BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 10 1956

LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING

A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS

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On October 31, 1951, we sent a simple questionary to all members of the medical profession in the United Kingdom. In addition to giving their name, address, and age, they were asked to classify themselves into one of three groups—namely, (*a*) whether they were, at that time, smokers of tobacco; (*b*) whether they had smoked but had given up; or (*c*) whether they had never smoked regularly (which we defined as having never smoked as much as one cigarette a day, or its equivalent in pipe tobacco or cigars, for as long as one year). All smokers and ex-smokers were asked additional questions. The smokers were asked the ages at which they had started smoking and the amount of tobacco that they were smoking, and the method of smoking it, at the time of replying to the questionary. The ex-smokers were asked similar questions but relating to the time at which they had last given up smoking.

On the basis of their replies to the questionary, we classified the doctors in a few broad groups according to their sex and age, the amount of tobacco they smoked, their method of smoking, and whether smoking had been continued or abandoned. Subsequently we have recorded the deaths occurring in each of these groups. To ensure a high proportion of replies we intentionally made the questionary extremely short and simple. In particular, we did not ask for a life-history of smoking habits, though in studying the incidence of lung cancer, with a long induction period, we realized that the habits of early adult life might be more relevant than the most recent habits. In addition, we have made no further inquiry into any change of habits that may have taken place since October, 1951. In short, we have related the deaths of doctors that have occurred since October, 1951, to the non-smoking, present smoking, and ex-smoking groups as constituted at that date.

It follows that, while we can make an accurate comparison between life-long non-smokers and all smokers *past or present,* any gradient of mortality that we may observe in relation to the amount of smoking will be an *understatement* of the true relationship. We shall, for instance, have included in the group of "light" smokers persons who had previously smoked "heavily" but at November 1, 1951, had reduced their consumption. Similarly, a "heavy" smoker at November 1, 1951, may previously have been a light smoker or may since then have given up smoking altogether; we shall have continued to count him, or her, as a heavy smoker. If there is a differential death rate with smoking, we must by such errors tend to inflate the mortality among the light smokers and to reduce the mortality among the heavy smokers. In other words, the gradients we present in this paper may be understatements but (apart from sampling errors due to the play of chance) cannot be overstatements.

In 1954 we published a preliminary report on the results of this inquiry (Doll and Hill, 1954a). The number of deaths from lung cancer was then small (36) and standing alone they would not have justified a firm conclusion. In showing a steadily rising mortality from lung cancer as the amount of smoking increased, they were, however, in close conformity with the figures we had previously found in our extensive retrospective inquiries into the smoking histories of patients with cancer of the lung and other diseases. With the passage of another two years we are now able to present from this prospective inquiry a considerably increased body of data, and, in consequence, a more exhaustive analysis. The four main questions to which we have sought answers are: (1) What are the relative risks of lung cancer associated with the smoking of different amounts of tobacco by different methods? (2) Is there a reduction in the risk if smoking is given up? (3) What is the most likely explanation of the observed association? (4) Is there a relationship between smoking and any other cause of death?

The Exposed to Risk

The questionary was sent out to 59,600 men and women on the *Medical Register.* Of the 41,024 replies received 40,701 were sufficiently complete to be utilized; 34,494 of these were received from men and 6,207 from women.* For the purposes of the present report the doctors concerned have been followed until March 31, 1956—that is, for four years and five months. No new additions have been made to the population and the total

*These numbers are slightly different from those given in our preliminary report, as a re-examination of the forms enabled an additional 137 to be utilized, while in a few cases it was found that the age group had been allocated incorrectly.

number of survivors exposed to risk at the beginning of each new period of twelve months has therefore steadily diminished. At the same time each of the survivors has grown older and mortality has, of course, fallen more heavily on the older age groups; as a result, the age distribution of the population has altered. These changes are shown for men in Table I as well as the total numbers of years of exposure in each age group during

TABLE I.—*Number of Men Living in Each Age Group at the Beginning of Each Year of the Study and the Total Number of Years of Exposure*

Age in Years	No. of Men Living at:						Total No. of Years of Exposure
	1/11/51	1/11/52	1/11/53	1/11/54	1/11/55	1/4/56	
Under 35	10,140	9,145	8,232	7,389	6,281	5,779	35,489
35–44	8,886	9,149	9,287	9,414	9,710	9,796	41,211
45–54	7,117	7,257	7,381	7,351	7,215	7,191	32,156
55–64	4,094	4,212	4,375	4,601	5,057	5,243	19,909
65–74	2,694	2,754	2,823	2,873	2,902	2,928	12,462
75–84	1,382	1,433	1,457	1,485	1,483	1,513	6,431
85 and over	181	200	223	256	278	296	1,028
All ages	34,494	34,150	33,778	33,369	32,926	32,746	148,686

the course of the study. The total number of years for all age groups is 148,686 for men and 27,187 for women. (These figures have been obtained by taking the average of the numbers of survivors at the beginning and at the end of each year and summing for the four years and five months of the study. For example, the number of male doctors aged 45–54 was 7,117 on November 1, 1951, and 7,257 on November 1, 1952; on average, therefore, there were 7,187 male doctors alive in that age group throughout that year. Similarly there were 7,319 male doctors alive in the same age group throughout the second year, 7,366 throughout the third year, 7,283 throughout the fourth year, and 7,203 throughout the first five months of the fifth year. The total number of years lived by male doctors in that age group is therefore calculated to be $7,187+7,319+7,366+7,283+5/12$ of 7,203, or 32,156 years.)

Figures for the number of years of exposure of men and women with different smoking habits have been obtained in the same way. Table II shows the figures

TABLE II.—*Total Number of Man-Years of Exposure by Non-smokers and Smokers of Different Amounts of Tobacco: Men Only, Divided by Age*

Age in Years	Non-Smokers*	All Smokers	Men Smoking a Daily Average of:		
			1–14 g.†	15–24 g.	25 g. or More
Under 35	10,143	25,346	12,548	10,002	2,796
35–44 ..	7,130	34,081	13,625	13,380	7,076
45–54 ..	4,136	28,020	9,477	10,371	8,172
55–64 ..	1,907	18,002	6,333	6,514	5,155
65–74 ..	1,078	11,384	5,201	3,893	2,290
75–84 ..	720	5,711	3,334	1,701	676
85 and over	136	892	616	230	46
All ages	25,250	123,436	51,134	46,091	26,211

* A non-smoker is defined as a person who has never consistently smoked as much as 1 g. of tobacco a day for as long as one year.
† 1 cigarette is equivalent to 1 g. of tobacco.

for men, divided according to the daily amount of tobacco stated to have been smoked at the time of the inquiry in 1951, or immediately before smoking had last been given up. It will be seen that the distribution of smoking habits varies considerably from one age group to another, and it will therefore be necessary to use death rates at specific ages, or a rate standardized for age, in comparing the mortality experiences of men in the different smoking categories.

The Deaths

Through the courtesy of the Registrars-General in the United Kingdom a form showing particulars of the cause of death has been provided, since the questionary was sent out, for every death identified as referring to a medically qualified person. Lists of the deaths of doctors notified to them since October 31, 1951, have also been obtained from the General Medical Council and the British Medical Association. These extra sources of information have proved necessary since it is not always possible for the Registrars-General to determine at registration of death that the deceased person was, in fact, a doctor. For example, occasionally the occupation of a doctor who had served in the Army, or who had held a university appointment, may be described at the time of death merely as "Colonel (retired)" or "University teacher." Similarly with a married woman who has ceased to practise medicine there may well be no reference at registration of death to the fact that she possessed a medical qualification. It must also be noted that the deaths of civilians occurring abroad do not form part of the records of the Registrars-General. It has therefore been necessary to seek information about them, and their cause of death, from other sources—from the records of the Service departments, from the Registrars' offices of Commonwealth countries, and, in a few instances, from relatives. For all deaths occurring in the United Kingdom, irrespective of the source of our information, we have ascertained the certified cause of death.

In the 53 months covered by the present study (November, 1951, to March, 1956) 1,854 deaths have been reported. Table III, in which they are set out by age and sex, shows that

TABLE III.—*Number of Deaths of Doctors Reported as Occurring Between November 1, 1951, and March 31, 1956, Inclusive*

Age in Years	Males	Females
Under 35	34	3
35–44	68	10
45–54	189	8
55–64	311	26
65–74	417	24
75–84	543	23
85 and over ..	186	12
All ages ..	1,748	106

their numbers are small for women and for men under 35 years of age. Our principal analyses in this paper have therefore been confined to the mortality experience of men aged 35 years and above, involving 1,714 deaths from all causes.

We first classified these 1,714 deaths according to the underlying cause as certified. The eight cases in which we obtained the cause of death only from the other sources mentioned above we classified according to the reported cause; in a further 12 cases we have not yet obtained any statement of cause. Of the total 1,714 deaths among men aged 35 years or more, 82 were certified as due to lung cancer, while in three others lung cancer was mentioned as having contributed to death without being the primary cause. No deaths from lung cancer were reported in men under the age of 35 years and only three such deaths at all ages have been reported among women.

For every one of these 88 deaths we sought confirmation of the diagnosis by writing to the doctor who certified the death and also, when necessary, to the hospital or consultant to whom the patient had been referred. Additional information on the nature of the evidence was thus obtained in every case and is summarized in Table IV. In two cases, one male and one female, we have not accepted the cause of death as established. With the man, histological examination of the operation specimen had failed to confirm the presence of a carcinoma. With the woman, the histological report was "sarcoma of lung." In 7 of the remaining 86 cases the site of the primary growth had been diagnosed by

TABLE IV.—*Criteria on Which Diagnosis of Primary Lung Cancer was Based*

Diagnostic Criteria	Male Cases		Female Cases
	No.	% of Total	No.
I. Necropsy evidence, with or without histological examination; or histological evidence plus evidence of the site of the primary tumour from operation, bronchoscopy, or radiological examination ..	39*	46	1†
II. Evidence of the site of the primary tumour from operation and or bronchoscopy and/or radiological examination, but without histological evidence	38	45	1
III. Evidence from clinical examination only	7	8	0
All cases, diagnosis accepted	84	99	2
Diagnosis not regarded as established ..	1	—	1

* 16 squamous-cell carcinoma, 16 oat-cell or anaplastic carcinoma, 3 adenocarcinoma, 3 cell-type undetermined, and 1 not examined histologically.
† Squamous-cell carcinoma.

clinical examination only. In 79 the site of the primary growth had been confirmed at necropsy or by operation, bronchoscopy, or radiological examination. Clearly the diagnosis may have been incorrect in some of the cases, but the evidence suggests that it is not likely to have been wrong in more than a small proportion. In making comparisons between the mortality of different groups within the investigation, we have therefore used the 84 male cases in which the additional information did not throw doubt upon the diagnosis of lung cancer.

RESULTS

The Amount Smoked

The complete data for the present 53 months of the follow-up have been used, and the death rates per annum from all causes of death and from five groups of diseases have been calculated for four categories of men—namely, non-smokers and smokers of small, moderate, or large amounts of tobacco. These rates have been standardized for age (by the direct method), using the total male population of the United Kingdom aged 35 years or above on December 31, 1951, as the standard population.‡ The results are shown in Table V and in the Figure.

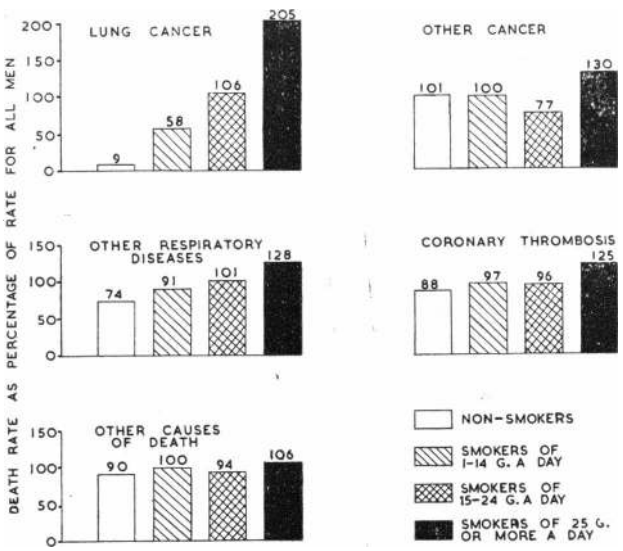
If all causes of death are taken first, it will be seen that the mortality is highest among men who smoked 25 g. or more of tobacco a day (18.84 per 1,000), and that the rates for light smokers (14.92 per 1,000) and moderate smokers (14.49 per 1,000) are 10 to 13% above the rate for non-smokers (13.25 per 1,000). Of the five groups of diseases separately considered, lung cancer is the only one to show a marked and steady increase with the amount smoked. Its death rate rises from 0.07 per 1,000 among non-smokers to 1.66 per 1,000 among heavy smokers—that is, an increase of approximately twentyfold. Other respiratory diseases and coronary thrombosis also show some increase with rising tobacco consumption, particularly the former. But in both instances the difference between the extreme rates is, compared with lung cancer, relatively small. For other respiratory diseases the rate for heavy smokers (1.41) is 74% above the rate of non-smokers (0.81), while for coronary thrombosis the corresponding figure is 42% (5.99 to 4.22). The equality of non-smokers and smokers in cancer of other sites is striking and no trend with the amount of smoking is apparent. (These death rates from diseases other than cancer of the lung are considered in more detail in a later section.)

‡Thus death rates for each cause of death were calculated separately for each age group for each of the smoking categories shown in Table II. These age rates for a smoking category were then applied to the corresponding U.K. populations in 1951 to obtain the death rate at all ages that would have prevailed in the U.K. population if it had experienced the rates at specific ages of the particular smoking group.

TABLE V.—*Standardized Death Rates Per Year Per 1,000 Men Aged 35 Years or More, in Relation to the Most Recent Amount Smoked**

Cause of Death	No. of Deaths	Death Rate Among: All Men	Non-smokers	All Smokers	Men Smoking a Daily Average of 1–14 g.	15–24 g.	25 g. or More
Lung cancer ..	84†	0·81	0·07	0·90	0·47	0·86	1·66
Other cancer ..	220	2·02	2·04	2·02	2·01	1·56	2·63
Other respiratory diseases ..	126	1·10	0·81	1·13	1·00	1·11	1·41
Coronary thrombosis ..	508	4·78	4·22	4·87	4·64	4·60	5·99
Other causes ..	779	6·79	6·11	6·89	6·82	6·38	7·19
All causes ..	1,714	15·48	13·25	15·78	14·92	14·49	18·84

* That is, at November 1, 1951, for those smoking at that time and at the date of giving up for those who had given up at November 1, 1951.
† The three cases in which lung cancer was recorded as a contributory but not a direct cause of death are included under both lung cancer and the cause to which death was assigned by the Registrar-General.



Relationship between death rate, expressed as a percentage of the rate for all men, and the amount smoked, for five disease groups.

The statistical significance of the differences in the death rates is best assessed from the actual numbers of deaths recorded—that is, by comparing them with the numbers which would have been expected to occur in each smoking category if smoking were unrelated to the cause of death under inquiry. For example, 31 men aged 65–74 died with lung cancer. The man-years of exposure in this age group of men who had always been non-smokers (at the time the questionary was completed) formed 8.65% of the total exposure of all men (Table II). If the mortality from lung cancer is quite unrelated to smoking, then the proportion of non-smokers among the 31 lung cancer deaths should also be 8.65%. A similar calculation has been made for the numbers of men dying with lung cancer in the other age groups—namely, 1 at ages 35–44, 9 at ages 45–54, 24 at ages 55–64, 16 at ages 75–84, and 3 at ages 85 and above. The total number of deaths expected among non-smokers of all ages was then obtained by adding the numbers for the separate age groups. Corresponding calculations were made to obtain the number of deaths which would be expected to have occurred in men who smoked small, moderate, or large amounts, and likewise for the other principal disease groups of Table V. The results are shown in Table VI.

If non-smokers are compared with smokers it is found that for all causes of death the observed difference is not quite statistically significant ($P=0.06$). Division by cause shows that it is highly significant for lung cancer ($P<0.01$) but not significant for any of the other four diseases or

TABLE VI.—*Observed Deaths From All Causes, and From Particular Causes, in Non-smokers and Smokers Compared With the Number of Deaths that Would Have Been Expected to Occur in Each Such Group if There Were No Association Whatever Between Smoking and Mortality*

	Non-smokers	All Smokers	Test of Significance* P	Men Smoking a Daily Average of: 1–14 g.	15–24 g.	25 g. or More	Test of Significance† P
All causes:							
Observed deaths	163	1,551	0·06	727	468	356	Less than 0·01
Expected deaths	187·4	1,526·6		751·2	510·2	289·6	
Lung cancer:							
Observed deaths	1	83	Less than 0·01	22	27	34	Less than 0·001
Expected deaths	8·5	75·5		36·9	28·3	17·9	
Other cancer:							
Observed deaths	25	195	Between 0·8 and 0·9	95	51	49	Between 0·3 and 0·5
Expected deaths	23·9	196·1		92·8	64·9	37·3	
Other respiratory diseases:							
Observed deaths	11	115	Between 0·3 and 0·5	55	36	24	Between 0·2 and 0·3
Expected deaths	13·8	112·2		59·8	36·5	18·7	
Coronary thrombosis:							
Observed deaths	44	464	Between 0·1 and 0·2	200	148	116	0·06
Expected deaths	53·9	454·1		211·2	156·7	96·1	
Other diseases:							
Observed deaths	82	697	Between 0·5 and 0·7	356	207	134	Between 0·7 and 0·8
Expected deaths	87·6	691·4		351·9	224·9	120·2	

* Based on χ^2 test with n=1.
† Based on χ^2 test applied to the trend with n=1.

groups of diseases. (The numbers of deaths of non-smokers are still small in some of these groups and it is quite possible that significant differences may be obtained with more extensive data.)

When comparisons are made between the different grades of smokers, it is proper to take account not only of the actual extent of the differences but also of the order in which they occur. The statistical test which has been applied to the results is therefore a test of the significance of the trend of the differences between the observed and expected numbers of deaths as the amount smoked increases (Armitage, 1955). It is thus found that there is a significant trend, with an excess of deaths among heavy smokers, for all causes of death ($P<0.01$) and a highly significant trend for cancer of the lung ($P<0.001$). Other forms of cancer and other diseases reveal no significant change with smoking, and the observed rise in other respiratory diseases and in coronary thrombosis is not, on present numbers, more than might quite easily be due to chance. (With the latter the rise is significant if the non-smokers are brought into the test of gradient along with the smokers of different amounts.)

TABLE VII.—*Mortality From Lung Cancer in Relation to the Amount Smoked at Different Ages Above 35 Years: Annual Rates Per 1,000 Men*

Age in Years	No. of Deaths	Death Rate Among: Non-smokers	Men Smoking a Daily Average of: 1–14 g.	15–24 g.	25 g. or More
35–54 ..	10	0·00	0·09	0·17	0·26
55–64 ..	24	0·00	0·32	0·52	3·10
65–74 ..	31	0·00	1·35	3·34	4·81
75 and over	19	0·70	2·78	2·07	4·16
All ages ..	84	0·07	0·47	0·86	1·66

We may also note, at this point, that a finer analysis of the lung cancer data has shown a marked gradient at each stage of life. The mortality rates for four age groups above 35 years are shown in Table VII.

Method of Smoking

For classifying our population into cigarette smokers, pipe smokers, or smokers by both methods our data are certainly faulty. As pointed out above, the questionary asked for smoking habits at a particular point of time (November 1, 1951) and not for a life-history. In a covering letter we invited doctors to add any information on their smoking habits or histories which they thought might be of interest to us, and a number of them did so. In those instances we have, of course, used all the information given. For example, if a man stated that in November, 1951, he was smoking 2 ounces of tobacco weekly in a pipe but added in a footnote that previously he had, in addition, smoked 20 cigarettes a day, we classified him as a "mixed" smoker. But we can be sure that some, and perhaps many, men who had changed their habits did not volunteer this extra information. It follows that some whom we have classified as "pure" cigarette smokers or as "pure" pipe smokers really belong to the mixed class. The rates we give in Table VIII cannot therefore indicate the full extent of

TABLE VIII.—*Standardized Death Rates Per Year Per 1,000 Men Aged 35 Years or More, in Relation to the Method of Smoking*

Cause of Death	No. of Deaths Among Smokers	Death Rate Among Men Smoking: Pipes	Pipes and Cigarettes*	Cigarettes	Test of Significance† P
Lung cancer ..	83‡	0·38	0·68	1·25	Less than 0·001
Other cancer ..	195	2·37	1·57	2·15	Over 0·95
Other respiratory diseases ..	115	0·79	0·62	1·52	Less than 0·01
Coronary thrombosis ..	464	4·22	4·37	5·17	Between 0·1 and 0·2
Other causes ..	697	5·75	5·79	7·70	0·02
All causes ..	1,551	13·52	13·03	17·71	Less than 0·001

* Including men who smoked cigars.
† Based on χ^2 test applied to the trend from pipes to cigarettes; n=1.
‡ See second footnote to Table V.

the difference in risk associated with the two methods of smoking; the difference must be blurred by this inclusion in each "pure" group of men who belong to the "mixed" group. (In the mixed group we have included the few men who smoked cigars.)

However, in spite of this blurring of the picture, we find an excess mortality among cigarette smokers compared with pipe smokers for all causes of death and for three of the specific groups. For all causes of death the trend of the differences is highly significant ($P<0.001$) though the mortality of the "mixed" group is not in step. For lung cancer the trend is continuous and also highly significant ($P<0.001$); the death rate among the cigarette smokers is over three times as great as the rate among the pipe smokers. The death rate among cigarette smokers is also higher than that among pipe smokers for other respiratory diseases, coronary thrombosis, and the miscellaneous group of other diseases. The excess is less marked than for lung cancer, but it is sufficiently great for the trend to be statistically significant for other respiratory diseases and for the miscellaneous group. The mortality from these diseases among mixed cigarette and pipe smokers is, however, either lower or inappreciably higher than that among pipe smokers. For cancer of other sites no relationship is apparent.

The pronounced differences of Table VIII for persons dying of lung cancer can be explained, to some extent, by the fact that pipe smokers use, on the average, less tobacco than cigarette smokers (in the present study the average was 12 g. a day for pipe smokers against 20 g. a day for cigarette

smokers). This difference in consumption can be allowed for by calculating at each different level the distribution of the observed deaths that would have been expected to occur if the method of smoking bore no relationship at all to the rate of mortality. The resulting figures still show a significant difference between the categories ($P<0.01$). The same conclusion can also be reached by calculating separately, for each level of smoking, the standardized death rate for pipe smokers and cigarette smokers. It is then found that the death rate of pipe smokers is less than that of cigarette smokers at each level. We may repeat, too, that the contrasts obtained must almost certainly be an understatement of the true difference.

Effects of Giving up Smoking

To measure any effects that might follow the giving up of smoking, we divided the doctors into three groups: (1) those who, on replying to the questionary, reported that they had given up smoking for at least 10 years; (2) those who reported that they had given up within the previous 10 years; and (3) those who, at November 1, 1951, reported that they were then smokers. We know nothing of any subsequent changes in habits, so again any contrasts we find between these groups will be minimal. The mortality rates for the three groups are shown in Table IX. It will be

TABLE IX.—*Standardized Death Rates Per Year Per 1,000 Men Aged 35 Years or More, in Relation to Giving Up of Smoking*

Cause of Death	Total No. of Deaths Among Smokers and Ex-smokers	Death Rate Among:			Test of Significance* P
		Ex-smokers, who had given up 10 Years or More at 1/11/51	Ex-smokers, who had given up Less than 10 Years at 1/11/51	Smokers at 1/11/51	
Lung cancer	83†	0·35	0·59	1·03	0·02
Other cancer	195	1·31	1·79	2·15	Between 0·1 and 0·2
Other respiratory diseases	115	1·17	1·28	1·11	Between 0·9 and 0·95
Coronary thrombosis	464	3·98	5·23	4·88	Between 0·3 and 0·5
Other causes	697	7·24	7·22	6·71	Between 0·2 and 0·3
All causes ..	1,551	14·04	16·11	15·84	Between 0·5 and 0·7

* Based on χ^2 test applied to the trend, n = 1.
† See second footnote to Table V.

seen that only for cancer of the lung is there a progressive and statistically significant reduction in mortality with the increase in the length of time over which smoking has been given up. Cancer of all other sites shows the same trend, but the observed differences are relatively small, and, with the numbers involved, might be due to chance. On the other hand, for cancer of the lung the mortality among the present smokers at November 1, 1951, has been three times as great as that among men who at that date had stopped smoking for 10 years or more, and 76% greater than the rate for men who had given up within the previous 10 years.

These differences cannot be accounted for by differences between the three groups in the amount smoked or in the method of smoking. The average amount smoked (at November 1, 1951, for the smokers and at the date of giving up for the ex-smokers) was practically the same—namely, men who had given up for 10 years or more, 18 g. a day; men who had given up within the previous 10 years, 19 g. a day; men who were still smoking, 18 g. a day. In regard to method, the proportion of "pure" cigarette smokers was also almost the same amongst those who had given up and amongst the continuing smokers—88% in men who had given up for 10 years or more; 87% in men who had given up within the previous 10 years; 84% in men who were still smoking.

We may also note at this point that the average age at which men had given up smoking was 44 years for those who had given up within the last 10 years and 42 years for those who had given up for 10 years or longer.

In spite of these equalities the three groups are, of course, self-selected, and it seems not unlikely that selective factors may play some part in the contrasts of mortality between continuing smokers and ex-smokers of different durations. Thus, amongst those who have more recently given up smoking there are likely to be some who have given up on grounds of ill-health. Such persons are likely to have a higher-than-average mortality in the ensuing years. There is in the figures for all causes of death given in Table IX a slight suggestion of such an effect—the death rate is 16.11 per 1,000, compared with 15.84 per 1,000 for those who were continuing to smoke. On the other hand, we would not expect such a selective influence to be very pronounced in our data, since many seriously ill persons would not have returned our questionary at all. In the course of time those with a higher-than-average mortality will have been eliminated and the death rate among the group of persons who gave up smoking many years ago may be expected to fall—the actual figure is 14.04.

While such selective factors might, we think, contribute to the observed trend of mortality from all causes (and from coronary thrombosis in particular), they will not explain the continuous trend of the lung cancer mortality to its highest point in those who were continuing to smoke.

Mortality Among Present Cigarette Smokers

Since the mortality from lung cancer has been shown to be greater (*a*) among cigarette smokers than among pipe smokers, and (*b*) among present smokers than among past smokers, it is clear that the highest rates of mortality must have been recorded among those doctors who were continuing to smoke cigarettes at the time of the inquiry (November 1, 1951). In fact, the mortalities among men in this group are substantially higher than the corresponding mortalities among all smokers—past and present, pipe, cigarette, and mixed (as shown in Table V). Thus, for men aged 35 years and over who at November 1, 1951, smoked 1–14 g. a day in cigarettes the subsequent annual mortality from lung cancer has been 0.95 per 1,000; for those similarly smoking 15–24 g. a day it has been 1.67 per 1,000; and for those similarly smoking 25 g. or more a day it has been 2.76 per 1,000. The corresponding rates for all smokers are 0.47, 0.86, and 1.66. In other words, the rates for the continuing cigarette smokers have been 102%, 67%, and 66% higher than the corresponding rates for all smokers, past or present. While remembering that the numbers involved are small, we may note that the rate for men who were continuing to smoke 25 or more cigarettes a day at the time of the inquiry (2.76 per 1,000) was almost 40 times the rate observed among non-smokers (0.07 per 1,000).

Histological Type

There is now evidence to suggest that the relationship holds only for epidermoid and anaplastic cancers (including oat-cell cancer) and that it applies to a less marked degree (if it applies at all) to adenocarcinoma (Wynder and Graham, 1950; Wynder, 1954; Kreyberg, 1955). In the present study only three of the histologically proved cases were diagnosed as adenocarcinoma. This is too few for rates to be calculated for different smoking categories, but it may, perhaps, be noted that the amount smoked by the three patients (3 cigarettes a day, 20 cigarettes a day, and 14 g. daily in a pipe) was, on average, somewhat less than the amount smoked by men of the same ages (12.3 against 16.3 g. a day), whereas the average amount smoked by men dying of epidermoid or anaplastic cancer was substantially greater (23.6 against 16.4 g. a day).

Mortality Among Women

The total number of deaths recorded among women (106) is still too small for reliable estimates to be made of the mortality from different causes among different categories of

smokers. Two deaths were attributed to carcinoma of the lung—one of a woman of 66 years who smoked 15 cigarettes a day at November 1, 1951, and the other of a woman of 55 years who smoked 30 cigarettes a day. A third woman, aged 44, was certified as having died of sarcoma of the lung; she had started smoking at the age of 27 years, and smoked 30 cigarettes daily.

The total mortality from all causes of death recorded among women aged 35 years and over has been much less than that recorded among men. Thus their standardized death rate is 7.82 per 1,000 for non-smokers, 7.87 per 1,000 for all smokers, and 16.90 per 1,000 for smokers of 25 or more cigarettes a day (a small group). The corresponding figures for men are 13.25, 15.78, and 18.84 per 1,000. It is very probable that these lower rates for women are not wholly due to a lower actual mortality but partly to a less complete recording. Deaths in women are likely to be certified according to the married name, whereas a number of the women are recorded in our series only under the name that they used professionally and which they entered upon our questionary. This has created considerable difficulty in identifying the women doctors who replied to the questionary and who have subsequently died. A number of deaths have certainly been missed. A more complete identification is in progress and the further analysis of female mortality in relation to smoking habits is therefore postponed to a subsequent report.

QUESTIONS OF BIAS

Diagnosis of Cause of Death

It might perhaps be argued that doctors have more readily diagnosed lung cancer in heavy smokers than in light smokers or in non-smokers, and have thus produced the gradient of mortality recorded here. As one means of investigating this possibility we wrote in the last two years of the inquiry to all the doctors who signed the death certificates referring to cancer of the lung. We asked them whether they knew the patient's smoking habits when they diagnosed the cause of death, and, if so, whether they thought their diagnosis was influenced by that knowledge. Of the 47 doctors involved, 40 replied that they had some knowledge of their patients' smoking habits and seven that they were ignorant of them. Of the 40 with some knowledge, 36 did not believe that it had in any way influenced their judgment, one thought that it had (the patient was a man of 68 years who smoked 18 cigarettes a day), another that it might have done so subconsciously (the patient was a man of 68 years who smoked 15 cigarettes a day), and two did not express an opinion.

A second, and perhaps more convincing, test of this possible bias can be made by comparing the mortality gradient with smoking for those cases in which the diagnosis was firmly established (category I in Table IV) with that observed for the cases in which the diagnosis contains a greater element of doubt (categories II and III in Table IV). The figures are given in Table X, from which it will be seen that with the firmly established cases the trend of mortality with smoking is certainly no less steep, and possibly steeper, than that shown by the remaining deaths.

TABLE X.—*Standardized Death Rates From Lung Cancer in Relation to the Amount Smoked, Divided According to the Basis of the Diagnosis*

Basis of Diagnosis		Standardized Death Rate per 1,000 Men Aged 35 Years and Above per Year			
		Non-smokers	Men Smoking a Daily Average of:		
			1–14 g.	15–24 g.	25 g. or More
Category I.* Firm diagnosis based on necropsy, histological evidence, etc. (39 cases)	Rate	0·00	0·22	0·31	0·94
	Rate as % of rate for all men	0	58	80	244
Categories II and III.* Less well established diagnosis lacking histological confirmation (45 cases)	Rate	0·07	0·24	0·55	0·71
	Rate as % of rate for all men	18	56	129	166

* For full definitions see Table IV.

In view of these results it seems to us most improbable that the relationship we have observed between smoking and lung cancer can be attributed merely to a biased attitude among the medical profession.

The Population at Risk

In our preliminary report on this inquiry (Doll and Hill, 1954a) we pointed out that the mortality we had recorded amongst doctors in the 29 months of follow-up was considerably less than that which we would have expected to occur at the death rates of the general population. We suggested that the main reason for this—and one which would apply to all causes of death and not only to lung cancer—was that doctors who were already ill of a disease, likely to prove fatal within a foreseeable space of time, would have been disinclined, or indeed unable, to answer our questionary. In other words, we should learn of their deaths but we would have no corresponding completed questionary on our files. The question we had to consider was whether such a bias in the population at risk would differentially affect the mortality of the non-smoking and smoking groups. Could it have artificially produced the gradient with smoking that we had observed with cancer of the lung whilst not producing any such gradient with other causes of death (excepting, possibly, coronary thrombosis)? Not only did that seem to us very unlikely on general grounds, but we noted two specific pieces of evidence in support of our view; (*a*) although the number of deaths from cancer of the lung was small we had not seen any obvious change in its gradient with smoking over the 29 months of inquiry; (*b*) the gradient we had observed in this prospective inquiry closely resembled that which we had already obtained in our earlier retrospective inquiry.

The preliminary results of the large-scale inquiry conducted by the American Cancer Society (Hammond and Horn, 1954) showed the same characteristic—namely, a low death rate from all causes in the subjects of the inquiry compared with that of the general population. Further, contrary to our own observations, Hammond and Horn reported an appreciably heavier mortality in smokers than in non-smokers for every disease group examined—for cancer of other sites, for coronary thrombosis, and for other diseases—though the gradient with lung cancer, we may note, was very much sharper than that shown by the other causes.

These results led Berkson (1955) to suggest that not only is the total population in these studies biased, by the absence of the seriously ill at the time of initial inquiry into smoking habits, but that the component smoking and non-smoking groups may be *differentially* biased to the advantage of the latter in the subsequent mortality experience. He points out that this would be the effect if non-smokers in good health came more readily into the study than smokers in good health—for example, because answering the questionary is a simpler task for the non-smoker—whereas the chances of inclusion in the study were low for men seriously ill and *unrelated to the smoking habits*. In such circumstances the already seriously ill component would be artificially low, but still representative of the parent population; the component in good health would be large but unrepresentative. It would contain proportionately too many healthy non-smokers. It follows that the total mortality would be lower than that anticipated from general population rates, and the mortality among non-smokers would be less than that amongst smokers—and for all causes of death.

The final test of Berkson's thesis lies with the passage of time. For as time passes it becomes progressively less likely that the shadow of death could have been foreseen at the start of the inquiry, less likely that such pre-knowledge could have influenced response to our questionary. As

stated in our preliminary report, and quoted above, we had seen over the first 29 months no signs of a change in the gradient of lung cancer mortality to suggest an initial selective bias. We are now able to analyse the observations over four complete years. The figures are given in Table XI

TABLE XI.—*Standardized Death Rates From Lung Cancer in Each Year of the Inquiry by Amount Smoked*

Year of Inquiry (and No. of Deaths)	Standardized Death Rate per 1,000 Men Aged 35 Years and Above per Year				
	Non-smokers	Men Smoking a Daily Average of:			All Men
		1–14 g.	15–24 g.	25 g. or More	
1st (12) ..	0·00	0·29	0·60	0·86	0·53
2nd(14) ..	0·00	0·26	0·43	1·80	0·57
3rd(31) ..	0·33	0·82	1·51	2·44	1·31
4th(21) ..	0·00	0·54	0·98	1·67	0·92
	As percentages of rate for all men				
1st ..	0	54	112	161	100
2nd ..	0	45	75	315	100
3rd ..	25	62	115	187	100
4th ..	0	59	107	182	100

and show, as expected, death rates in the third and fourth years of the inquiry substantially greater than those of the first and second years. (With the relatively small population at risk we think the steep rise in the third year and the fall in the fourth year are no more than chance fluctuations.) On the other hand, the *gradient* of mortality in relation to amount smoked has been remarkably constant in the first, third, and fourth years—that is, irrespective of the absolute levels of mortality. The second year shows a much steeper gradient, but with only 14 deaths involved we think no emphasis can be placed upon this. In short, it would seem that the association between death rate and amount smoked has shown very little change between the beginning of the inquiry and the later years. It certainly has not become any less pronounced with more representative death rates. The observations do not seem to us to support Berkson's thesis.

As regards the total mortality of our population of doctors we can also make a check as to how far it has been unrepresentative of the rate for all doctors. For this purpose we have accumulated details of the mortality that has occurred year by year amongst a 10% sample (randomly drawn) of all the doctors who did *not* reply to our questionary. This population of "non-answerers" was not obtained until several months after the start of the inquiry, when the names of doctors who had died in the first few months had already been erased. We cannot, therefore, reconstruct the total population nor measure the first year's mortality among those who did not reply. In the subsequent years, however, we can estimate the mortality rate of *all* doctors by combining the figures for those who *did* reply to the questionary with the figures for those who did *not* reply (multiplying the sample by ten). In the second year of the inquiry we thus reach a standardized death rate at all ages of 20.4 per 1,000 for all doctors, compared with a rate of 14.7 for those who replied to us. The latter is only 72% of the former, revealing, as we previously recognized, the initial effects of selection through the absence of the seriously ill. In the third year of observation the rate for all doctors is calculated to be 18.6 per 1,000; for those who replied it was 16.1; the ratio is 87%. In the fourth year the rates are respectively 18.4 and 17.0 per 1,000, and the ratio is 92%.

We see, therefore, that though the effect of self-selection initially present may still not have entirely worn off, it is certainly no longer large. Conceivably it may be rather larger than 92% suggests, since it is possible that we are able to trace the deaths of those who replied to us more fully than the deaths of those who did not reply. But we have no evidence to that effect. On the other hand, the difference may never wholly vanish. If non-smokers answered us proportionately more frequently than did smokers, then our population will always contain a higher proportion of the persons who suffer a relatively low mortality rate. In other words, we should *always* have a population which—in total—has a relatively favourable mortality experience. But it does not follow that its components (smokers and non-smokers) cannot be validly contrasted. That very marked contrast is not, as we have shown above, diminishing with the passage of years.

In this analysis we have compared the mortality observed amongst the doctors who answered us with our estimate of the mortality of all doctors whether they answered us or not. This latter figure is, in our view, the proper standard of comparison, to reveal how far our group is representative of the total. If, however, we compare our rate for all doctors with the corresponding figure for the general population of the whole country, we find that the doctors' rate in the last two years of the inquiry has been 83% of the national mortality. We cannot from this result deduce that the deaths of doctors have been incompletely recorded in our inquiry. It may well be that in these years the medical profession was experiencing lower death rates than the general population of all social classes. Unfortunately, in the absence of the national occupational mortality analysis since 1930–2 there is no evidence available.

ASSOCIATION, DIRECT OR INDIRECT

Site of Growth

In relation to the observed association between lung cancer and smoking it has been suggested that smoking does not produce cancer in a person in whom cancer would not otherwise have occurred at all, but merely determines the primary site of a growth that is destined to appear in some part of the body (Fairweather, 1954; Goodhart, 1956). In short, a man predestined to have cancer increases his chance of having it in the lung if he smokes and increases his chances of having it elsewhere in the body if he does not smoke. If he is not predestined to have cancer, smoking and other environmental factors obviously have no relevance. This hypothesis is in line with the general theory discussed by Cramer (1934) that cancer susceptibility is predetermined by heredity, that the effect of environmental stimuli is merely to elicit the response in particular tissues, and that, as a result, the total cancer incidence in a given population is a fixed sum uninfluenced by changes in the stimulus. The primary sites may change, the total does not. The final test of the theory will require accurate observations of cancer morbidity, but several recent studies of cancer mortality seem to us to provide strong evidence that the theory is untrue.

Thus Case (1954) has shown that among certain chemical workers exposed to β-naphthylamine mortality from bladder cancer has been almost double that expected for cancer of *all* sites; the excess in the particular site is certainly not balanced by a reduction in other sites. Similarly Doll (1952, 1955) has shown that the raised death rate from lung cancer among gas workers and asbestos workers is not compensated for by a reduction in mortality from other types of cancer, and Brinton, Frasier, and Koven (1952) have made a similar observation among chromate workers. Case and Lea (1955) have obtained a similar result in another field. They studied 1914–18 war pensioners with chronic bronchitis and found a substantial excess of cancer of the lung, while the mortality from cancer of other sites was normal and unreduced.

Specific to the present issue, Doll and Hill (1954b), in their retrospective study of patients' smoking habits, found no evidence that tobacco produced an effect by the mechanism postulated. While a large excess of heavy smokers was a feature of their lung-cancer group there was no deficit of heavy smokers in patients with cancer in other sites—that is, in comparison with patients with other diseases. The data from the present investigation are also inconsistent with the theory. If tobacco merely determines the site of the cancer without affecting the total incidence of the disease, then the mortality from *all* forms of cancer should be similar among non-smokers and smokers and

among the different grades of smokers. In fact it is seen from Table V that the annual death rate from all cancer rose from 2.11 per 1,000 among non-smokers to 2.91 per 1,000 among smokers.* The rise in lung cancer from 0.07 to 0.90 is not balanced by a reduction in cancer of other sites, the rates for which are almost identical—2.04 and 2.02 per 1,000 in non-smokers and smokers respectively. In the smoking grades the total cancer rates are almost the same in the 1–14 g. and 15–24 g. groups—namely, 2.48 and 2.42—but the substantial rise in lung cancer in the heavy smoking group (1.66) is certainly not balanced by any fall in cancer of other sites. The total incidence of 4.25 per 1,000 is significantly higher than that of the other two groups of smokers and of the non-smokers.* In short, our data, both retrospective and prospective, indicate a total incidence of cancer in the smoking groups in excess of the incidence that would have prevailed in the absence of smoking.

Constitutional Type

The observed association between the mortality from lung cancer and the amount of smoking could conceivably be explained in terms of some common factor which produced lung cancer and was also associated (directly or indirectly) with cigarette smoking. For example, it has been suggested that constitutional and psychological factors might have such an effect—that is, that persons of a certain "make-up" are peculiarly liable to lung cancer and to smoke. We know of no published evidence to this effect. It is difficult, too, to see how such an indirect association could explain the rise in lung cancer mortality of recent years.

Atmospheric Pollution

It has been argued that, since cigarette smoking is, in general, more prevalent in towns than in country districts, the comparison of different smoking groups is, in part, merely a comparison of urban and rural residents, the former being exposed to an atmospheric pollution which the latter escape. On the other hand, if the difference between the smoking habits of town and country were somewhat greater 20 to 30 years ago than it is to-day, there may be no reason at all to invoke atmospheric pollution as the explanation of the higher mortality from lung cancer in urban areas. Cigarette smoking could, in that event, be the answer. However that may be, atmospheric pollution could not account for the pronounced gradient in mortality that we record here. For example, the national figures record that the lung-cancer death rate among men in Greater London is about twice that among men in rural districts. Our data, prospective and retrospective (Doll and Hill, 1952) give a mortality among the heavy smokers more than twenty times the mortality among non-smokers. Further, the association with smoking has been shown to persist when the observations are limited to men living within a particular type of area. We ourselves found it for male patients resident in Greater London (Doll and Hill, 1952); Stocks and Campbell (1955) have reported a most marked gradient within two wholly rural counties of North Wales and a slighter gradient in the City of Liverpool; Hammond and Horn (1955) have found consistently higher death rates for smokers compared with non-smokers within specific types of areas in the U.S.A.

Finally, in this present study we have analysed the smoking habits of doctors resident in different types of areas (using a 10% sample randomly drawn from the questionaries returned by doctors aged 35 years and over). The results show (Table XII) that within this occupationally relatively homogeneous population there is remarkably little difference between the smoking habits of the residents in the specified areas. The tendency is for more non-smokers and fewer heavy smokers to be found in the large urban communities.

*The death rates for all cancer shown for smokers (2.91 per 1,000) and for heavy smokers (4.25 per 1,000) are slightly lower than the sum of the rates for lung cancer and for other cancer, since one doctor suffered from primary cancer in both lung and larynx and his death was included in both categories in Table V.

TABLE XII.—*Numbers of Doctors Aged 35 Years or Over Smoking Different Amounts of Tobacco (Most Recent Amount Smoked) According to Place of Residence at November 1, 1951*

Amount Smoked Daily	Percentage Smoking given Amount in:			
	Greater London (525 Doctors)	Large Towns in the U.K.* (716 Doctors)	Elsewhere in the U.K. (1,147 Doctors)	Abroad or Unspecified Place (46 Doctors)
Nil	16	13	11	13
1–14 g.	31	32	35	35
15–24 g.	34	38	31	33
25 g. or more ..	19	17	23	19
Total ..	100	100	100	100

* County boroughs in England and Wales together with Belfast, Edinburgh, and Glasgow.

It follows that the contrasts in lung cancer mortality that we have observed between smokers and non-smokers, and between light, medium, and heavy smokers, cannot be explained in terms of a differential exposure to atmospheric pollution which happens to be associated with smoking habits.

SMOKING IN RELATION TO DISEASES OTHER THAN LUNG CANCER

For the large number of deaths attributed to other causes further information was not specially sought from the certifying doctors, and these deaths have therefore been classified according to the cause of death as certified (or by the informant in the few cases where no such information was available). In the main the Registrar-General's rules for the classification of causes of death have been followed, but occasionally some other classification seemed more appropriate and was adopted. The observed death rates for individual diseases other than lung cancer are not, therefore, strictly comparable with the national rates.

Cancer of Other Sites

Deaths attributed to cancer of sites other than the lung are shown in Table XIII. In none of the groups is the difference between smokers and non-smokers significant, and

TABLE XIII.—*Standardized Death Rate Per 1,000 Men Aged 35 Years and Over Per Year, for Cancer of Sites Other than the Lung*

Site of Primary Cancer	No. of Deaths	Death Rate Among:					
		All Men	Non-smokers	All Smokers	Men Smoking a Daily Average of:		
					1–14 g.	15–24 g.	25 g. or More
Upper respiratory and upper digestive tracts	13	0·12	0·00	0·14	0·13	0·09	0·21
Stomach ..	32	0·29	0·41	0·28	0·36	0·10	0·31
Colon and rectum	57	0·52	0·44	0·53	0·54	0·37	0·74
Prostate ..	30	0·28	0·55	0·25	0·26	0·22	0·34
Other sites (excluding lung)*	88	0·81	0·64	0·83	0·72	0·76	1·02
All cancer, other than cancer of the lung ..	220	2·02	2·04	2·02	2·01	1·56	2·63

* Including 7 of unspecified primary site.

in none is there a steady—or significant—increase in death rate with the amount smoked. One group consists of deaths attributed to cancer of the upper respiratory or upper digestive tracts, types of cancer which, it has been suggested, may also be related to smoking. It will be seen that no death occurred among non-smokers and the highest death rate occurred among heavy smokers, but the total number of cases is at present too small to give reliable results. The 13 deaths include one from cancer of the buccal cavity, eight from cancer of the oesophagus, and four from cancer of the larynx; the average amount smoked by these men was 17.3 g. a day, against an average of 15.1 g. for all men of corresponding ages in the inquiry.

Coronary Thrombosis

The data for deaths from coronary thrombosis have already been given in Tables V, VI, VIII, and IX, and in the Figure. The increase in mortality with the amount smoked (from 4.22 per 1,000 non-smokers to 4.64 for men smoking 1–14 g., 4.60 for men smoking 15–24 g. a day, and to 5.99 per 1,000 men smoking 25 or more g. a day) is consistent with the existence of a slight relationship, and this, as noted previously, is not very likely to be due to chance (P = 0.02). To test whether this result might, however, be due to a selective bias on the part of the doctors replying to the questionary (as previously discussed) the data obtained in the first two and a half years of the inquiry have been compared with those obtained in the subsequent 23 months. Table XIV shows that in the second period the increase

TABLE XIV.—*Death Rates From Coronary Thrombosis in Relation to the Amount Smoked, Recorded During the Earlier and Later Parts of the Inquiry*

Period		Standardized Death Rate per 1,000 Men Aged 35 Years and Above per Year			
		Non-smokers	Men Smoking a Daily Average of:		
			1–14 g.	15–24 g.	25 g. or More
First 30 months (278 cases)	Rate ..	4·20	4·46	4·83	5·59
	Rate as % of rate for all men	89	95	103	119
Subsequent 23 months (230 cases)	Rate ..	4·32	4·85	4·33	6·37
	Rate as % of rate for all men..	89	100	89	131

in mortality is certainly less regular than that observed in the first period, though in both periods the highest rate falls on heavy smokers. It does not seem likely that the trend is entirely due to bias arising from the method of investigation.

Our findings agree broadly with those of Hammond and Horn (1954), in that both sets of data show an increase in mortality with smoking. But in our experience the increase is distinctly less marked. These different results might, we thought, be due to the difference in the age of the subjects, our population of doctors being of all ages over 35 and Hammond and Horn's men being limited to 50–69 years. Analysis of our death rates from coronary thrombosis by age, however, reveals an even greater discrepancy. We find a distinct gradient of mortality with amount of smoking at ages under 55 and a rather less distinct gradient at ages 75 and above. We observe none at ages 55–74 (see Table XV).

TABLE XV.—*Relationship at Different Ages Between Mortality From Coronary Thrombosis and Most Recent Amount Smoked: Standardized Death Rates Per Year Per* 1,000 *Men Aged* 35 *Years or More*

Age in Years	No. of Deaths	Death Rate Among:			
		Non-Smokers	Men Smoking a Daily Average of:		
			1–14 g.	15–24 g.	25 g. or More
35–54	90	0·44	0·95	1·47	1·84
55–64	122	7·34	6·79	4·45	6·98
65–74	143	11·13	10·77	10·53	14·85
75 and over ..	153	15·18	20·00	22·27	24·95
All ages 35 and over	508	4·22	4·64	4·60	5·99

A possible explanation of this paradox may lie in the fact that we have classified men as dying of coronary thrombosis solely on the basis of the certified cause. It is, perhaps, reasonable to suppose that, for this group of deaths, the diagnosis is most likely to be accurate at the youngest ages.

Other Causes of Death

The results for other causes of death are shown in Table XVI. They reveal a steady increase in mortality from non-smokers to heavy smokers in three instances—pulmonary tuberculosis, chronic bronchitis, and peptic ulcer.

TABLE XVI.—*Standardized Death Rates Per Year Per* 1,000 *Men Aged* 35 *Years or More, in Relation to the Most Recent Amount Smoked: Diseases Other than Cancer and Coronary Thrombosis*

Cause of Death	No. of Deaths	Death Rate Among:					
		All Men	Non-smokers	All Smokers	Men Smoking a Daily Average of:		
					1–14 g.	15–24 g.	25 g. or More
Pulmonary tuberculosis ..	19	0·18	0·00	0·20	0·16	0·18	0·29
Chronic bronchitis	42	0·37	0·12	0·39	0·29	0·39	0·72
Other respiratory diseases ..	65	0·56	0·69	0·54	0·55	0·54	0·40
Cardiovascular diseases other than coronary thrombosis ..	279	2·36	2·23	2·37	2·15	2·47	2·25
Cerebral haemorrhage or thrombosis ..	227	2·03	2·01	2·02	1·94	1·86	2·33
Peptic ulcer ..	18*	0·17	0·00	0·19	0·14	0·16	0·22
Violence ..	77	0·68	0·42	0·73	0·82	0·45	0·90
Other diseases (including 12 of unspecified nature) ..	183	1·60	1·45	1·63	1·81	1·47	1·57

* Including 5 cases in which peptic ulcer was referred to as a contributory cause, but not the direct cause of death.

For chronic bronchitis the increase is sixfold (from 0.12 per 1,000 among non-smokers to 0.72 per 1,000 among smokers of 25 g. or more a day) and the trend is statistically significant (P<0.01). Further analysis shows that the death rate is higher among cigarette smokers (0.61 per 1,000) than among mixed pipe and cigarette smokers (0.21 per 1,000) or pure pipe smokers (0.21 per 1,000), and these differences are significant (P<0.01). With such a chronic disease it is obvious that the disease itself may influence the amount smoked and thus obscure any relationship. It may also be that the presence of a "smoker's cough" may influence the physician to attribute death to chronic bronchitis when, in its absence, he would have diagnosed some other respiratory (or cardiovascular) condition. Table XVI does, in fact, show some fall in the mortality from "other respiratory diseases" as smoking increases, suggesting a transference from one label to another. But this fall does not wholly compensate for the rise in chronic bronchitis mortality.

The differences observed between the various categories of smokers dying with pulmonary tuberculosis or peptic ulcer are not statistically significant; but the numbers of deaths are so small that strong relationships with smoking might exist, without significant results being obtained. The average amount smoked by the 19 men who died of pulmonary tuberculosis was 19.5 g. a day, against an average of 15.2 g. for all men in the inquiry of corresponding ages; for the 18 men who died with a peptic ulcer the average was 18.8 g. a day, against an expected average of 15.3 g.

Possibly Related and Unrelated Causes

In the causes of death that we have analysed there are six which have from time to time been regarded as possibly related to smoking—namely, cancer of the lung, cancer of the upper respiratory and upper digestive tract, coronary thrombosis, chronic bronchitis, peptic ulcer, and, recently (Lowe, 1956), pulmonary tuberculosis. In the present study 676 doctors died of these causes—nearly 40% of all the deaths in the doctors aged 35 years and over. We have set out the death rates from these causes in Table XVII. Alongside them we give the rates derived from all other causes of death. The relative stability of these other rates (based upon over 1,000 deaths) is, we think, striking. They provide, we suggest, a further answer to the question of selective bias.

TABLE XVII.—*Standardized Death Rates Per Year Per* 1,000 *Men Aged* 35 *Years or More in Relation to Amount Smoked; a Summation of Groups of Causes of Death*

Causes of Death	No. of Deaths	Death Rate Among:			
		Non-smokers	Men Smoking a Daily Average of:		
			1–14 g.	15–24 g.	25 g. or More
Lung cancer Cancer of upper respiratory and upper digestive tracts Pulmonary tuberculosis Chronic bronchitis Peptic ulcer *	168	0·19	1·13	1·62	2·99
Coronary thrombosis ..	508	4·22	4·64	4·60	5·99
Diseases possibly related to smoking	676	4·41	5·77	6·22	8·98
All other diseases	1,038	8·84	9·15	8·26	9·87

* The figures given are lower than those obtained by summing the figures for the five individual groups of diseases, because 8 deaths included in Tables V and XVI under lung cancer and peptic ulcer have been excluded. For these deaths, lung cancer and peptic ulcer were certified only as associated causes; they are included here in the disease group to which death was primarily attributed.

If the association suggested by the upper part of the table were due merely to a bias in our method of investigation, we would expect to see that bias operating to some extent in all, or nearly all, causes of death. It does not appear to do so. Secondly, if the effect of smoking were merely to influence the apparent cause of death, without in any way determining the occurrence of death, the second group of diseases should show a negative association complementary to the positive association of the first group. They do not do so.

SUMMARY AND CONCLUSIONS

1. In reply to a questionary sent out at the end of 1951, over 40,000 men and women on the British *Medical Register* informed us of their smoking habits at that time or, in the case of ex-smokers, when they previously gave up smoking. On the basis of these answers we classified them into a few broad groups—namely, non-smokers and smokers (or ex-smokers) of three different amounts by cigarette, pipe, or both (Tables I and II). The subsequent mortality of each of these groups has now been recorded for nearly four and half years (Table III). The present study relates to men aged 35 years and above, amongst whom there were 1,714 deaths, including 81 from lung cancer (in three others lung cancer was mentioned as a contributory cause).

2. The analysis shows that in this population there has been a marked and steady increase in the death rate from lung cancer as the amount smoked increases. Its death rate per year rises from 0.07 per 1,000 in non-smokers (based upon the observations of one death only) to 0.47 per 1,000 in " light " smokers of 1 to 14 g. a day, to 0.86 per 1,000 in " medium " smokers of 15 to 24 g. a day, and finally to 1.66 per 1,000 in smokers of 25 g. or more a day (1 g. is almost equal to one cigarette). The death rate of the heavy smokers is approximately twenty times the death rate of the non-smokers (Tables V and VI).

3. This rising mortality from lung cancer in smokers compared with non-smokers, and in heavy smokers compared with lighter smokers, has been a feature of each stage of life, 35–54 years, 55–64, 65–74, and 75 years and over (Table VII).

4. The mortality from lung cancer has been substantially and significantly greater in cigarette smokers than in pipe smokers, with smokers by both methods falling in between (Table VIII). This difference between pipe and cigarette smokers is to be observed for each of the smoking categories, light, medium, and heavy, and therefore appears to be a function of the method of smoking irrespective of the amount.

5. Those who reported themselves as smokers at November 1, 1951, have been compared with those who had given up smoking at that time within the previous 10 years or for more than 10 years. The comparison reveals a progressive and significant reduction in mortality with the increase in the length of time over which smoking has been given up (Table IX).

6. From conclusions 4 and 5 it follows that the highest mortalities have occurred amongst those who reported themselves as continuing to smoke cigarettes at November 1, 1951. Among them the annual death rate rose from 0.95 per 1,000 for smokers of 1 to 14 cigarettes a day, to 1.67 per 1,000 for smokers of 15 to 24 cigarettes a day, and to 2.76 per 1,000 for smokers of 25 cigarettes or more a day—that is, to approximately forty times the death rate of the non-smokers.

7. For every death attributed to cancer of the lung confirmation of the diagnosis was sought from the certifying doctor and, when necessary, from hospital or consultant. Additional information was obtained in every case. The deaths can thus be divided into those quite firmly established by necropsy, histological evidence, and the like, and those less well established and lacking histological evidence (Table IV). The increased death rate associated with the increase in smoking is found to be just as great with the firmly established cases as it is with the remainder (Table X). The relationship cannot therefore be attributed to a biased attitude in the medical profession in certifying cancer of the lung as the cause of death.

8. Analysis of the deaths from lung cancer separately in each of the first four years of the inquiry shows that the increase in mortality associated with increase in smoking has been a feature of each year. On the whole, there has been a remarkably constant gradient which has become no less marked with the passage of time (Table XI). We also estimate that in the fourth year of the inquiry the mortality of the doctors who answered the questionary was as much as 92% of the mortality of all doctors, whether they answered us or not. On these grounds we do not believe that the gradient of mortality with smoking can be regarded as merely an artifact due to bias in those who chose to reply to the questionary.

9. An analysis of a random sample of the questionaries shows that there was remarkably little difference between the smoking habits of doctors resident (at November 1, 1951) in Greater London, in large towns, or in other districts (Table XII). The contrasts in lung cancer mortality between smokers and non-smokers, and between light, medium, and heavy smokers, cannot therefore be attributed to a differential exposure to atmospheric pollution which happens to be associated with smoking habits. This observation supports those of previous investigations.

10. Study of the deaths from cancer in sites other than the lung reveals, with one possible exception, no association between mortality and smoking. The exception is cancer of the upper respiratory and upper digestive tracts, from which the number of deaths is at present insufficient to substantiate a possible trend. In total,

cancer of sites other than the lung shows a mortality of 2.04 per 1,000 in non-smokers and 2.02 per 1,000 in smokers. It reveals no gradient by amount smoked (Table XIII). In other words, the marked and steadily increasing mortality from lung cancer in association with smoking is not compensated for by a decrease in cancer of other sites. The result indicates a total mortality from cancer in the smoking groups in excess of the mortality that would have prevailed in the absence of smoking.

11. If the causes of death as certified are accepted at their face value, mortality from coronary thrombosis reveals a slight but significant relationship with smoking (Table V). Division by age, however, shows that the trend is distinct only at the youngest ages, 35–54 years (Table XV).

12. Three other causes of death show a steady increase in mortality from non-smokers to heavy smokers—chronic bronchitis, peptic ulcer, and pulmonary tuberculosis (Table XVI). Only with chronic bronchitis is the gradient statistically significant. The remaining causes of mortality reveal no trend (Table XVII).

13. From our retrospective studies of the smoking habits of nearly 1,500 patients with lung cancer and over 3,000 patients with other illnesses we concluded that if large groups of persons of different smoking habits were observed for a number of years they would reveal distinct differences in their rates of mortality from lung cancer. They would show, we believed, (1) a higher mortality in smokers than in non-smokers, (2) a higher mortality in heavy smokers than in light smokers, (3) a higher mortality in cigarette smokers than in pipe smokers, and (4) a higher mortality in those who continued to smoke than in those who gave it up. In each case the expected result has appeared in the prospective inquiry here reported. These results are evident in spite of the fact that our method of inquiry is such as constantly to *underestimate* the mortality differences. The reason for the underestimate is that our classifications are based, for the most part, upon a statement of the smoking habits at one point of time. We have seldom been able to take previous habits into account, and any subsequent changes have been unknown to us. As a result we shall sometimes have included in the light smoking group persons who had previously smoked heavily for a long time; we shall sometimes have included as "pure" pipe smokers persons who had previously smoked cigarettes and vice versa; we shall sometimes have continued to class as smokers persons who have given up. All such errors in classification must inevitably have reduced the, nevertheless, clear associations between the mortality from lung cancer and the smoking of cigarettes which we have observed in these British doctors.

This work was made possible by the co-operation of the thousands of doctors who completed our questionaries. We are most grateful to them and to the many consultants who have provided us with further details of the evidence on which the diagnosis of lung cancer was made. We are deeply indebted to the British Medical Association, who dispatched the questionaries on our behalf and who subsequently helped us in tracing the deaths of doctors; to the Registrars-General of the United Kingdom and the Registrars of the General Medical Council and of its Branch Councils in Ireland and Scotland for information about the deaths of doctors; and to the Statistical Department of the Ministry of Labour for the mechanical analysis of the results. We are grateful to Dr. R. Bignall for advice on the clinical classification of some of the deaths from lung cancer. We also offer our thanks to Mrs. Joan Bodington, Mrs. Jean Gilliland, Miss Keena Jones, and Mrs. M. Lloyd for the onerous work of sorting and analysing the mass of data.

REFERENCES

Armitage, P. (1955). *Biometrics*, **11**, 375.
Berkson, J. (1955). *Proc. Mayo Clin.*, **30**, 319.
Brinton, H. P., Frasier, E. S., and Koven, A. L. (1952). *Publ. Hlth Rep. (Wash.)*, **67**, 835.
Case, R. A. M. (1954). *British Medical Journal*, **2**, 987.
—— and Lea, A. J. (1955). *Brit. J. prev. soc. Med.*, **9**, 62.
Cramer, W. (1934). *Lancet*, **1**, 1.
Doll, R. (1952). *Brit. J. industr. Med.*, **9**, 180.
—— (1955). Ibid., **12**, 81.
—— and Hill, A. B. (1952). *British Medical Journal*, **2**, 1271.
—— —— (1954a). Ibid., **1**, 1451.
—— —— (1954b). Ibid., **2**, 240.
Fairweather, R. F. (1954). Ibid., **2**, 100.
Goodhart, C. B. (1956). Ibid., **1**, 1296.
Hammond, E. C., and Horn, D. (1954). *J. Amer. med. Ass.*, **155**, 1316.
—— —— (1955). Report read to the Annual Meeting of the American Medical Association, June, 1955.
Kreyberg, L. (1955). *Brit. J. Cancer*, **9**, 495.
Lowe, C. R. (1956). *British Medical Journal*, **2**, 1081.
Stocks, P., and Campbell, J. M. (1955). Ibid., **2**, 923.
Wynder, E. L. (1954). *Penn. med. J.*, **57**, 1073.
—— and Graham, E. A. (1950). *J. Amer. med. Ass.*, **143**, 329.

AN ASSOCIATION BETWEEN SMOKING AND RESPIRATORY TUBERCULOSIS

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In England and Wales mortality from respiratory tuberculosis has been falling for at least a century. The rate of decline has not been the same at all ages, however, and in the two sexes the pattern of mortality, which seventy-five years ago was not dissimilar, is now strikingly different (Fig. 1). During the decade 1871–80 mortality for both males and females was highest in early adult life. Seventy years later this is still true for females, but for males death rates in young adult life have fallen so much more rapidly than in middle and late life that maximum mortality now occurs at a much later age.

A number of partial explanations have been offered for this change in the age pattern of mortality, but they do not add up to a very convincing whole, and the sex difference remains an incompletely solved epidemiological

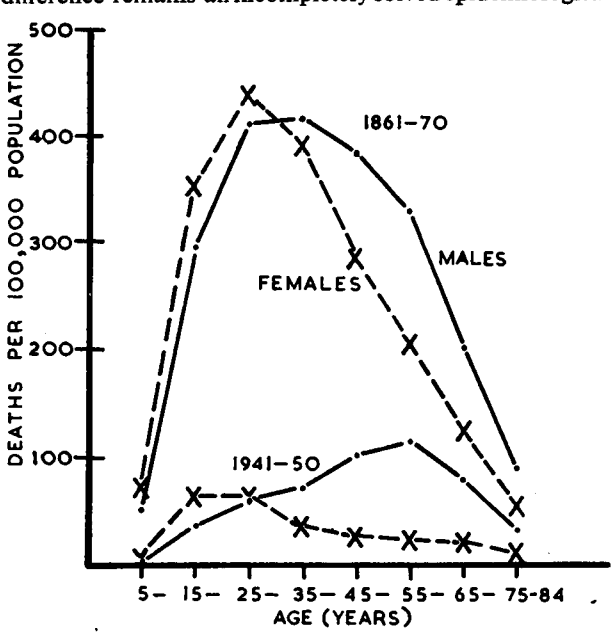

FIG. 1.—Mortality from respiratory tuberculosis in England and Wales (1861–70 and 1941–50 compared).