any of the series.

3. *Atmospheric Pollution*

A. *Mortality in Town and Country.* The principal reason for thinking that atmospheric pollution may be responsible for some cases of lung

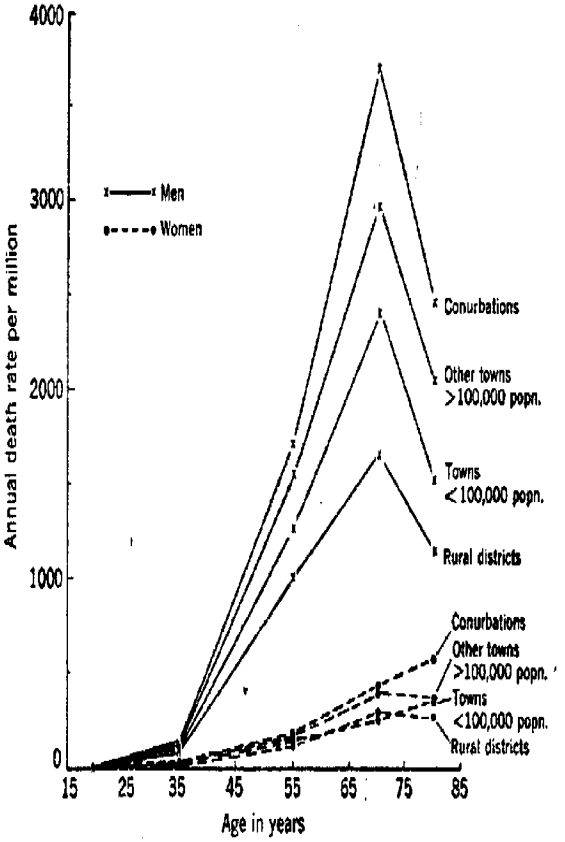

FIG. 8. Male and female death rates from lung cancer in England and Wales in 1953, by age and place of residence.

cancer is that the mortality has consistently been recorded as being higher in urban than in rural areas (Stocks, 1947, 1952; Clemmesen, Nielsen, and Jensen, 1953; McKinlay, 1953; Curwen, Kennaway and Kennaway, 1954; Hoffman and Gilliam, 1954; Kreyberg, 1954c; Saxén, 1955). The difference has not been great—the mortality in Copenhagen, London, Oslo, and American and Finnish cities being some one and a half to four times the rate in the corresponding countryside—but in each country for which detailed data are available the mortality has increased steadily with the degree of urbanization. Data for England and Wales for 1953 are illustrated in Figure 8. Particularly striking was the correlation demonstrated by Stocks (1952) between lung cancer mortality in men and the number of occupied houses in 84 large towns (Table X) and the finding that a similar correlation between density of population and male lung cancer mortality also holds for rural areas (Table XI, Curwen, Kennaway, and Kennaway, 1954).

Three explanations of these findings are possible: (1) that they are artifacts due to a greater efficiency of diagnosis in the areas of greater

TABLE X

Standardized Mortality Ratios Due to Lung Cancer for Men in 84 Towns of England and Wales (1946-1949) Compared with No. of Occupied Dwellings and Density of Population per Acre*

Towns	No. of Occupied Dwellings (1931)	Persons per Acre (1951)	Standardized Mortality Ratio for Lung Cancer in Men (1946–49)
†London, Croydon, East Ham, and West Ham	862,500	41	156
† Birmingham, Smethwick, Walsall, and West Bromwich	297,600	20	134
† Manchester, Salford, and Stockport	259,900	25	159
† Liverpool, Bootle, Birkenhead, and Wallasey	242,400	25	162
† Leeds, Bradford, and Halifax	237,700	11	132
Sheffield	123,800	13	135
† Newcastle on Tyne and Gateshead	86,700	26	114
Average of 6 towns	66,700	19	113
Average of 3 towns	43,600	16	106
Average of 12 towns	33,100	16	105
Average of 13 towns	24,000	16	101
Average of 29 towns	14,700	11	89

* After Stocks, 1952. Some of the mortality ratios shown differ very slightly from those quoted by Stocks, because the data for the last 5 groups are, for simplicity of tabulation, shown as averages.
† Groups of adjacent towns treated as one unit.

population density, (2) that they result from the presence of a carcinogenic pollutant in town air, and (3) that they result from differences in the way of life of individuals in town and country.

The first possibility cannot be entirely excluded. Bonser and Thomas (1955) found, for example, that during the years 1950 to 1952 the number of cases diagnosed in hospital in a largely rural region of Scotland was 21% less than the number of persons recorded as having died of the disease, whereas in Leeds the deficiency was only 8%. Clemmesen, Nielsen, and Jensen (1953) found a similar difference between the proportion of cases not admitted to hospital in the rural districts of Denmark and in

Copenhagen (25% against 8%). There has, therefore, clearly been less ready access to hospital for patients in rural areas, and the possibility must be admitted that some of the difference in mortality may be spurious. Doll and Hill (1952), on the other hand, found that the proportion of lung cancer patients who had lived for 10 or more years in the country was less than that among a matched group of control patients—irrespective of the place of residence at the time of interview. The differences were small and were not statistically significant, but they were all in the same direction and provide some support for the belief that the risk of developing lung cancer has been, in fact, lower in the countryside.

TABLE XI

Standardized Mortality Ratios Due to Lung Cancer in the Rural Districts of 11 Geographical Regions of England and Wales (1946–1949) Compared with the Average Population per 100 Acres*

Density of Population, Persons per 100 Acres	39	38	36	32	27	24	22	20	19	13	12
S.M.R. Male	69	63	76	60	60	65	55	50	58	55	45
S.M.R. Female	(22†)	(77)	96	(84)	67	61	(61)	(65)	72	(60)	(84)

Coefficient of correlation between density of population and male S.M.R. ..... 0.81, S.E. 0.30

Coefficient of correlation between density of population and female S.M.R. ..... −0.11, S.E. 0.30

* After Curwen, Kennaway, and Kennaway, 1954.

† Based on 17 deaths; other figures in parentheses on 25–100 deaths and all others on more than 100 deaths.

B. *Pollution of Town Air.* Three known carcinogens have been detected among the pollutants of town air: arsenic, 3,4-benzpyrene, and radium. The amount of arsenic was, however, of the order of 6 μg. As_2O_3 per 100 m.³ (Goulden, Kennaway, and Urquhart, 1952) and was minute in comparison with the amount to which men have been exposed in industry, without the apparent production of any great excess of lung cancer (see page 33). Waller (1952), Kotin, Falk, Mader, and Thomas (1954), and Kotin, Falk, and Thomas (1954) reported that 3,4-benzpyrene was present in town smoke and in the exhaust fumes of cars, but if, as is likely, it occurs adsorbed onto particles of carbon it must be presumed to be biologically inactive (Steiner, 1954). The extent to which the radium (and radon) content of coal smoke may be significant is uncertain (Anderson, Mayneord, and Turner, 1954) (see page 42).

The chemical findings do not, as yet, give material support to the suggestion that the increased mortality from lung cancer in urban areas may be due to pollution of the atmosphere, but it is possible that further work may show the pollutants to be effectively carcinogenic. For example, the petrol vapors present with benzpyrene in motor exhaust fumes may themselves act as adequate eluents (Kotin, Falk, Mader, and Thomas, 1954). In the present state of knowledge conclusions about the role of atmospheric pollution must be based on the epidemiological findings.

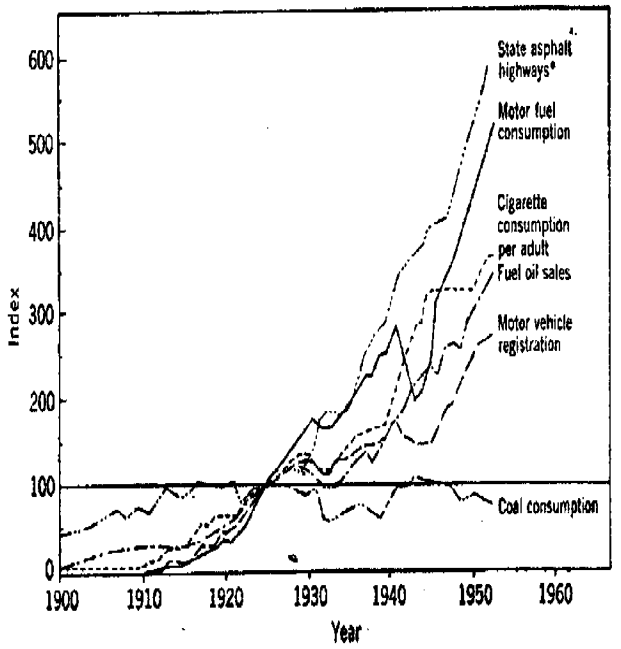

FIG. 9. Trends in prevalence of selected environmental factors expressed as a percentage of the prevalence in 1928, U.S.A. 1900–1953. (Reproduced from a paper by Dr. E. C. Hammond, in *Cancer* 7, 1100–1109, 1954.)

From this point of view, it is difficult to believe that the increase in mortality from lung cancer can have been directly due to pollution with chimney smoke or with petrol or oil fumes. On the one hand, the amount of coal consumed in the industrialized countries has not increased greatly, and the total amount of smoke pollution has probably decreased because of greater efficiency of combustion (in Britain, for example, coal consumption increased from about 165 million tons in 1900 to 206 million tons in 1953, but the amount burnt in gasworks and electricity-generating stations increased from 23 million tons in 1921* to 64 million tons in 1953. The pattern of coal consumption in the U.S.A. is shown in Fig. 9). On the other hand, there has been a marked increase in the amount of petrol and oil burnt (Hammond, 1954, see Fig. 9), but men who have

* Earlier figures not available.

had special occupational exposure to the fumes do not appear to have suffered any abnormally high mortality from the disease (see page 35). Diesel fumes are a special case in that oil-burning engines have not been in general use on the roads for a sufficient length of time—to judge from the induction time of industrial cancers—to have exerted any significant carcinogenic effect.

In England and Wales the excess urban mortality has, until recently, increased *pari passu* with the total lung cancer mortality; in Denmark it has increased even more rapidly. Unless, therefore, it is postulated that the whole increase in mortality is due to improved diagnosis (which is contrary to the general opinion, see page 4), it must be concluded either that atmospheric pollution acts as a co-carcinogen to some other substance which has increased in prevalence (for example, in cigarette smoke) or that it cannot be responsible for more than a relatively small and constant part of the specific urban mortality. In either of these cases a number of apparently anomalous findings will have to be accounted for:

1. The difference between urban and rural mortality is greater for Copenhagen and the Danish countryside (4 to 1) than it is for large English towns and the English countryside (2 to 1), although the smoke pollution of Copenhagen air—judged colorimetrically—is only about one-tenth of the level of a typical English industrial town (Kennaway and Wilkins, personal communications).

2. A general atmospheric pollutant could be expected to affect both sexes equally, whereas, in fact, (*a*) urban areas with a high mortality show a greater predominance of male cases than rural areas with a low mortality (Stocks, 1952, Clemmesen, Nielsen, and Jensen, 1953) and (*b*) the correlation between mortality and density of population in rural regions which Curwen, Kennaway, and Kennaway (1954) found to be strong for men was absent for women (see Table XI).

3. No consistent difference in lung cancer mortality has been found among nonsmokers in areas of different population densities (Doll, 1953b).

C. *Differences in Urban and Rural Habits.* The urban excess may also be due to differences in the personal habits of townsmen and countrymen. Kreyberg (1954c, 1954d) came to the conclusion that this was the most probable explanation from comparing the place of residence and the occupation of patients with his "group I" and "group II" tumors. He found that the ratio was greater for towns than for rural areas, but that it was unaffected by the degree of industrialization of the town or by the extent to which the town was exposed to wind from the sea.

One possibly relevant difference to have been recorded is a difference in smoking habits. Doll and Hill (1952) found that townsmen tended to smoke more than countrymen and that a higher proportion of townsmen who smoked, smoked cigarettes. Moreover the difference was greater for men in big towns than for men in small towns. Stocks (1954), Hammond and Horn (1954), and Kreyberg (personal communication) have reported similar differences. The differences are not, themselves, great enough to account for more than a small part of the excess urban mortality. Present habits are, however, unlikely to be relevant to present mortality, and it is possible that the differences may have been greater 20 or 30 years ago. Unfortunately, precise data about prewar differences are not available.

D. *Conclusion.* The present evidence is inadequate to allow an explanation of the urban-rural difference in mortality to be given with confidence. Several considerations weigh against the suggestion that it is primarily due to atmospheric pollution with chimney smoke or motor exhaust fumes; but the possibility has not been excluded that chimney smoke may be responsible for a proportion of cases—perhaps as a consequence of its radium content—or that it may act as a co-carcinogen with, say, tobacco. The urban-rural difference can be partly accounted for by (1) geographical differences in the efficiency of diagnosis and (2) differences in the past smoking habits of townsmen and countrymen. The effect of these factors is likely to diminish, and it may, therefore, be anticipated that the differences will also gradually diminish. Postwar experience in England and Wales suggests that this may, in fact, have begun to happen (Waller, personal communication).

	1950	1953
Standardized male D.R.* in Greater London	667 per million	782 per million
Standardized male D.R. as a percentage of the rate in Greater London		
Greater London	100	100
Other conurbations	87	90
Towns more than 100,000 popn.	82	83
Towns 50,000-100,000 popn.	64	72
Towns less than 50,000 popn.	58	64
Rural districts	47	49

* Standardized on the age distribution of the male population of England and Wales in 1950.

4. *Atmospheric Radioactivity*

Uranium and thorium are widely distributed throughout the earth's crust; both materials decay through radioactive series, one member of which is gaseous. The radioactive gases, *i.e.*, radon and thoron, escape into the atmosphere, where their respective decay products eventually attach themselves to dust particles.* In addition a small amount of radon and

* The small amount of radioactivity attributable to thoron is not distinguished from that attributable to radon in the remainder of this discussion.

of radium is released into the atmosphere by the combustion of coal. Minute quantities of the radioactive isotopes of the common elements (*e.g.*, potassium and carbon) are also present, but their effect would be insignificant in comparison with the effect of members of the uranium and thorium series.

Whether atmospheric radioactivity is a cause of any cases of lung cancer is uncertain. It cannot have been responsible for the increase in incidence which took place before 1954, and there is no evident reason why it should affect men more than women. There is, however, a possibility that it might contribute to the increased incidence in towns, because of the presence of radium in coal smoke (Anderson, Mayneord, and Turner, 1954). During conditions of fog both coal smoke and the radon naturally diffusing from buildings and the soil are likely to be retained near the surface of the earth, and a considerable increase in radioactivity may be observed. On the first day of the London smog of December, 1952, Anderson, Mayneord, and Turner found a level 400 times that previously recorded on a clear sunny day. Dawson (1952) found that radioactivity indoors was approximately double that in the open air, and in a closed cellar it was increased a hundredfold. On the other hand, he could not find any appreciable difference between the average radioactivity of the air in towns and country. The large day-to-day variations which occurred in all districts were chiefly related to meteorological conditions.

The average amount of radioactivity present was estimated by Dawson (1952) to be of the order of 5×10^{-11} μc. per milliliter, and this agrees fairly well with estimates made earlier in the century in England, Canada, and the United States (2×10^{-12} to 2×10^{-10} μc. per milliliter). Dawson's estimates were, however, made by drawing air through filter papers and deducing the radon content of the air samples by assuming that the radon was in equilibrium with the radium A, B, and C on the retained particles. Anderson, Mayneord, and Turner (1954) suggest, however, that the method may underestimate the amount when the suspended particles are small. By measuring whole air samples in an ion-chamber apparatus, they obtained values 10 to 100 times greater than with the filter paper method; and the average value for air on the roof of the Institute of Cancer Research, London, was found to be 2 to 3×10^{-9} μc. per milliliter.

The "tolerance concentration" of radon is at present set at 10^{-7} μc. per milliliter; but it is not possible to determine whether atmospheric radioactivity can ever be carcinogenic by reference to such an arbitrary standard, since the standard has been set in relation to the safety of individuals. The only way at present available of testing whether a given

level might produce an incidence of, say, 1 in 100,000 in a large population is by comparison with the effects produced by the known levels in the highly radioactive mines in Schneeberg and Jachymov and in other similar areas.

According to Evans (1950) the mean concentration of radon in the air of the mines was equivalent to an activity of 3×10^{-6} μc. per milliliter. The content of the air varied in different parts of the mines, and other estimates have set the average value 10 times higher (Mitchell, personal communication). Evans calculates that an activity of 3×10^{-6} μc. per milliliter would have delivered a dose of approximately 0.5 r.e.m. per working day to the epithelium of the larger bronchi. The average induction time for the development of the tumors was 17 years (Šikl, 1950), so that the total dose received would, in this case, have been of the order of 3000 r.e.m. Shapiro (1954) and Anderson, Mayneord, and Turner (1955) point out that Evans ignored the effect of the particulate matter in the air bearing the radioactive breakdown products of radon and they estimate that the total dose received by some areas of the bronchi is likely to have been 70 times higher. Since persons suffering from chronic radium poisoning who developed bone sarcoma are estimated to have received local doses of about 35,000 r.e.m. (Evans, 1950), the physical data may be considered reasonably consistent with the hypothesis that the Jachymov cancers were due to exposure to radon in the air.

If it is assumed that there is a linear relationship between strength of dose and cancer incidence—and the assumption is not necessarily justifiable, particularly for very small doses—it is possible to estimate the incidence of lung cancer which may be produced by normal atmospheric radiation. According to Šikl (1950) the mortality among the miners of Jachymov was approximately 1% per year, so that exposure to normal atmospheric radioactivity for the length of time the miners were exposed to the air of the mines, might be expected to produce an annual mortality of between $\frac{5 \times 10^{-11}}{3 \times 10^{-6}} \times 1\%$ (the ratio of the minimum estimate of normal atmospheric radioactivity and the maximum estimate of the radioactivity of the air in the mines, times the mortality among the miners) and $\frac{2.5 \times 10^{-9}}{3 \times 10^{-6}} \times 1\%$ (the ratio of the maximum estimate of normal atmospheric radioactivity and the minimum estimate of the radioactivity of the air in the mines, times the mortality among the miners) *i.e.*, between 0.017 and 8.333 per million.

Evans assumed that the miners were exposed for 12 hours out of the 24, whereas people are exposed to normal atmospheric radiation throughout the day. More importantly, people are normally exposed from birth,

whereas the miners were exposed, on the average, for 17 years from the age of 33 years. If the effect were proportional to the total dose irrespective of the period of life at which it was administered the expected annual mortality would be between $0.017 \times 2 \times 3$ and $8.333 \times 2 \times 3$ per million, *i.e.*, between 0.1 and 50.0 per million.

In England and Wales the annual mortality from lung cancer among men aged 25 to 74 was 912 per million in 1953, but much of this appeared to be attributable to smoking. Estimates of the rates among nonsmokers have been made by Doll (1953b), from which it can be calculated that the mortality in this age group attributable to causes other than smoking may be of the order of 69 per million. The Jachymov population cannot have contained as high a proportion of old people as does the adult population of England and Wales, so that the comparable mortality due to causes other than smoking is certainly much less than 69 per million—perhaps as little as 30 or 40 per million.*

On the basis of these calculations, it seems that atmospheric radiation might well be a significant cause of lung cancer in Britain. This conclusion is strengthened if it is considered, from analogy with other types of cancer, that the total dose of the carcinogenic agent is not the only determinant of the incidence of the disease. As with other types of cancer there appears to have been an appreciable induction time between initial exposure and the appearance of the Jachymov cancers, and it is possible that exposure to a given dose of radiation early in life may have a greater effect at the age of 50 years than exposure to the same dose at the age of, say, 35 years. In these circumstances, the expected mortality due to atmospheric radiation may be many times greater than the annual rate estimated above. On the other hand, the fact that the Jachymov and Schneeberg cancers were almost invariably squamous, oat-cell, or undifferentiated cancers (Schmorl, 1928; Hueper, 1942; Šikl, 1950), whereas an important part of the nontobacco cancers appears to consist of adenocarcinomas, weighs against the concept that radioactivity could account for all the cancers not attributable to smoking or to specific industrial hazards.

5. *Previous Respiratory Infections*

Previous inflammation and the formation of scar tissue in the lungs have long been thought to be possible precursors of lung cancer, but there is little firm evidence to implicate them. Woodruff and Nahas (1951) and Woodruff *et al.* (1952) found that large calcified foci—larger than in any other part of the lung—were present in the same lobe as the tumor,

* If the entire population of miners and retired miners observed by Šikl is assumed to have been aged 25 to 44 years, the comparable mortality among nonsmokers would be 20 per million.

or in the tracheobronchial nodes draining the lobe, in 27 out of 40 cases of squamous and anaplastic bronchial cancer. They suggested that calcified foci might increase the susceptibility of the neighboring bronchial mucosa to carcinogenic substances reaching it from the inspired air, or that bronchiectasis following primary tuberculosis might be a predisposing factor. A similar type of conclusion was suggested by Schwartz* (1950), who described cases of bronchial carcinoma in association with lesions of the bronchial wall brought about by neighboring tuberculous lymph nodes.

Raeburn and Spencer (1953) reported a close histological association between the site of origin of cancer and lung fibrosis and bronchiectasis. They sectioned the whole of both lungs at autopsy and removed all suspicious nodules and scars for microscopy. In 750 autopsies, they found 9 unsuspected microscopic cancers in association with scars in the periphery of the lung and one unsuspected small carcinoma in a large bronchus. The authors acknowledged that "great difficulty has been experienced in determining the borderline between innocent reparative proliferation and true malignant change," but they were satisfied that "only cases which have shown obvious malignant change have been included in the series." If the lesions were, in fact, true cancers, it must be postulated that their evolution into clinical malignancy would have taken many years, since otherwise their incidence was much greater than could be explained by the known rate of cancer mortality. The observation emphasizes the need for a long-term study of the end results of respiratory infection.

It has often been noted that a long-standing bronchitis is a common complaint of persons with lung cancer (*e.g.*, Bryson and Spencer, 1951), but there have been few studies of the frequency of its occurrence in comparable control series. Doll and Hill (1952) compared the history of previous respiratory disease in 1465 patients with carcinoma of the lung and in 853 patients with cancer in other sites. After making allowance for the age and sex of the patients they found that the proportions of patients complaining of attacks of respiratory tuberculosis, pleural effusion, asthma, or chronic nasal catarrh more than five years previously were practically the same in both groups, but that the proportions complaining of chronic bronchitis or of pneumonia more than five years previously were significantly greater in the lung carcinoma group. When, however, the lung carcinoma patients were compared with another group of 335 patients who had been thought to have lung cancer at the time they were interviewed but who were finally proved not to have it, no significant difference was detected. This latter group, however, contained a high proportion of patients with other respiratory diseases and may not

have been a suitable control group. All that could be concluded was that either chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders, including bronchial carcinoma, or that patients with respiratory disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases in other systems.

Lea (1952) compared the incidence of long-standing pulmonary symptoms in men with different histological types of lung cancer and found that it was significantly higher in men with squamous carcinoma than in men with oat-cell carcinoma or adenocarcinoma (20 out of 91 against 33 out of 303). He did not, however, allow for the greater average age of the patients with squamous carcinoma, and this may have accounted for some of the difference.

Direct evidence implicating chronic bronchitis has recently been obtained by Case and Lea (1955). In a large group of chronic bronchitics who were followed for more than 30 years, they found that the mortality from cancer in sites other than the lung was close to the expected mortality, whereas the mortality from lung cancer was about double what they had calculated it should be. A result of this type might be accounted for if the development of bronchitis was itself closely related to smoking habits. According to Palmer (1954) bronchitis is commoner among smokers than among nonsmokers, and its incidence increases with the amount smoked; the data are, however, insufficient to exclude the possibility that the association between bronchitis and lung cancer may be, at least in part, independent and direct. On the other hand, bronchitis cannot be the effective intermediate stage in the carcinogenic process initiated by smoking, since the relationship between smoking and cancer is closer than the relationship between cancer and bronchitis.

IV. Conclusion

From the work which has been reviewed in the preceding sections, a fairly distinct picture of the etiology of the disease is beginning to appear.

Firstly, there is the rise in incidence which has taken place in many countries and which has principally affected men. Corresponding to this rise, it must be postulated that there has been an increased prevalence of one or more causal factors in the environment.

Secondly, there is the evidence that cigarette smoking is an important factor in the production of squamous, oat-cell, and undifferentiated lung cancer, and that a few individual cases result from exposure to five or more independent industrial processes. Whether the increase in cigarette consumption and the growth of the specific industries can together account for the real increase in mortality and for the extent of the male

preponderance, cannot be seen with certainty. Knowledge of the true extent of the change in mortality and of the fundamental mechanisms of carcinogenesis is, unfortunately, insufficient to permit the preparation of a precise balance sheet. There is, however, no direct evidence to implicate those other environmental factors which are also known to have increased in prevalence in the last four or five decades; and it is a reasonable presumption that the changes which have taken place in tobacco consumption (in amount and in method) are responsible for the major part of the real increase in mortality. Whether the action of cigarette smoke is due to its 3,4-benzpyrene content or to some other substance, and why it should be different from that of smoke from pipes and cigars, is unknown.

Thirdly, there is a group of cases, of relatively stable incidence and occurring almost equally in men and women, which is characterized histologically by the inclusion of a high proportion of adenocarcinomas. Some of these cases—though perhaps not the adenocarcinomas—may be due to atmospheric radioactivity; others may conceivably result from long-standing respiratory infections.

Two other factors have at times received considerable prominence, namely, atmospheric pollution and hereditary susceptibility. The evidence concerning the former permits no definite conclusion, save only that it is not independently responsible for a large proportion of cases nor for the recent increase in mortality. There is no evidence concerning the latter, though doubtless susceptibility to inspired carcinogens varies as does susceptibility to other environmental stimuli.

Perhaps the most striking conclusion is the wide range of substances —several of them inorganic—which can induce cancer in the bronchial mucosa. Whether there may be a common mechanism, through which each exerts its effect, remains one of the principal problems for future research.

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