BRONCHIAL CARCINOMA: INCIDENCE AND AETIOLOGY*

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Unit of the Medical Research Council

Consumption of Tobacco

The possibility that a relationship exists between the smoking of tobacco and the development of bronchial carcinoma has been suggested often—and over a period of many years. At first the suggestion was made either on theoretical grounds or because of the clinical observation that the patients tended to be heavy smokers. In support it was pointed out that national figures for tobacco consumption showed increases over the same period in which the recorded lung cancer death rates had increased. In the absence of positive animal experiments, or of detailed knowledge of normal smoking habits, such considerations carried little weight, and it is invidious to try to determine who first suggested that tobacco might be a factor.

Direct evidence of a relationship was first secured in 1939 by Müller, in Germany. He obtained the smoking histories of 86 male patients with bronchial carcinoma from hospital notes, by personal interview, or from a questionary sent to the relatives of the patients who had died; he compared them with histories given by 86 healthy men of the same ages. The results showed gross differences between the groups in the proportions of non-smokers and of heavy smokers, but the different methods by which the data were collected made it difficult to draw firm conclusions from the comparison.

Subsequently other workers have used similar methods to study the problem—that is to say, they have obtained records of the smoking habits of patients with bronchial carcinoma and have compared these with records of other subjects, assumed to be representative of the population from which the bronchial carcinoma patients were drawn. The principal results obtained in the reports to which I have been able to refer are shown in Table III.

TABLE III.—*Smoking Habits of Men With and Without Lung Cancer*

Author	Date	No. of Men		Percentage of Non-smokers* 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	65·1	36·0
Schairer and Schöniger..	1943	93	270	3·2	15·9	51·6	26·7
Wassink ..	1948	134	100	4·8	19·0	82·0	45·0
Schrek *et al.*..	1950	82	522	14·6	23·9	18·3*a*	9·2*a*
Mills and Porter ..	1950	444*b*	430	7*b*	31	—	—
Levin *et al.* ..	1950	236	481	15·3	21·7	—	—
Wynder and Graham ..	1950	605*c*	780	1·3*c*	14·6	51·2*c*	19·1
McConnell *et al.* ..	1952	93	186	5·4	6·5	35·0*d*	21·5*d*
Doll and Hill	1952	1,357	1,357	0·5	4·5	25·0	13·4

* Definition varies from one author to another.
a. Percentage of heavy cigarette smokers.
b. Figures relate to all respiratory cancers.
c. Figures relate to lung cancer other than adenocarcinoma.
d. Percentage among men and women (93 men and 7 women and 186 men and 14 women respectively).

The proportions of "non-smokers" and of "heavy smokers" found among both groups of men—those with and those without lung cancer—vary considerably from one author to another. This is not surprising, since the observations were made in four different countries, the definitions of "non-smoker" and "heavy smoker" varied considerably, and so did the methods by which the records were obtained. The notable fact is the consistency with which the proportions of non-smokers were lower and the proportions of heavy smokers were higher among the male patients with lung cancer than among the other men investigated.

In only one report is the difference in doubt. According to McConnell, Gordon, and Jones (1952) the proportion of non-smokers among 93 male patients with lung carcinoma in the Liverpool area was only slightly less than that among 186 male patients of similar ages but with other diseases. It is, however, possible that the definition of a non-smoker may not have been applied with equal rigour in both groups, since most of the lung cancer patients were interviewed two years before the controls and before the form of the investigation had been finally determined. In contrast, the proportion of "heavy" smokers was found to be significantly higher in the cancer group than in the control group—as in all other reports.

The consistency of the results of investigations carried out with various techniques in four different countries is, in itself, suggestive that a real relationship between smoking and lung cancer exists. The possibility that all the results could be due to bias in the selection or interviewing of patients has been eliminated, and there are strong reasons for believing that the control patients—in at least some of the investigations—were adequately representative of the populations from which the lung-cancer patients were drawn (Doll and Hill, 1950, 1952). The results amount, I believe, to proof that smoking is a cause of bronchial carcinoma. No proof is, however, absolute—all are susceptible to greater or smaller degrees of confidence. It is only by further experiment, by testing the hypothesis under fresh conditions, that confidence can be gradually increased until finally its truth is unquestioned.

In the present case, the simplest way of checking the conclusion is by observation of the mortality from bronchial carcinoma in subjects whose smoking habits have been previously defined. Such a check is being carried out by Hammond in the U.S.A., by Kreyberg in Norway, and by Bradford Hill and Doll in this country. In the British investigation, questionaries were sent to 59,600 doctors asking them to classify themselves into three groups, according to whether they continued to smoke, had given up smoking, or had never smoked regularly. If they fell into either of the first two categories they were asked additional questions—namely, the age at which they started to smoke, the amount smoked, and whether they smoked pipes or cigarettes. The questions were made short and few, to ensure the maximum number of replies and because the experience of interviews with nearly 5,000 patients in the earlier inquiry had shown that classification of smokers according to the present amount smoked and the number of years given up gave almost as sharp a differentiation between the bronchial carcinoma and other patients as the use of more complex statistics.

Altogether 40,603 replies have been received. The fact that this is only 68% of the number of questionaries sent out is immaterial, since we are not concerned to estimate the smoking habits of doctors as a profession for comparison with those of other professions, but to define groups within the profession who differ in the amount they smoke.

By the courtesy of the Registrars-General of Great Britain and Northern Ireland, it has been possible to receive details of the causes of death of all doctors who have died since the questionaries were sent out. In the first eleven months, nine deaths have been recorded due to lung cancer, among doctors aged 55 and over for whom details of the previous smoking histories are available. From the knowledge of the smoking histories of all the doctors who replied, mortality rates can be calculated for different levels of tobacco consumption—making allowance for the variation of smoking habits with age. Whilst the deaths are so few,

*Second part of the Milroy Lectures delivered at the Royal College of Physicians of London on February 10 and 12, 1953. (*Abridged.*) The first part was printed in last week's *Journal* (p. 521).

the calculated mortality rates are extremely unreliable, but so far as they go they are not inconsistent with the results recorded previously.

All forms of smoking are, it appears, not equally dangerous. Pipe-smoking (Wynder and Graham, 1950; Levin *et al.*, 1950; Schrek *et al.*, 1950; Doll and Hill, 1952) has, with one exception (McConnell *et al.*, 1952), been found to be less closely associated with bronchial carcinoma than has cigarette-smoking. This can be partly accounted for by the lower average consumption of tobacco by pipe-smokers; on the other hand, Doll and Hill have estimated that the risk is lower among pure pipe-smokers than among pure cigarette-smokers at each level of tobacco consumption. According to the American authors, cigar-smoking provides the same order of risk as pipe-smoking (Table IV).

TABLE IV.—*Relative Proportions of Cigarette-, Cigar-, and Pipe-smokers; Lung Cancer and Other Patients (American Authors)*

Authority	Ratio of Cigarette- to Pipe-smokers		Ratio of Cigarette- to Cigar-smokers	
	Lung-cancer Patients	Other Patients	Lung-cancer Patients	Other Patients
Wynder and Graham (1950)	22·8 : 1	5·3 : 1	26·1 : 1	8·4 : 1
Schrek *et al.* (1950) ..	16·4 : 1	5·1 : 1	21·7 : 1	5·9 : 1
Levin *et al.* (1950)	5·0 : 1	1·7 : 1	5·9 : 1	1·9 : 1

Users of cigarette-holders and smokers of filter-tipped cigarettes have been found less frequently among lung carcinoma patients than among patients with other diseases. The proportion of persons who have been accustomed to smoke in this way is small and the number of recorded observations is too few for firm conclusions; they are, however, consistent with the observations on pipe-smokers, and it seems probable that each of these methods of smoking may partly separate out an active agent before it reaches the respiratory tract (Doll and Hill, 1952).

In discussing the conclusions to be drawn from their preliminary data, Doll and Hill (1950) pointed out that to say that a real association existed between carcinoma of the lung and smoking was not the same as saying that smoking caused carcinoma of the lung. "The association would occur if carcinoma of the lung caused people to smoke or if both attributes were end-effects of a common cause. The habit of smoking was, however, invariably formed before the onset of the disease (as revealed by the production of symptoms), so that the disease cannot be held to have caused the habit; nor can we ourselves envisage any common cause likely to lead both to the development of the habit and to the development of the disease 20 to 50 years later. We therefore conclude that smoking is a factor, and an important factor, in the production of carcinoma of the lung."

In the two and a half years that have since passed there has been no reason to think that that conclusion needs to be modified. It has been challenged on a number of grounds, but only one appears to require serious consideration. The fact that no carcinogen has been identified in tobacco smoke does not invalidate the evidence; the recognition of the risk run by chimney-sweeps and tar-workers came many years before the carcinogenic polycyclic hydrocarbons were isolated. Nor is it significant that the increase in the recorded death rate has been greater than the increase in tobacco consumption, since we have so little idea what proportion of the recorded increase in mortality is real. The more serious objection is that it is theoretically possible for both smoking and the development of bronchial carcinoma to be themselves related to some third common factor. In view of the apparently linear increase in the mortality from lung cancer with increasing tobacco consumption, we should need to postulate that this third factor was also linearly related both to smoking and to the risk of developing the disease. In the absence of positive evidence that such a factor exists it is more reasonable to adopt the philosophical principle of Occam's razor, which has served science so well in the past, and to proceed on the basis of the simplest explanation; that is, that the more people smoke the more likely they are to develop carcinoma of the lung.

It has often been suggested that it is not so much the tobacco which is responsible for the carcinogenic action of the smoke as the cigarette paper or the associated use of a petrol lighter. Such a position cannot, I think, be maintained. In the first place, there would appear to be some risk associated with pipe-smoking (even though it may be appreciably smaller than that associated with cigarettes) and tar from tobacco burnt as in pipe-smoking has been shown to have a carcinogenic effect experimentally (Sanders *et al.*, 1932; Flory, 1941). Secondly, petrol lighters have not been used any more extensively by patients with bronchial carcinoma than by other patients.

Arsenic is present in most forms of tobacco, probably through 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) estimate 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. This is not a large amount, and in any case arsenic is unlikely to be the carcinogenic agent, since (1) a high proportion of cancer cases in Istanbul are found at necropsy to arise from the bronchi (Schwartz, reported by Daff, Doll, and Kennaway, 1951) and Turkish tobacco contains no, or very little, arsenic; and (2) tar from tobacco smoke, applied externally to the skin of animals, is capable of inducing cancer, which arsenic is not.

The last observation also tells to some extent against the suggestion that the agent in tobacco might be a co-carcinogen, which acted by enhancing the effect of another substance present in, say, the atmosphere of towns.

Benzpyrene has not been detected in tobacco smoke, and it would seem probable that the substance concerned is one which has not hitherto been recognized to be carcinogenic.

Other Aetiological Factors

Of other factors suggested as being of possible aetiological importance, the greatest attention has been paid to previous respiratory disease and hereditary predisposition.

Shaw suggested, in 1924, that patients who recovered from influenzal pneumonia might have an increased susceptibility to lung cancer, and he added, in relation to the pandemic of 1918–19, that it would be "of interest to see whether, as a late manifestation, there is an increase in the number of cases of pulmonary cancer, which at present is a relatively rare tumour." His surmise was based on observation of metaplastic changes in the bronchial mucosa of patients dying of subacute influenzal pneumonia; it has certainly been borne out in regard to the increased incidence of the disease, but the reason for the increase which he suggested seems unlikely to be correct. Firstly, there has been little increase of lung cancer in Iceland (Dungal, 1950), although that country suffered severely from the pandemic of influenza; and, secondly, influenza affected both sexes almost equally in Britain in 1918–19 (as judged by mortality), while deaths from lung cancer occur predominantly in men.

Schwartz (1950) has described cases of bronchial carcinoma arising in association with lesions of the bronchial wall brought about by neighbouring tuberculous lymph nodes. Woodruff and Nahas (1951), and Woodruff *et al.* (1952) have found that large calcified foci—larger than in any other part of the lung—were present in the same lobe as the tumour, or in the tracheo-bronchial nodes draining the lobe, in two-thirds of 40 cases of squamous and anaplastic bronchial tumours, while they found a similar focus in only

one of six bronchial adenocarcinomas. Woodruff suggests that calcified foci may increase the susceptibility of the neighbouring bronchial mucosa to carcinogenic substances reaching it from the inspired air or that bronchiectasis following primary tuberculosis may be a predisposing factor. On these assumptions, he suggests that part of the recent increase in bronchial carcinoma may be explained by the *fall* in mortality from pulmonary tuberculosis in young adult males, leading to the occurrence of an *increase* in the incidence of healed primary foci in older men a generation later. Whether such a corollary has in fact occurred is open to doubt and cannot be assumed in the absence of direct evidence. It is at least as likely that the decreased mortality in young males should have been followed by a decreased incidence of healed primary foci.

Through the courtesy of Dr. Norman Smith, of the Ministry of Health, I am able to refer to the statistics of mass radiography; these show that the incidence of healed primary tuberculosis, striking enough to be reported in miniature films, is practically constant above the age of 35—that is, the incidence was 1.0% for men aged 35–44 and 1.1% for men aged 45–54 and for men over 60.

Bronchiectasis and chronic bronchitis have also been thought to predispose to the disease. No such action can, however, be deduced from the observation that a number of patients with bronchial carcinoma have suffered from these diseases. Neither disease is rare, and their incidence in bronchial carcinoma patients needs to be compared with some standard rate before any conclusion is justified. Doll and Hill (1952) have attempted to do this, and they concluded that either chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders, including bronchial carcinoma, or else—and this seems more likely—that patients with respiratory disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases in other systems. Whether previous respiratory disease plays any part in the aetiology of bronchial carcinoma is certainly not proved.

From analogy with pulmonary tumours in animals and with some types of cancer in man, it might be expected that hereditary predisposition would be of some importance in the development of carcinoma of the lung. Differences in incidence in different parts of the world may be partly attributable to racial differences in susceptibility, but the contrast between the experience of native Africans in Africa and of negroes in the U.S.A. suggests that large differences can readily be accounted for by the environment. The recent increase in incidence of the disease and the clear effect of occupation in certain industries demonstrate the importance of environmental factors; they do not, however, exclude the possibility that predisposition may also be variable. The presumption must be that it is, but that under optimum conditions it would seldom be strong enough to result in clinical disease.

Conclusion

It is now becoming possible to piece together the various independent observations and to begin to get a picture of the aetiology of the disease as a whole. Industrial hazards of great variety are responsible for a proportion of cases, but, with the exception of the production of gas, the industries with a recognized risk employ few workers and the total number of cases resulting each year is small. Although the incidence of industrial cases varies from one country to another, and falls most heavily on townsmen and almost exclusively on men, it does not contribute any significant part to the difference in incidence between countries, nor—except very locally—to the differences between urban and rural areas and between men and women. The importance of the observations is twofold. Firstly, they indicate the sources of risks which it is none the less essential to eliminate although only few men are exposed to them; and, secondly, they provide evidence of the nature of substances which can cause bronchial carcinoma and which may therefore, when derived from other sources, contribute to the production of the common non-industrial cases. Such substances appear to be radon and benzpyrene, products associated with the refining of nickel and the manufacture of chromates and asbestos, and probably arsenic.

Two other sources for the production of the disease have been recognized—namely, residence in towns and the smoking of tobacco. The carcinogenic factors concerned are, however, not necessarily distinct. There are, for example, fewer non-smokers, more cigarette-smokers, and more heavy smokers among Londoners than among the inhabitants of other towns and of rural districts, so that the effect of the tobacco factor alone will result in the incidence of bronchial carcinoma being higher in the big cities. On the other hand, from the death rates which have been calculated for persons smoking different average amounts over a ten-year period, the differences in smoking habits seem to be insufficient to account for the observed differences in mortality. These rates may not, however, be the appropriate ones to apply. The amount consumed over earlier periods must also be of some—and possibly of major—significance, and differences in cigarette consumption between areas may have been greater 20 or 30 years ago than they are now. In the present state of knowledge such possible differences cannot be allowed for and the most effective test of the independent action of the "urban factor" is the comparison of the mortality rates between different parts of the country in persons who do not now smoke and who have never done so in the past.

The material collected by Doll and Hill has already been used to calculate the mortality rates among non-smokers of different ages in Greater London. It is less suitable for estimating the mortality rates in other areas, since it was drawn from a few places only and may well not have been representative of the rest of the country. Nevertheless, it is of interest to see what indications may be obtained from it. The material has therefore been divided into three parts according to the patient's place of residence, and mortality rates have been calculated for non-smokers in towns other than London and in rural districts, in the same way as rates were previously calculated for Greater London (Doll, 1953). As a check, the rates have been recalculated, using the figures obtained by the Government Social Survey for the estimation of the total numbers of non-smokers at risk. The results are shown in Table V.

The greatest numbers of patients with bronchial carcinoma were interviewed in the age group 45–64, and this age group therefore provides the most reliable data. The similarity of the results obtained for each of the three areas is striking; it suggests that, in the absence of smoking, the "urban factor" is of little relevance. This may mean either that the "urban factor" is nothing but a reflection of the tendency for cigarette consumption per person to be greater in the larger towns or that it acts principally by increasing the effect of the tobacco factor. If this is so it may be easier to understand why the male mortality in Greater London should be only 2.1 times the mortality in English and Welsh rural districts, while the ratio of the rates between Norwegian towns and rural districts should be 2.5 to 1 and that between Copenhagen and Danish rural districts 4.3 to 1. It is unlikely that the air of Copenhagen and

TABLE V.—*Mortality from Lung Cancer among Non-smokers in Different Types of Area*

Age	Estimated Annual Death Rate per 1,000 Non-smokers			Source of Data for Estimate of Proportion of Non-smokers in Population
	Greater London	Other Towns	Rural Districts	
25– ..	0·005	0·026	(Less than 0·017)	Doll and Hill (1952)
45– ..	0·09	0·09	0·08	
65–74 ..	0·31	0·16	0·31	
25– ..	0·006	0·030	(Less than 0·017)	Government Social Survey
45– ..	0·09	0·09	0·07	
65–74 ..	0·28	0·16	0·37	

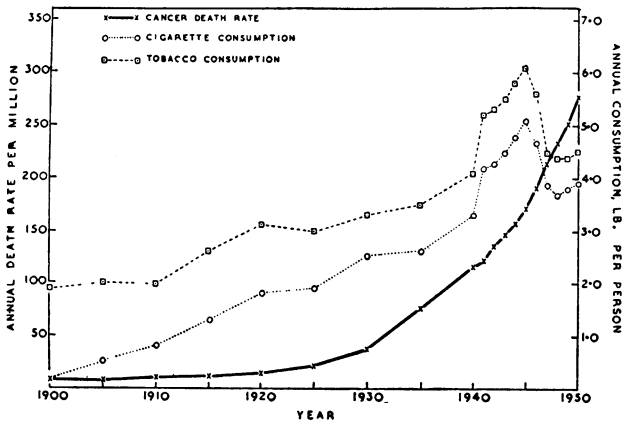

FIG. 7.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, England and Wales, 1900–50. Cigarette and tobacco consumption estimated for Great Britain and Ireland prior to 1922, for Great Britain and Northern Ireland subsequently (Board of Trade Statistics).

Oslo should be relatively more polluted than the air of London. It may be, on the other hand, that the habit of cigarette smoking has spread less rapidly and less completely over the rural districts of Denmark and of Norway than it has over the countryside of Britain.

The other outstanding epidemiological observations relating to bronchial carcinoma are the dramatic increase in the recorded mortality over the last 25 years, the differences in incidence between different countries, and the predilection of the disease for men. Fig. 7 shows the recorded mortality in England and Wales and the consumption of cigarettes and of all tobacco products in Britain from 1900 to 1950. The increase in the annual consumption of tobacco has been moderate—from 1.9 lb. (0.86 kg.) to a maximum of 6.1 lb. (2.77 kg.) per person in 1945—but a marked change has taken place in the manner in which tobacco is used and a much larger increase has taken place in the annual consumption of cigarettes—from approximately 0.2 to 3.9 lb. (0.09 to 1.77 kg.) per person with a maximum, in 1945, of 5.1 lb. In other countries, changes in the pattern of tobacco consumption have taken place more recently and have been even more marked; in the U.S.A., for example, chewing-tobacco and cigars accounted for large fractions of the tobacco consumed until 1930. In the present state of knowledge, it is not possible, in my opinion, to relate such changes directly to the changes in mortality. We do not know the relative weights to give the different tobacco products, nor the length of the latent period before the tobacco factor exerts its effect—which Clemmesen believes may be as long as 30 years; nor do we know what proportion of the recorded increase in mortality is real. All that can reasonably be concluded is that changes in national smoking habits in Britain are such as would have been expected to result in an increased incidence of carcinoma of the lung; but whether they are adequate to account for the whole increase is uncertain.

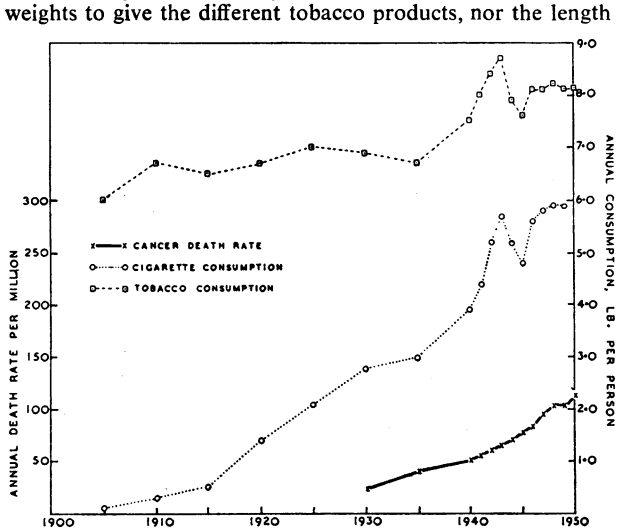

FIG. 8.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, U.S.A. For cigarette and total tobacco consumption see Garner (1946); later figures provided by the Commercial Attaché of the American Embassy.

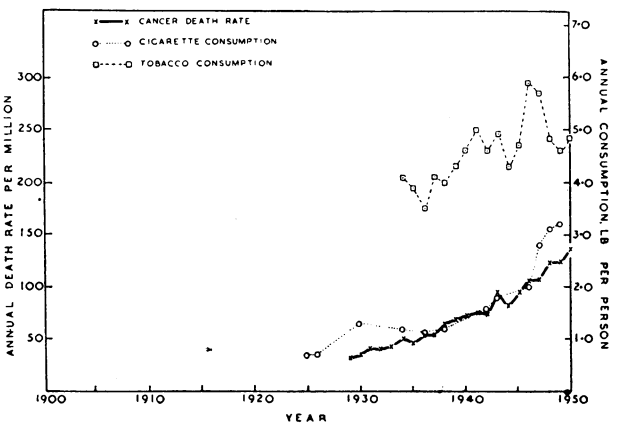

FIG. 9.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Switzerland. Statistics of cancer death rate and total tobacco consumption provided by Bureau Fédéral de Statistique, Berne; of cigarette consumption calculated from figures published by Gsell (1951).

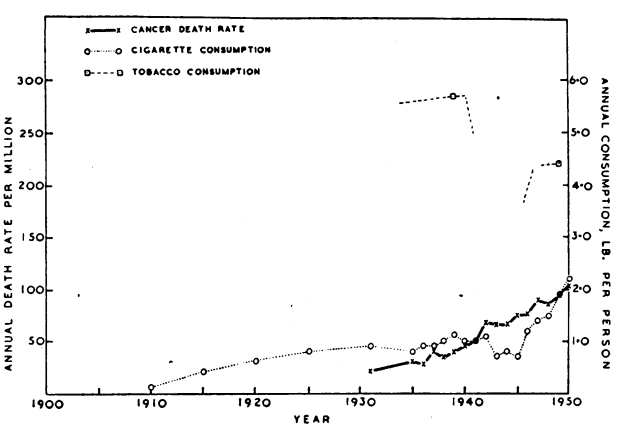

FIG. 10.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Denmark. For cancer death rate and cigarette consumption see Clemmesen, Nielsen, and Jensen (1953); for total tobacco consumption see "Anon." (1950).

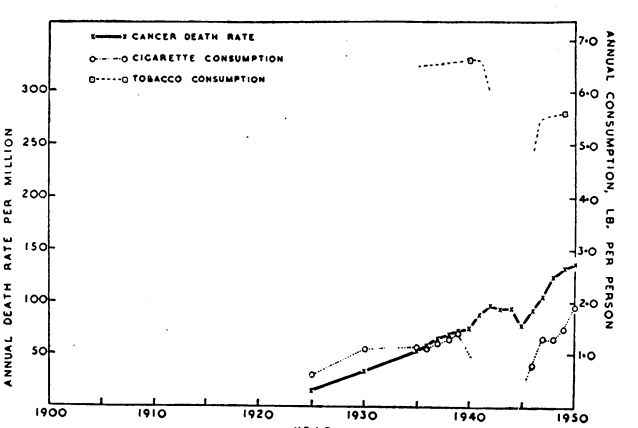

FIG. 11.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Holland. For cancer death rate and cigarette consumption see Kortweg (1953); for total tobacco consumption see "Anon." (1950).

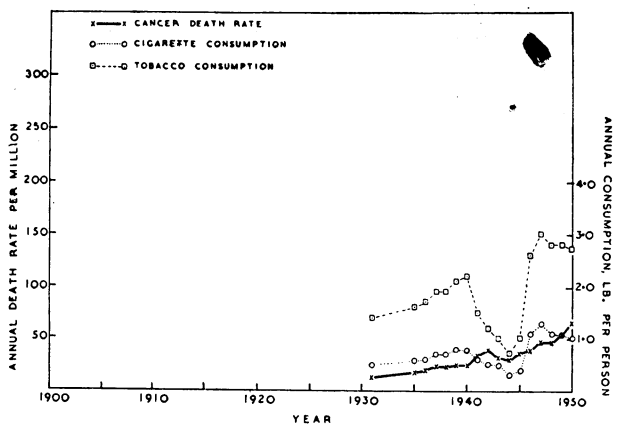

FIG. 12.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Norway. Statistics of cigarette and tobacco consumption provided by Professor L. Kreyberg (personal communication).

Attempts to relate mortality rates and tobacco consumption in different countries encounter the same difficulties. Estimates of the cigarette and total tobacco consumptions, together with the recorded mortality rates, for as far back as I have been able to obtain data, are shown in Figs. 8, 9, 10, 11, and 12 for the U.S.A., Switzerland, Denmark, Holland, and Norway. In each case mortality rates show a closer correspondence with cigarette consumption than with tobacco consumption. Falls in mortality occurred in Holland and in Norway towards the end of the war, shortly after there had been a great reduction in the consumption of tobacco; but it is difficult to believe that they are causally related to the fall in tobacco consumption, in view of the long latent period usually present in human cancer.

Fig. 13 shows the crude death rate in 1950 plotted against the average annual consumption of cigarettes per person over the preceding 20 years, for the six countries for which I have obtained data. I doubt whether much significance should be attached to the result, but it is not inconsistent with the existence of a relationship between lung cancer and cigarette-smoking. The mortality in England and Wales is, however, higher than would be expected, while in the U.S.A. it is lower.

It is a common observation that men smoke more than women, but it is not evident whether the difference in smoking habits is sufficient to account for the extent of the preponderance of men among subjects with the disease. The mortality rates which have been estimated for different levels of smoking among men and women in London suggest that sex differences still persist at each level (Doll and Hill, 1952). Women, however, did not start smoking at all until after the first world war, and trade statistics show that, although 22% of all tobacco was smoked by women in 1950, the proportion smoked by them 25 years earlier was only 2.5%. Consequently there must be a much greater difference in the total amounts smoked by men and women now in the cancer age than is revealed by the histories of their recent smoking habits. It would seem likely, therefore, that the rates which have been calculated for smokers of different average amounts are not truly comparable for men and for women. This objection does not apply to the rates which can be calculated for non-smokers, and I believe that it is within this group that the most proper comparison can be made. The estimated rates for each sex and for three age groups are shown in Table VI. In view of the smallness of the numbers from which the rates in the two extreme groups were calculated, the differences between the rates for each sex are quite insignificant. The implication of the results can be appreciated more clearly if the female rates—more reliable because derived from larger numbers—are used to calculate the numbers of non-smokers expected among the men with bronchial carcinoma who were interviewed; the expected number is then 6.1.* The number actually observed was 7. Despite the large total number of patients interviewed, the observed number of non-smokers is small, and it is not possible to dogmatize from the results. Nevertheless, the similarity of the observed and expected numbers is striking, and it seems probable that, save for smoking and exposure to certain industrial risks, the disease may affect men and women equally.

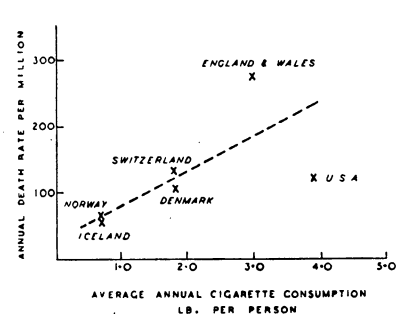

FIG. 13.—Death rate from lung cancer in 1950, and average cigarette consumption, 1931–50.

TABLE VI.—*Mortality from Lung Cancer among Non-smokers in Men and Women*

Age	Estimated Annual Death Rate per 1,000 Non-smokers		
	Men	Women	Persons
25–	0·03	0·02	0·02
45–	0·07	0·09	0·09
65–74	0·51	0·20	0·22

If this is so, and if, as has been suggested, the mortality among non-smokers is similar in town and country, death rates can be calculated for non-smokers of both sexes combined, which are based on reasonably sized numbers, and which, therefore, from this point of view justify some confidence. In submitting the rates I would, however, re-emphasize that the calculations are based on a number of fairly bold assumptions. The figures are therefore provisional, and it is recognized that the errors may be large. So long as this is borne in mind, it is of interest to use the rates to estimate the number of cases of lung cancer which would have been expected in England and Wales if none of the population had ever smoked. In 1950 the number between the ages of 25 and 74 would have been—in round figures—1,900; that is, 17% of the number which actually occurred.

No detailed figures are available to indicate the extent of the change in atmospheric pollution over the last half-century. The amount of coal consumed has varied little—from about 165 million to 190 million tons annually (Parker, 1950)—but the amount burnt efficiently in gasworks and electricity generating stations has increased enormously. It is likely, therefore, that there has actually been a decrease in smoke pollution, though not all the constituents of smoke will have decreased equally. The changes in mortality from lung cancer clearly cannot be attributed to changes in the amount of coal smoke in the atmosphere. Nor does there appear to be any reason why, if smoke is a responsible factor, men should be affected more than women.

To summarize, most of the known epidemiological facts about bronchial carcinoma are consistent with the effects of a limited number of industrial carcinogens and the presence of a carcinogenic substance in tobacco smoke—particularly in that derived from cigarettes. An exception may be the relatively low mortality from the disease in the U.S.A. Animal experiments confirm the carcinogenic potency of tobacco smoke, but the active agent has yet to be isolated. The position with regard to pollution of the atmosphere with chimney smoke is uncertain. The higher mortality in urban areas and the larger towns may perhaps be explicable on the grounds that cigarette-smoking has been heavier in these areas; on the other hand, as suggested by Stocks,

*The detailed calculations made in obtaining the expected number will be published elsewhere (Doll, 1953).

chimney smoke may be found to exacerbate the effect of the tobacco factor. Apart from certain mass radiography statistics, the meaning of which is difficult to assess, there is no epidemiological evidence to implicate pollution of the air with the exhaust fumes of cars or with road dust. Other weakly carcinogenic factors must, however, be postulated to account for a few remaining cases, evenly distributed among men and women and throughout town and country.

This year and next are centenaries of the great cholera epidemics in London, when the observations of Snow led to the realization that cholera was spread by water. I therefore make no apology for reminding you that it was purely statistical and epidemiological observations which provided the reasons for the measures which were responsible for the control of the disease. It is, however, with relief that I realize that measures of prevention are not within the scope of these lectures; for I have no desire to incur such a reaction as was expressed by *The Times* when it rejoiced over the fall of the first General Board of Health. "Aesculapius and Chiron," it said, " . . . have been deposed, and we prefer to take our chance of cholera and the rest than be bullied into health." The writer did indeed take his chance of cholera, which was raging in London within a month. But the chance was not to persist much longer. On the advice of the medical profession, led by such men as Sir John Simon, and concerned like Dr. Milroy to remedy "the neglect . . . of those laws of healthy existence with the consideration of which the science of Public Health professes to deal," the last major cholera epidemic in Britain was brought under control in 1866—seventeen years before Koch isolated the cholera vibrio. It may also prove that it will be unnecessary to await the isolation and identification of the specific active agent before steps can be taken to halt the rapid increase in the mortality from bronchial carcinoma and to turn it into an even more dramatic decline.

In concluding, I would like to acknowledge my indebtedness to Sir Ernest Kennaway for his encouragement and for the stimulation provided by his ideas; and to Professor Bradford Hill, not only for his constant advice, but also because so much of the work which has been referred to was his in origin, design, and execution.

My thanks are due to Mrs. Julie E. Backer (of the Central Bureau of Statistics, Oslo), Dr. J. Clemmesen, Mr. H. F. Dorn, Professor N. Dungal, Mr. A. Koller (Director of the Federal Bureau of Statistics, Berne), Dr. R. Korteweg, Professor L. Kreyberg, Dr. W. Logan, Dr. E. Pedersen, Dr. J. A. Scott, Mr. R. H. Thompson (of the Office of the Commercial Attaché, American Embassy), and Dr. G. Watkinson, for providing me with figures; and to Miss Freda Wadsworth and Mrs. Mary Young for drawing the diagrams.

REFERENCES

Andervont, H. B. (1937). *Publ. Hlth Rep., Wash.*, **52**, 1584.
" Anon." (1950). *J. roy. statist. Soc.*, **113**, 487.
Bidstrup, P. L. (1951). *Brit. J. industr. Med.*, **8**, 302.
Bonser, G. M. (1934). *J. Hyg., Lond.*, **34**, 218.
Brinton, H. P., Frasier, E. S., and Koven, A. L. (1952). *Publ. Hlth Rep., Wash.*, **67**, 835.
Brooks, W. D. W., Davidson, M., Thomas, C. P., Robson, K., and Smithers, D. W. (1951). *Thorax*, **6**, 1.
Bryson, C. C., and Spencer, H. (1951). *Quart. J. Med.*, n.s. **20**, 173.
Campbell, J. A. (1934). *Brit. J. exp. Path.*, **15**, 287.
—— (1936). Ibid., **17**, 146.
—— (1937). Ibid., **18**, 215.
Chief Inspector of Factories (1949). Ann. Rep. Chief Inspector of Factories and Workshops, 1948. H.M.S.O., London.
Clemmesen, J., and Busk, T. (1947). *Brit. J. Cancer*, **1**, 253.
—— Nielsen, A., and Jensen, E. (1953). Rep. C.I.O.M.S. Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Council for International Organizations of Medical Sciences (1953). Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Daff, M. E., Doll, R., and Kennaway, E. L. (1951). *Brit. J. Cancer*, **5**, 1.
—— and Kennaway, E. L. (1950). Ibid., **4**, 173.
Davies, J. N. P. (1948). *E. Afr. med. J.*, **25**, 117.
Dawson, K. B. (1952). *Brit. J. Cancer*, **6**, 22.
Doll, R. (1952). *Brit. J. industr. Med.*, **9**, 180.
—— (1953). *Brit. J. Cancer*. In press.
—— and Hill, A. B. (1950). *British Medical Journal*, **2**, 739.
—— —— (1952). Ibid., **2**, 1271.
Dublin, L. I., Spiegelman, M., and Leland, R. G. (1947). *Postgrad. Med.*, **2**, 188.
Dungal, N. (1950). *Lancet*, **2**, 245.
Essenberg, J. M. (1952). *Science*, **116**, 561.
Evans, R. D. (1950). *Acta Un. int. Cancr.*, **6**, 1229.
Flory, C. M. (1941). *Cancer Res.*, **1**, 262.
Fulton, J. S. (1949). *Proc. roy. Soc. Med.*, **42**, 775.
Garner, W. W. (1946). *The Production of Tobacco*. Blakiston, Philadelphia.
Gharpure, P. V. (1948). *Indian med. Gaz.*, **83**, 5.
Gloyne, S. R. (1951). *Lancet*, **1**, 810.
Goulden, F., Kennaway, E. L., and Urquhart, M. E. (1952). *Brit. J. Cancer*, **6**, 1.
Grady, H. G., and Stewart, H. L. (1940). *Amer. J. Path.*, **16**, 417.
Graham, E. A., Wynder, E. L., and Croninger, A. B. (1952). *Science*, **116**, 521.
Gsell, O. (1951). *Schweiz. med. Wschr.*, **81**, 662.
Haerting, F. H., and Hesse, W. (1879). *Vjschr. gerichtl. Med.*, **30**, 296; **31**, 102.
Heady, J. A., and Kennaway, E. L. (1949). *Brit. J. Cancer*, **3**, 311.
Hill, A. B., and Faning, E. L. (1948). *Brit. J. industr. Med.*, **5**, 1.
Hueper, W. C. (1952). *Tex. Rep. Biol. Med.*, **10**, 167.
Kennaway, E. L., and Kennaway, N. M. (1947). *Brit. J. Cancer*, **1**, 260.
Korteweg, R. (1951). Ibid., **5**, 21.
—— (1953). Rep. C.I.O.M.S. Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Kouwenaar, W. (1950). In Symposium on Geographical Pathology and Demography of Cancer. Council for the Co-ordination of International Congresses of Medical Sciences (World Health Organization and United Nations Educational, Scientific, and Cultural Organization).
Lange, K. (1935). *Z. Krebsforsch.*, **42**, 306.
Leiter, J., Shimkin, M. B., and Shear, M. J. (1942). *J. nat. Cancer Inst.*, **3**, 155.
Levin, M. I., Goldstein, H., and Gerhardt, P. R. (1950). *J. Amer. med. Ass.*, **143**, 336.
Lisco, H., and Finkel, H. P. (1949). *Fed. Proc.*, **8**, 360.
Lorenz, E., Stewart, H. L., Daniel, J. H., and Nelson, C. V. (1943). *Cancer Res.*, **3**, 123.
McConnell, R. B., Gordon, K. C. T., and Jones, T. (1952). *Lancet*, **2**, 651.
McDonald, S., and Woodhouse, D. L. (1942). *J. Path. Bact.*, **54**, 1.
Machle, W., and Gregorius, F. (1948). *Publ. Hlth Rep., Wash.*, **63**, 1114.
Mackay, D. (1951). Studies on Medical and Population Subjects, No. 4. General Register Office. H.M.S.O., London.
Mason, G. A. (1949). *Lancet*, **2**, 587.
Mills, C. A., and Porter, M. M. (1950). *Cancer Res.*, **10**, 539.
Miners' Phthisis Medical Bureau (1936). Report for the three years ended July 31, 1935. Union of South Africa Government Printers, Pretoria.
Müller, F. H. (1939). *Z. Krebsforsch.*, **49**, 57.
Nath, V., and Grewal, K. S. (1935). *Indian J. med. Res.*, **23**, 149.
Parker, A. (1950). *J. roy. Soc. Arts*, **99**, 85.
Passey, R. D., and Holmes, J. McD. (1935). *Quart. J. Med.*, n.s. **4**, 321.
Peller, S. (1939). *Human Biol.*, **11**, 130.
Perry, K., Bowler, R. G., Buckell, H. M., Druett, H. A., and Schilling, R. S. F. (1948). *Brit. J. industr. Med.*, **5**, 6.
Rigdon, R. H., and Kirchoff, H. (1951). *Sth. med. J.*, **44**, 506.
—— —— (1952). *Tex. Rep. Biol. Med.*, **10**, 76.
Sanders, E., Thomson, A. P., Cooper, E. A., and Lamb, F. W. M. (1932). *J. Hyg., Lond.*, **32**, 293.
Schairer, E., and Schöniger, E. (1943). *Z. Krebsforsch.*, **54**, 261.
Schrek, R., Baker, L. A., Ballard, G. P., and Dolgoff, S. (1950). *Cancer Res.*, **10**, 49.
Schwartz, P. (1950). *Beitr. Klin. Tuberk.*, **103**, 192.
Shaw, A. F. B. (1924). *Newc.-upon Tyne med. J.*, April, 1924. Quoted by W. E. M. Wardle, *Lancet*, 1951, **2**, 737.
Shik, R. G. (1946). *Amer. Rev. Soviet Med.*, **4**, 142.
Smith, W. E. (1950). *J. exp. Med.*, **91**, 87.
Steiner, P. E. (1944). *Arch. Path.*, **37**, 185.
—— Butt, E. M., and Edmondson, H. A. (1950). *J. nat. Cancer Inst.*, **11**, 497.
Stocks, P. (1950). Studies on Medical and Population Subjects, No. 3. General Register Office. H.M.S.O., London.
—— (1952). *Brit. J. Cancer*, **6**, 99.
Strachan, A. S. (1934). *J. Path. Bact.*, **39**, 209.
Turner, H. M., and Grace, H. G. (1938). *J. Hyg., Lond.*, **38**, 90.
—— and Martin, W. J. (1949). *British Medical Journal*, **2**, 1148.
Twort, J. M. (1939). *Sixteenth Annual Report of the British Empire Cancer Campaign*, p. 239.
Waller, R. E. (1952). *Brit. J. Cancer*, **6**, 8.
Wassink, W. F. (1948). *Ned. T. Geneesk.*, **92**, 3732.
Willis, R. A. (1948). *Pathology of Tumours*. Butterworth, London.
Woodruff, C. E., and Nahas, H. C. (1951). *Amer. Rev. Tuberc.*, **64**, 620.
—— Sen-Gupta, N. C., Wallace, S., Chapman, P. T., and Martineau, P. C. (1952). Ibid., **66**, 151.
Wynder, E. L., and Graham, E. A. (1950). *J. Amer. med. Ass.*, **143**, 329.
—— —— (1951). *Arch. industr. Hyg.*, **4**, 221.

The World Health Organization has approved a $25,000 supply programme to aid the victims of the recent earthquakes in the Ionian Islands. Supplies to be sent out, which are essentially to prevent epidemic diseases, will include water purifiers, tetanus prophylactics, rat poison, and galvanized piping. There is an estimated rat population of 100,000 in the islands, which could not only make serious inroads into food supplies but might rapidly spread disease. Dr. Duurt Rijkels, from the W.H.O. Regional Office in Europe, has recently returned from a visit to the affected areas made at the request of the Greek Government. He reports that the relief work is proceeding excellently, and the food supplies are now well organized. Many of those who were evacuated are returning home to repair their houses and to see to the grape harvest, which is expected to be very good this year.