

LUNG CANCER AND TOBACCO

THE B.M.J.'s QUESTIONS ANSWERED BY

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AND

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In place of the usual "Refresher Course" article we print below answers by Professor Bradford Hill and Dr. Richard Doll to questions on smoking and lung cancer we put to them last week. So much of the evidence is embodied in long and technical articles—the first in this country being published in the "British Medical Journal" of September 30, 1950—that the general reader needs a clear guide to the facts. We are much indebted to Professor Hill and Dr. Doll for giving so much of their time and effort to provide one.—ED., B.M.J.

Question 1.—What led to smoking being investigated as a possible cause of lung cancer?

Answer.—From time to time in the present century clinical observers have suggested a possible association between lung cancer and smoking. The stimulus for the intensified modern epidemiological research of the last ten years was the striking and continuing increase in the mortality rate from cancer of the lung revealed by the national vital statistics. Such a pronounced change called for scientific inquiry on a wide scale. From the nature of the disease there appeared to be at least two environmental factors worthy of investigation. These were atmospheric pollution—whether from homes, factories, or the internal combustion engine—and the habit of smoking tobacco.

Question 2.—To what extent has lung cancer increased over the past ten years?

Answer.—In England and Wales in 1944 there were 5,331 deaths of men and 1,237 deaths of women attributed to cancer of the trachea, lung, and bronchus. In 1955 the corresponding numbers were 14,820 deaths of men and 2,451 deaths of women. At ages 45–74 years the death rate of men has risen from 829 per million in 1944 to 1,852 per million in 1954. For women the corresponding rates are 148 per million and 224 per million.

Question 3.—Have any other forms of cancer increased to anything like the same extent in these years?

Answer.—No other form of cancer has shown a similar increase. The death rate from some major forms, such as cancer of the digestive organs, rectum, and uterus, have declined somewhat; others have remained almost stationary—for example, cancer of the breast. The type of cancer which shows the next greatest increase is leukaemia; its crude death rate has increased by almost 60% in the last decade.

Question 4.—Is the increase in lung cancer apparent or real? That is, is it possibly due to such things as improved methods of diagnosis, or to an increase in the numbers of older persons in the community?

Answer.—It seems unlikely that improved methods of diagnosis could have contributed much to the rising mortality of the last few years. Over a longer period, covering the development of x rays, bronchoscopy, and other

means of diagnosis, they undoubtedly played some part. But even over this longer period there are several reasons which make it extremely difficult to believe that better diagnosis could account for the whole increase in mortality. We may note that the death rate of men in 1955 was nearly 13 times the rate in 1930, while the death rate of women has gone up only five times in the same period. It does not seem possible for better diagnosis to affect one sex so much more than the other. Similarly, the rates of increase for persons of different ages have been unequal. It also appears that some histological types, squamous, oat-cell, and undifferentiated, have increased more than the adenocarcinomas. It is difficult to attribute that entirely to better diagnosis.

The number of older persons in the population has contributed to a rise in the *crude* death rate—that is, the total deaths at all ages related to the total population. That effect can be allowed for by the calculation of a death rate standardized for age, or, more simply still, by a study of the death rates at each age. In the last 10 years the lung cancer death rates of men and women have risen in every age group above 45 years.

Question 5.—What is the statistical evidence for believing that cigarette smoking may cause cancer?

Answer.—The evidence is derived from two types of inquiry, termed retrospective and prospective:

(a) *The Retrospective Inquiry.*—Patients with lung cancer have been questioned about their *previous* smoking habits. Their histories of smoking thus obtained have been compared with the histories similarly obtained from patients without lung cancer and selected as "controls." The results of seventeen such inquiries (in this country, the U.S.A., Finland, Germany, Holland, and Switzerland) have been published. They agree in showing many more heavy smokers, and fewer non-smokers, among the patients with lung cancer. Thus in our own inquiry 1,357 men with cancer of the lung were interviewed and 1,357 "control" patients of the same age. The heavy smokers of 25 or more cigarettes a day (or the equivalent amount in pipe tobacco) numbered 340 in the lung cancer group (25% of the group) and only 182 (13%) in the other patients. In the lung cancer group there were only 7 non-smokers (0.5%); in the other patients there were 61 (4.5%).

(b) *The Prospective Inquiry.*—The smoking habits of a large population have been recorded at some point of time. On this basis the population has been divided into groups—for example, heavy, moderate, light, and non-smokers. The deaths in each of these groups have been *subsequently* observed. There have been two such investigations. In certain States of the U.S.A. particulars of 190,000 men aged 50–69 were collected in 1952. In this country we ourselves approached in 1951 60,000 men and women whose names appear on the *Medical Register*. Over 40,000 of them replied giving us brief details of their smoking

habits. A preliminary study of the subsequent deaths of these doctors in 1951-4 has shown that mortality of men from cancer of the lung has fallen most heavily on the heavy smokers and least on the non-smokers. Thus there were recorded 13 lung cancer deaths in the group of smokers of 25 or more cigarettes daily (or the equivalent in pipe tobacco) and no such deaths in the non-smoking group. If smoking played no part in the causation of lung cancer we would have expected to see only 7 deaths amongst the heavy smokers and 4 amongst the non-smokers. These numbers are small, but the further deaths that have occurred in 1954-6 are confirming this pattern. The American inquiry, on its much larger scale, has given similar results.

Evidence that the substantial increase in the national mortality followed an increase in the national consumption of cigarettes, and the observation that smoking and lung cancer are both more common in men than in women, obviously support the conclusions drawn from these special inquiries but contribute little in themselves.

Question 6.—Does the statistical evidence provide a proof that cigarette smoking directly causes cancer of the lung?

Answer.—No; the statistical evidence, which is now extensive and very detailed, permits one to deduce the most probable and reasonable interpretation. In scientific work it is never possible to exclude entirely an alternative explanation of the observations. These particular inquiries have been subjected to keen scrutiny in this and other countries, and so far no other interpretation has been advanced that adequately fits or explains the observed facts. We ourselves believe that the accumulated evidence to-day is such as to denote a cause-and-effect relationship.

Question 7.—Can cancer of the lung occur in someone who has never smoked?

Answer.—Yes, in both men and women. We would think it most unlikely that tobacco smoke contributes to the development of all cases of the disease.

Question 8.—What proportion of persons who die of lung cancer are non-smokers?

Answer.—Our studies on patients in this country revealed 7 non-smoking males in the 1,357 with lung cancer (0.5%) and 40 non-smoking women in the 108 with lung cancer (37%). (A non-smoker was defined as a person who reported that he, or she, had never smoked as much as one cigarette per day or a quarter of an ounce of tobacco per week for as long as one year.) We may note that in spite of the relatively large proportion of women non-smokers in the 108 cases, the actual *death rate* of women non-smokers will still be quite small—because the general population contains so very many non-smoking women (over half of our other women patients were non-smokers).

Question 9.—How is the risk of dying from lung cancer affected by the amount smoked?

Answer.—The figures available suggest that the risk of dying from lung cancer is directly proportional to the amount smoked. There is no evidence of any "threshold" amount below which there is no added risk whatever.

Question 10.—What proportion of heavy smokers die of lung cancer?

Answer.—Calculation of a precise figure presents difficulties owing partly to the fact that a man's smoking habits may not remain constant during his lifetime. However, on the basis of the figures we derived from the smoking histories of 1,357 male lung cancer patients and the national death rates recorded in 1950, it has been estimated (by Heady and Barley) that approximately 9% of men aged 25 years who smoke between 25 and 50 cigarettes a day might be expected to die of lung cancer before they reach the age of 75—that is, 1 man in 11. In the light of the increasing national death rates since 1950 the estimate may be an understatement.

Question 11.—To what extent does the chance of dying of lung cancer diminish for a heavy smoker of cigarettes who gives up smoking in middle age?

Answer.—Published data are not sufficient to allow a precise figure to be calculated. They do, however, indicate that there is advantage to those who give up. We hope in time to derive more exact information from the deaths of doctors.

Question 12.—It is said that pipe smokers incur less risk than cigarette smokers. Is this because of the method of smoking or because of the amount of tobacco smoked?

Answer.—"Pure" pipe smokers who never smoke, or never have smoked, cigarettes are relatively few and far between. However, the available evidence strongly supports the conclusion that they incur less risk than cigarette smokers. How much less is not so certain. The statistical data indicate that the difference is not due merely to differences in the amount of tobacco smoked. The reason for it is not known.

Question 13.—Is the risk increased by inhaling?

Answer.—Some investigators have found a higher proportion of "inhalers" among patients with lung cancer than among control patients with other diseases. We ourselves found no difference. Of our lung cancer patients 65% said that they inhaled and of our control patients with other diseases 67%. The explanation of these conflicting reports is unknown.

Question 14.—Does the use of a cigarette holder or filter diminish the risk of getting lung cancer?

Answer.—We asked questions on these points only in the final part of our inquiry into patients. Of 504 cigarette-smoking patients with lung cancer only 10, or 2%, said that they had used a cigarette holder regularly. Of the 467 cigarette-smoking patients with other diseases the number was 27, or 6%. Only 3 of the lung cancer group had regularly smoked filter-tipped cigarettes, compared with 15 of the other patients. These observations suggest that some protection is afforded by cigarette holders or filter tips, but the numbers are so small that we would hesitate to draw a firm conclusion. Few people in this country have smoked filter-tipped cigarettes or used cigarette holders regularly for any length of time. For this reason it is difficult to obtain adequate evidence.

Question 15.—Does the use of hand-rolled cigarettes diminish the risk ?

Answer.—Not according to the data we collected from patients. Of the 1,297 male lung cancer patients who had ever smoked cigarettes, 20.7% smoked mostly hand-rolled cigarettes. Of the 1,203 similar control patients the proportion was 19.1%. Since a number of men who roll their cigarettes use pipe tobacco this result of the inquiry would also seem to show that the different degrees of risk associated with cigarette and pipe smoking are not likely to be due to the different *types* of tobacco thus consumed.

Question 16.—Does the use of matches instead of a petrol lighter diminish the risk ?

Answer.—This question was also studied in our inquiry into patients but has not, to our knowledge, been taken up elsewhere. We found no material difference in the use of petrol lighters between the cigarette-smoking patients with lung cancer and the cigarette-smoking patients with other diseases: 42.9% of the former and 41.3% of the latter reported that at some period they had regularly used petrol lighters.

Question 17.—How much greater is the risk of dying from lung cancer for town dwellers than for country dwellers ?

Answer.—In a number of countries the recorded mortality rate of residents in the big towns has been reported as about twice to four times the rate of residents in the country districts. The death rate in Greater London is, at present, twice that of the rural districts of England and Wales.

Question 18.—Can that difference between lung cancer mortality in town and country be due entirely to a difference in smoking habits between town and country ?

Answer.—Cigarette consumption is to-day rather greater in the large towns than in the countryside, but not sufficiently to account for the present difference in mortality. On the other hand, this information is quite insufficient. We clearly need to know the difference between town and country smoking habits of 20 to 30 years ago, not merely the difference that exists to-day. Possibly cigarette smoking a generation ago was still more predominantly a function of town life.

Question 19.—Does pollution of the air with smoke from chimneys play a part in causing lung cancer ?

Answer.—We do not know. The main evidence that smoke from chimneys may play a part is (a) the broad mortality difference between town and country (as referred to in our answers to Questions 17 and 18); (b) a more detailed analysis of that difference showing an association between lung cancer mortality and the density of population in the areas of England and Wales; and (c) the presence of 3,4-benzpyrene in chimney smoke, a substance with known carcinogenic properties in animals. On the other hand, while lung cancer has been increasing in the last generation it would seem that chimney smoke pollution might have decreased through a greater efficiency in the combustion of coal (in producing gas and electricity). We must also note that the excess mortality from lung cancer amongst men compared with women is *even greater* in the large towns. If a common factor like smoke in the atmosphere were

important one might expect its presence to diminish rather than to increase the sex disparity.

Question 20.—Do exhaust gases from petrol-engined vehicles play a part ?

Answer.—We know of no clear evidence. Chemical analysis of the exhaust gases from petrol-engined vehicles reveals 3,4-benzpyrene. On the other hand, men who by virtue of their occupation are especially exposed to such fumes have not been observed disproportionately amongst patients suffering from lung cancer. For example, road transport drivers, garage workers, and policemen do not appear to have any heightened incidence of lung cancer.

Question 21.—Is there any evidence implicating the diesel engine ?

Answer.—Under certain conditions the exhaust fumes from diesel-engined vehicles also contain 3,4-benzpyrene. In view, however, of the long latent period observed before the appearance of cancer, we would think that the diesel engine has not been in use sufficiently long or sufficiently widely to produce epidemiological evidence. It is therefore most unlikely that it could have been responsible for any significant part of the increase in lung cancer mortality that has taken place over the last 20 years. But we have no knowledge at all as to whether it is now contributing to the risk.

Question 22.—Are there any other contaminants in the air which may play a part in causing cancer of the lung ?

Answer.—There appear to be certain contaminants—not necessarily identified—in a few specific industries; for example, in the refining of nickel and in the production of asbestos, chromates, and coal gas.

In our investigation of lung cancer and other patients we found no evidence to implicate coal gas as a general contaminant. Of the lung cancer patients 23% and of the control patients 22% said that they had resided near a gasworks for a year or more. They had used gas-fires in the living-rooms of their home with equal frequency.

Radioactive substances in the air are believed to have been responsible for much lung cancer in pitchblende mines of central Europe. They occur in minute quantities everywhere, and it is possible that they contribute to the general incidence of lung cancer.

Question 23.—Does cigarette smoking give an added risk of lung cancer in a rural environment or does it act only in the presence of added contaminants in the atmosphere of a town ?

Answer.—In a large-scale inquiry (still in progress) Stocks and Campbell have shown a clearly increasing mortality from lung cancer with increasing amounts of smoking among the inhabitants of some rural districts of North Wales. In other words, a town environment is *not* necessary for smoking to produce effects. On the other hand, from their preliminary results Stocks and Campbell suggest that 50% of the cases in the City of Liverpool are due to smoking and 40% due to a contamination of the atmosphere (they stress that these figures are provisional and may need revision).

Question 24.—Have any carcinogens been identified in tobacco smoke, and if so what are they ?

Answer.—Yes, 3,4-benzpyrene and 1,2-benzanthracene. Both of these, in certain circumstances, can cause

cancer in animals. Arsenic has also been found in tobacco smoke and is known to be capable of producing cancer of the skin in man. In large quantities it is believed to be capable of producing lung cancer. The amount present in tobacco smoke, however, is minute, and it is difficult to believe it to be the agent responsible. Radioactive potassium is present in tobacco as a naturally occurring isotope, but the amount in smoke appears to be negligible. We may add that the finding of a substance carcinogenic to animals may be of very great practical value in defining the responsible agent. On the other hand, failure to find one does not invalidate the evidence derived from observations made on man himself.

Question 25.—Have different brands of tobacco and cigarette paper been found to produce different quantities of carcinogens when burnt?

Answer.—We know of no evidence. In our investigation of patients we found that none of four main proprietary brands of cigarettes was more closely associated with lung cancer than another. Nor was there any difference between the lung-cancer patients and their controls in the use of hand-rolled versus manufactured cigarettes (see Question 15).

Question 26.—Is there any connexion between smoking and cancers elsewhere in the body?

Answer.—Smoking (not necessarily of cigarettes) has been shown to be associated with several types of cancer of the buccal cavity and of the upper respiratory passages. It has not been shown to be associated with specific types of cancer elsewhere in the body.

Question 27.—Is there any evidence for or against the idea that smoking determines merely the site of a cancer rather than its origin? In other words, is it probable that people who get lung cancer after smoking heavily for years would have got cancer at some other site if they had not smoked?

Answer.—There is no significant evidence to suggest that people who get lung cancer through smoking would have got cancer at some other site if they had not smoked. In some of the special industrial risks quoted above (Question 22) it is quite certain that the extra risk produced by a contaminant was over and above the ordinary risks of cancer in general—that is, the excess of lung cancer in the workpeople was not compensated for by a deficiency in other sites. These carcinogens, in other words, determine the origin of a cancer and not solely the site. If heavy cigarette smokers would in the absence of smoking have developed cancer in some other site, it follows that they must have a lower cancer death rate from sites other than lung in comparison with the lighter smoking and non-smoking groups. This does not appear to be so.

Question 28.—It has been said that the kind of constitution that makes a man smoke heavily is the kind that predisposes him to lung cancer. Is there evidence for this?

Answer.—None whatever (and it is not easy to see how the rising death rate of recent years could be explained in such terms. Have our constitutions so changed?)

Question 29.—Are any other diseases thought to be associated with cigarette smoking?

Answer.—Several other diseases have been thought to be associated with smoking. They include coronary thrombosis, Buerger's disease, duodenal and gastric ulcer, amblyopia, and chronic bronchitis. So far the evidence is less comprehensive and for the most part less clear-cut than that relating to cancer of the lung.

Question 30.—Do any other diseases predispose to lung cancer—for example, the influenza in the pandemic of 1918?

Answer.—There is some evidence to implicate chronic bronchitis as a predisposing disease. On the other hand, there is evidence that this disease itself may be related to smoking. We know of no direct evidence regarding the influenza of 1918. We may note (a) that up to 1950 there had been no appreciable increase in lung cancer in Iceland, though the influenza pandemic struck there severely; and (b) that the pandemic fell equally on men and women in this country (judged by mortality), but lung cancer strikes men predominantly.

Question 31.—Do the variations in the incidence of lung cancer in different countries bear any relation to the variations in tobacco consumption?

Answer.—For those countries for which adequate statistics are available there is very little correlation between the lung cancer mortality and the *total tobacco* consumption. There is, however, quite a close association in ten countries when the consumption of cigarettes twenty years ago is related to the present lung cancer death rate. An exception, with a relatively low death rate, is the U.S.A. The reason is not known, but it must be realized that the national statistics of cigarette "consumption" relate to cigarettes purchased and not to cigarettes smoked. Observation would suggest that the American citizen compared with his English counterpart more often discards his cigarette before reaching the bitter (and query more highly carcinogenic) end!

The answers we have given have been based on a general review of the literature. Most of the numerical examples, however, have been taken from our own work. For those interested the following is a very short list of the publications including those specifically referred to in our answers. A more detailed bibliography will be found in the second paper referred to below.

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