BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 13 1952

A STUDY OF THE AETIOLOGY OF CARCINOMA OF THE LUNG

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In a previous paper (Doll and Hill, 1950) we reported the first results of a large-scale investigation undertaken to determine whether patients with carcinoma of the lung differed materially from other persons, either in their smoking habits or in some way which might be related to the theory that atmospheric pollution is responsible for the development of the disease. We concluded that smoking is a factor in the production of carcinoma of the lung, and this conclusion was in conformity with the results of some other investigations. Our first observations were, however, limited to patients drawn mainly from London and the adjacent counties. We have now extended the investigation to other parts of the country and have made more detailed inquiries into smoking habits. Many further patients have been interviewed (during January, 1950, to February, 1952) in hospitals in Bristol, Cambridge, Leeds, and Newcastle-upon-Tyne, and also in eight of the twenty London hospitals which co-operated in the first part of the inquiry.

Method of the Investigation

The method of inquiry was described in detail in the previous paper. In brief, we obtained notifications of patients admitted with cancer of the lung, stomach, or large bowel to each co-operating hospital, and these patients were interviewed by almoners, engaged wholly on our research, who recorded the answers to a prearranged questionary. The patients with carcinoma of the stomach or large bowel provided one "control" group, but another, and more important, "control" was obtained by interviewing patients with diseases other than cancer. Each of these latter patients was chosen so as to match a lung-carcinoma patient—namely, of the same sex, within the same five-year age group, and in the same hospital as nearly as possible at the same time.

In the extension of the inquiry this same method has been used, but with modifications. First, notifications were made of patients with lung cancer but no longer of those with cancer of the stomach or large bowel. Secondly, the interviewers could not visit hospitals outside London whenever a suitable patient was admitted; they therefore visited the provincial centres at intervals and interviewed those patients suspected of having lung cancer who were then in the hospitals. At Bristol, Cambridge, and Leeds they also interviewed a few who were attending the outpatient departments.

An important modification was in the choice of the matched control patients. It was impossible to obtain at the provincial centres a group confined, as before, to patients with diseases other than cancer. Our previous analysis, however, had shown that patients with cancer other than lung carcinoma (mainly patients with carcinoma of the stomach or large bowel) gave smoking histories indistinguishable from those given by non-cancer patients; we therefore widened the matched control group to include, with certain exceptions, other forms of cancer. The exceptions which we continued to exclude were cancer of the lip, tongue, mouth, pharynx, nose, larynx, and oesophagus, since it has at times been suggested that cancer of these sites may also bear some relationship to tobacco consumption. We also excluded all other cancers arising inside the chest.

Even then it was still difficult in the provincial centres to find an adequately "matched" control for each lung-carcinoma patient. The provincial hospitals had been chosen so that a large number of lung-cancer patients could be interviewed at each visit. They were therefore thoracic or radiotherapeutic centres serving regions—that is, town and country. We could not seek control patients in the adjacent general hospitals, since these mainly serve the towns they are situated in, and smoking habits vary between town and countryside. On consideration the field of choice was finally extended to other hospitals or units in the same area, but *only* to those serving as regional centres—that is, like the thoracic or radiotherapeutic centres. Thus the cases and their controls should be drawn from equally wide areas of town and country. We have also included in the control series some patients interviewed as having lung cancer but in whom the condition was finally excluded (as at the Brompton and Harefield hospitals in the first part of the investigation). It will be shown that this procedure does not influence the results.

The classification of each patient was, as a general rule, based upon the hospital discharge diagnosis, obtained from a study of the hospital records after the patient's discharge or death. Where that record was indefinite information was obtained from the practitioner or hospital to whose care the patient had been transferred. Occasionally evidence contradicting the hospital discharge diagnosis became available—for ex-

ample, by histological examination at necropsy—and in these cases the diagnosis was based upon the best evidence. Five cases with no record of any final diagnosis have been excluded.

The Data

Between April, 1948, and February, 1952 (the whole period of this investigation), 3,446 cancer patients were notified (lung, stomach, and large bowel). Of these, 156 were aged 75 years or more and were not interviewed, since we limited the inquiry to younger patients who could give more reliable histories of smoking and other personal characteristics. In 82 cases the diagnosis was changed before the almoner paid her visit. Of the remaining 3,208 patients, 85% were interviewed and 498 (15%) were not. The reasons why patients were not interviewed were: already discharged from hospital, 213; too ill, 165; dead, 72; too deaf, 33; unable to speak English clearly, 14; while in one case the interview was abandoned because the patient's replies appeared wholly unreliable. No patient refused to be interviewed. With the lung-cancer group alone the proportion not interviewed was also 15%. We can see no reason why failure to interview all the patients should have biased the results, since it was mainly due to the time that had to elapse between the date of notification and the date of the almoner's visit. Such losses were, of course, few in the provincial centres, since here the almoner was required to interview only those in the hospital at the time of her visit.

The remaining 2,710 patients initially presumed to be suffering from cancer of the lung, stomach, or large bowel and the 1,632 general medical and surgical patients interviewed as matched controls to the lung-carcinoma patients form the subjects of this analysis. Table I gives the numbers in each disease group (final classifications based on the hospital discharge diagnosis, etc., as described above). The 1,488 cases of carcinoma of the lung include 23 for which matched controls had not been interviewed when the investigation ended. Most of our results therefore relate to the 1,465 cases paired with the 1,465 matched controls ("other diseases, A").

Cases diagnosed as carcinoma, or cancer, of the lung or bronchus, pleural endothelioma, and alveolar-cell carcinoma of the lung have been included in the "carcinoma of the lung" group. Classification of the diagnoses according to the recommendation of the International Symposium on the Endemiology of Cancer of the Lung (Council for the International Organizations of Medical Sciences, 1952) gave 70% of the first order of reliability (evidence from biopsy of the primary tumour, from operative, bronchoscopic, or radiographic examination of the primary tumour together with cytological examination of the sputum or biopsy of a secondary tumour, or from necropsy), 29% of the second order of reliability (cytological examination of the sputum alone or operative, bronchoscopic, or radiographic examination without biopsy), and only 1% of the third order of reliability (case history and physical examination alone or death certificate).

The 70 cases classified in Table I as "carcinoma of other special sites" are all other cancers arising inside the chest (for example, sarcoma of lung and cancer of the mediastinum and of the trachea) and those other cancers of the respiratory passages, buccal cavity, and oesophagus for which a possible relationship with smoking has at times been postulated. The 36 cases of "carcinoma of uncertain primary site" include patients with carcinomatosis and some in whom there was doubt whether the lung growth was primary or secondary.

The 1,278 "other diseases, B" include: (1) patients with carcinoma of the stomach or large bowel interviewed in the earlier part of the investigation as a second control group; (2) patients initially interviewed as having carcinoma of the lung, stomach, or large bowel, but later found to have other diseases; and (3) others interviewed as matched controls and not required when the patients with whom they were paired were found not to have carcinoma of the lung.

TABLE I.—*Numbers of Patients Interviewed in Each Disease Group*

Disease Group	No. of Patients Interviewed
Carcinoma of lung	1,488
,, ,, other special sites	70
,, ,, uncertain primary site	36
Other diseases, A (matched controls)	1,465
,, ,, B (other controls)	1,278
Uncertain diagnosis (records untraced)	5
All groups*	4,342

* A further 531 patients were interviewed in rural hospitals, with regard to smoking habits in country areas—see section on estimated risks in town and country.

In Table II the matched patients in the lung-carcinoma and control groups are compared for sex and age distribution, places of interview, places of residence, and, for males, social status. The method of selecting control patients leads automatically to an exact correspondence in sex, age, and places of interview. Differences in social status show no regular trend and are no greater than might be due to chance ($\chi^2=5.28$, n=4, $0.20<P<0.30$). On the other hand, the places of residence reveal considerable differences: fewer of the lung-carcinoma group were residents of Greater London ($\chi^2=17.22$, n=4, $P<0.01$). The meaning of this inequality is considered later (section on place of residence). Since our observations show that the consumption of tobacco tends to be greatest in London the inequality will, if anything, have somewhat reduced the contrasts we find between the groups in their smoking habits. In our previous report, however, we showed that the inequality was unlikely to be of importance.

TABLE II.—*Comparison Between Lung-carcinoma Patients and Matched Control Patients with Other Diseases*

Attribute for Comparison	No. of Lung-carcinoma Patients		No. of Control Patients		Attribute for Comparison	No. of Lung-carcinoma Patients, M and F	No. of Control Patients, M and F
	M	F	M	F			
Age:					Place of interview:		
25– ..	17	3	17	3	Greater London	1,035	1,035
35– ..	116	15	116	15	Bristol ..	73	73
45– ..	493	38	493	38	Cambridge ..	36	36
55– ..	545	34	545	34	Leeds ..	58	58
65–74 ..	186	18	186	18	Newcastle ..	263	263
All ages..	1,357	108	1,357	108	All places ..	1,465	1,465
Social class (Registrar-General's categories):					Place of residence:		
I	39	—	53	—	Greater London	791	900
II	165	—	172	—	Other county boroughs ..	225	181
III	750	—	720	—	Other urban districts ..	275	213
IV	172	—	198	—	Rural districts	155	164
V	231	—	214	—	Abroad ..	19	7
All social classes ..	1,357	—	1,357	—	All places ..	1,465	1,465

Assessment of Smoking Habits

The difficulties of acquiring and assessing accurately a smoking history and the measures taken to overcome them were discussed in our previous paper. It will be sufficient

to repeat here that the patients were asked (*a*) if they had smoked at any period of their lives; (*b*) the ages at which they had started and stopped; (*c*) the amount they were in the habit of smoking before the onset of the illness which had brought them into hospital; (*d*) the main changes in their smoking history and the maximum they had ever been in the habit of smoking; (*e*) the proportions smoked in pipes and cigarettes; and (*f*) whether they inhaled. A test was made of the accuracy of the answers by cross-examining 50 patients again, six months or more after their first interview. While there was, as expected, some variability of reply, we concluded that the data were reliable enough *to indicate general trends and to substantiate material differences between groups.*

Fortunately the difficulties of inquiry have been reduced through the level of taxation remaining almost constant throughout the investigation. National figures show that the total home consumption remained fairly steady—namely, 213.7, 211.5, 213.8, 221.2 million lb. in the four years ending March 31, 1951 (Board of Trade, 1952). (The last major change in the standard rate of duty payable on tobacco was on April 16, 1947, when it rose from 35s. 6d. to 54s. 10d. a lb.; on April 7, 1948, it became 58s. 2d.)

In the latter stages of the inquiry somewhat fuller smoking histories were sought, and the last 557 lung-carcinoma patients (523 men, 34 women) and their matched controls were asked questions on their use of (*a*) different types and brands of tobacco; (*b*) filter-tipped cigarettes; (*c*) cigarette-holders; and (*d*) petrol lighters.

The Amount Smoked

The results of the inquiry provide a number of ways in which the smoking habits of the patients can be categorized and compared. The simplest is the amount smoked immediately before the onset of the illness which brought the patient into hospital. This, however, can be very misleading, since some persons—including heavy smokers—give up smoking periodically, and it would be wrong to classify them as non-smokers merely because they were interviewed during a period of abstention. In Table III, therefore, the comparison is made in a modified form: non-smokers are defined, as in our previous study, as persons who have never consistently smoked as much as one cigarette a day for as long as one year; the smokers are subdivided either according to the amount they were smoking immediately before the onset of their illness or, if they had previously stopped smoking, according to the amount they were smoking before they last gave up. This is described as "the most recent amount smoked."

Table III shows that in both men and women there were fewer non-smokers and considerably more of the heavier

TABLE III.—*Most Recent Amount of Tobacco Smoked Regularly Before the Onset of the Present Illness: Lung-carcinoma Patients and Matched Control Patients with Other Diseases*

Disease Group	No. of Non-smokers	No. Smoking Daily*				
		1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+
Men:						
1,357 lung-carcinoma patients (99·9%)	7 (0·5%)	49 (3·6%)	516 (38·0%)	445 (32·8%)	299 (22·0%)	41 (3·0%)
1,357 control patients with other diseases (100%)	61 (4·5%)	91 (6·7%)	615 (45·3%)	408 (30·1%)	162 (11·9%)	20 (1·5%)
Women:						
108 lung-carcinoma patients (100%)	40 (37·0%)	14 (13·0%)	30 (27·8%)	12 (11·1%)	12 (11·1%)	0
108 control patients with other diseases (100%)	59 (54·6%)	18 (16·7%)	22 (20·4%)	8 (7·4%)	1 (0·9%)	0

Difference between proportions of non-smokers and smokers—Men: $\chi^2=43{\cdot}99$, n=1, $P<0{\cdot}000001$. Women: $\chi^2=6{\cdot}73$, n=1, $P<0{\cdot}01$.
Difference between proportions of smokers smoking different amounts—Men: $\chi^2=69{\cdot}74$, n=4, $P<0{\cdot}000001$. Women: $\chi^2=8{\cdot}99$, n=3, $0{\cdot}02<P<0{\cdot}05$.

* Ounces of tobacco have been expressed as being equivalent to so many cigarettes. There is 1 oz. of tobacco in 26·5 normal-size cigarettes, so that the conversion factor has been taken as: 1 oz. of tobacco a week=4 cigarettes a day.

TABLE IV.—*Most Recent Amount of Tobacco Smoked Regularly Before the Onset of the Present Illness: Lung-carcinoma Patients and Matched Control Patients with Other Diseases, Subdivided by Place and Date of Interview*

Disease Group	Place and Date of Interview	Percentage Non-smokers	Percentage Smoking Daily*				No. Interviewed
			1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+	
Carcinoma of lung (men)	Greater London, 1948–9	0·3	5·1	38·5	30·2	25·9	649
	Greater London, 1950–1	1·0	3·3	38·2	31·4	26·1	306
	Bristol, 1950–1	2·8	0·0	22·5	40·8	33·8	71
	Cambridge, 1951	0·0	0·0	50·0	29·4	20·6	34
	Leeds, 1950–1	0·0	1·9	47·2	34·0	17·0	53
	Newcastle, 1950–1	0·0	2·1	37·3	39·3	21·3	244
	Whole investigation	0·5	3·6	38·0	32·8	25·0	1,357
Control patients with other diseases (men)	Greater London, 1948–9	4·2	8·5	45·1	29·3	12·9	649
	Greater London, 1950–1	4·2	4·9	46·1	28·4	16·3	306
	Bristol, 1950–1	4·2	2·8	49·3	28·2	15·5	71
	Cambridge, 1951	2·9	8·8	52·9	29·4	5·9	34
	Leeds, 1950–1	5·7	7·5	39·6	35·8	11·3	53
	Newcastle, 1950–1	5·3	4·9	43·9	34·0	11·9	244
	Whole investigation	4·5	6·7	45·3	30·1	13·4	1,357
Carcinoma of lung (women)	Greater London, 1948–9	31·7	11·7	31·7	15·0	10·0	60
	Greater London, 1950–1	25·0	15·0	20·0	10·0	30·0	20
	Bristol, 1950–1	(50·0)†	—	(50·0)	—	—	2
	Cambridge, 1951	(50·0)	—	—	(50·0)	—	2
	Leeds, 1950–1	(20·0)	(20·0)	(60·0)	—	—	5
	Newcastle, 1950–1	68·4	15·8	15·8	—	—	19
	Whole investigation	37·0	13·0	27·8	11·1	11·1	108
Control patients with other diseases (women)	Greater London, 1948–9	53·3	20·0	16·7	10·0	0·0	60
	Greater London, 1950–1	55·0	10·0	20·0	10·0	5·0	20
	Bristol, 1950–1	(50·0)	(50·0)	—	—	—	2
	Cambridge, 1951	(50·0)	—	(50·0)	—	—	2
	Leeds, 1950–1	(60·0)	—	(40·0)	—	—	5
	Newcastle, 1950–1	57·9	15·8	26·3	—	—	19
	Whole investigation	54·6	16·7	20·4	7·4	0·9	108

* See footnote to Table III. † The percentages in parentheses are based upon very small numbers and have no reliability.

smokers among the lung-carcinoma patients than among the control patients. Amongst 1,357 men with carcinoma of the lung, only 7, or 0.5%, were non-smokers; there were 61, or 4.5%, among the same number of men with other diseases. At the other end of the scale, 25% of the men with lung carcinoma had smoked 25 or more cigarettes a day (or the equivalent in pipe tobacco); the proportion in the control patients was only 13.4%. Similarly, amongst the 108 women with carcinoma of the lung, 37.0% were non-smokers against 54.6% of the women with other diseases. Among women with carcinoma 11.1% had smoked 25 or more cigarettes a day; among those with other diseases this proportion was 0.9%.

These results are essentially the same as those recorded in our preliminary report. In Greater London, indeed, the results for the two periods 1948–9 and 1950–1 are remarkably alike (see Table IV, where they are set out separately and alongside figures from the provincial centres). Table IV also shows that the contrast between the smoking habits of the men in the two disease groups was observed quite consistently at the provincial centres. In each case the proportions of non-smokers and of men smoking less than five cigarettes a day were *lower*, and the proportion smoking 25 or more cigarettes a day was substantially *higher*, among the lung-carcinoma patients. In women similar results were obtained during the two periods of inquiry in Greater London, while at Bristol, Cambridge, and Leeds the numbers are too small to warrant attention. At Newcastle, however, the smoking habits of the female lung-carcinoma patients did not differ appreciably from those of their matched controls—in fact, the proportion of non-smokers was slightly higher in the lung-carcinoma group. Though the number interviewed was small (19 cases), the divergence from the experience of the lung-cancer groups elsewhere is sufficient to be statistically significant. Adding the provincial centres together gives the following figures for women:

	Non-smokers	Smoking 1–14 Cigs.	Smoking 15+ Cigs.	Total
Lung-carcinoma group ..	16	11	1	28
Control group	16	12	—	28

The presence of only one woman with lung carcinoma who had smoked 15 or more cigarettes a day is not, perhaps, surprising; it seems that very few women in the provinces smoke so much. Of all the 58 women interviewed at provincial centres, and who suffered from "other diseases" (other than lung carcinoma, carcinoma of other sites possibly related to tobacco, and carcinoma of uncertain primary site) none gave a history of smoking 15 or more cigarettes a day. In contrast, this amount was smoked by nearly 8% of 553 similar women with all other diseases interviewed in Greater London. There is, however, an absence in the provinces of any difference between the two groups in the numbers of non-smokers and of women smoking fewer than 15 cigarettes a day.

The "most recent amount smoked" will not necessarily give the best representation of a smoking history, even though defined, as here, to include the amount smoked by ex-smokers at the time they last gave up. Its advantage as a criterion is that the information is easily obtained and likely to be reasonably accurate. Its disadvantage is that smoking habits vary over a lifetime, sometimes considerably, and previous habits, which may be relevant, are being ignored. We have therefore calculated other quantitative estimates of the amount smoked as revealed in the patient's history. These are (*a*) the amount smoked immediately before the patient's illness, (*b*) the maximum amount ever smoked regularly, (*c*) the total amount smoked since smoking was begun, and (*d*) the average amount smoked daily over the 10 years preceding the patient's illness, over the penultimate 10 years, and over the whole of the patient's life since the age of 15, taking into account recorded changes during these periods.

Qualitatively similar results are obtained whichever of these estimates is used. The sharpest differentiation between the lung-carcinoma and control patients, for both men and women, appears to be given by the average daily amount smoked over the 10 years preceding the patient's illness. The results of this calculation are shown in Table V and differences between the groups of patients—particularly in the women—are more pronounced than those in Table III.

For men, the amount smoked immediately before the patient's illness is equally good, but the estimates of the total amount consumed throughout life, the average daily amount since the age of 15, and the average daily amount over the penultimate 10 years give differences only of the same order as those shown by "the most recent amount smoked"; the maximum daily amount ever smoked differentiates the groups less clearly. For women, all the estimates except the amount smoked immediately before the patient's illness are more discriminating than "the most recent amount smoked," though the maximum daily amount ever smoked gives only a slightly increased divergence between the two groups.

In view of these results with varying measures of the smoking history we have used in subsequent tables *the average amount smoked daily over the 10 years preceding the patient's illness* as the most appropriate criterion. A whole life history should perhaps be a truer measure of the "exposure to risk," but, as we pointed out in our previous paper, too much inaccuracy may result from requiring the patient to remember habits of many years past.

The Duration of Smoking

Comparisons of the ages at which the patients reported that they began to smoke, the number of years they had smoked, and, when appropriate, the number of years since they last gave up are shown in Table VI.

The lung-carcinoma patients are seen, on the average, to have begun smoking rather earlier, to have continued longer, and to have been rather less inclined to stop. In men, these differences are all statistically significant. In women they are not significant, but they are in the same direction, and no less distinct, so that it is reasonable to accept them as real.

The most pronounced difference appears in the number of years since smoking had last been given up. Since the control group contained more light smokers (Table III) the higher proportion of ex-smokers in it here seen might, it was thought, be due to the fact that it is light smokers who more readily give up. In fact, the opposite appeared to be true. Of the 124 male control patients who had given up smoking nearly one-third (31.5%) were smoking 25 or more cigarettes a day when they gave up; of those who continued to smoke, only 12.2% consumed as much.

TABLE V.—*Average Amount of Tobacco Smoked Daily Over the 10 Years Preceding the Onset of the Present Illness; Lung-carcinoma Patients and Matched Control Patients with Other Diseases*

Disease Group	No. of Non-smokers	No. Smoking Daily Average* of				
		Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+
Men:						
1,357 lung-carcinoma patients (99·9%) ..	7 (0·5%)	55 (4·0%)	489 (36·0%)	475 (35·0%)	293 (21·6%)	38 (2·8%)
1,357 control patients with other diseases (100%)	61 (4·5%)	129 (9·5%)	570 (42·0%)	431 (31·8%)	154 (11·3%)	12 (0·9%)
Women:						
108 lung-carcinoma patients (100%)	40 (37·0%)	16 (14·8%)	24 (22·2%)	14 (13·0%)	14 (13·0%)	0
108 control patients with other diseases (100%) ..	59 (54·6%)	25 (23·1%)	18 (16·7%)	6 (5·6%)	0 (0·0%)	0

Difference between proportions of smokers smoking different amounts—Men: $\chi^2=93·77$, n=4, P<0·000001. Women: $\chi^2=17·41$, n=3, P<0·001.
* Ounces of tobacco have been expressed as being equivalent to so many cigarettes. There is 1 oz. of tobacco in 26·5 normal-size cigarettes, so that the conversion factor has been taken as: 1 oz. of tobacco a week = 4 cigarettes a day.

TABLE VI.—*Age at Starting to Smoke, Number of Years Smoked, and Number of Years Since Smoking was Given Up, Lung-carcinoma Patients and Matched Control Patients*

Sex	Age at Starting	Lung-carcinoma Patients		Control Patients		No. of Years Smoking	Lung-carcinoma Patients		Control Patients		No. of Years Given Up	Lung-carcinoma Patients		Control Patients	
		No.	%	No.	%		No.	%	No.	%		No.	%	No.	%
Men	Under 20	1,077	79·8	992	76·5	1–	12	3·4	15	6·2	0–	1,280	94·8	1,172	90·4
	20–	251	18·6	264	20·4	10–	34		65		1–	56	4·1	75	5·8
	30–	18	1·6	33	3·1	20–	746	55·3	725	55·9	10–	6	1·0	26	3·8
	40+	4		7		40+	558	41·3	491	37·9	20+	8		23	
	All ages	1,350	100·0	1,296	100·0	All periods	1,350	100·0	1,296	100·0	All periods	1,350	99·9	1,296	100·0
	$\chi^2=7·95$; n=2; 0·01<P<0·02					$\chi^2=12·66$; n=2; P<0·01					$\chi^2=25·87$; n=2; P<0·001				
Women	Under 20	20	29·4	12	24·5	1–	14	38·2	18	53·1	0–	58	85·3	41	83·7
	20–	23	33·8	15	30·6	10–	12		8		1–	9	13·2	6	12·2
	30–	10	36·8	7	44·9	20–	36	52·9	20	40·8	10–	0	1·5	0	4·1
	40+	15		15		40+	6	8·8	3	6·1	20+	1		2	
	All ages	68	100·0	49	100·0	All periods	68	99·9	49	100·0	All periods	68	100·0	49	100·0

The Method of Smoking

So far the only distinction we have drawn between smokers is in the *quantity* of tobacco consumed. There are, however, qualitative differences which might be important—namely, whether the smoker inhales, smokes a pipe, uses a cigarette holder, smokes filter-tipped cigarettes, rolls his own cigarettes, or lights his tobacco with matches or a petrol lighter.

Inhaling.—All the smokers and ex-smokers were asked whether they inhaled (with the exception of three lung-carcinoma and two control patients, in whom the question was inadvertently omitted). Of 1,415 lung-carcinoma patients (men and women), 64.6% said yes and 35.4% said no; of the 1,343 control patients with other diseases, 66.6% said yes and 33.4% said no. The differences are negligible. Similar results were obtained for men and women considered separately. (Further consideration is paid to inhaling in the section dealing with site of tumour.)

Cigarettes and Pipes.—Some persons usually smoke cigarettes, others usually smoke a pipe. Habits, however, do not remain constant, and it has been necessary to divide male smokers into three broad categories: (*a*) those who have never smoked a pipe regularly for as long as one year ("pure cigarette-smokers"); (*b*) those who have smoked cigarettes and a pipe; and (*c*) those who have never smoked cigarettes regularly for as long as one year ("pure pipe-smokers"). Among the 1,350 male lung-carcinoma patients who smoked, 3.9% were pure pipe-smokers and 74.4% were pure cigarette-smokers; among the 1,296 male control patients who smoked the corresponding proportions were 6.9% and 69.4%. The differences, though not striking, are statistically highly significant (χ^2 for the three groups, pure pipe, mixed, pure cigarette=15.85; n=2, P<0.001). It would appear that pipe-smoking is less closely associated with the development of lung carcinoma than cigarette-smoking. Pipe-smokers, however, consume, on the average, less tobacco than cigarette-smokers, and this must account for some of the relative deficiency of pipe-smokers in the lung-carcinoma group. It does not seem that it can account for the whole difference, since the proportion of pure pipe-smokers is somewhat lower at each level of tobacco consumption. The relevant figures are as follows:

	Percentage of Pure Pipe-smokers among all Smokers at Each Average Daily Consumption Level (Measured in Terms of Cigarettes)			
	Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.+
Male lung-carcinoma patients	9·1%	7·2%	1·3%	2·1%
Male control patients with other diseases	10·9%	10·5%	3·5%	2·4%

On the other hand, studying the pure pipe-smokers alone we find that 9.4% of those with lung-carcinoma smoked the equivalent of less than five cigarettes a day and 13.2% smoked the equivalent of 25 or more a day; in the control group the proportions were 15.1% and 4.3%. In other words, a higher proportion of the pure pipe-smokers with carcinoma of the lung fall into the higher smoking categories—as with the cigarette-smokers.

We conclude, as in our earlier report, that the method of smoking is of importance and that smoking a pipe, though also related to carcinoma of the lung, appears to carry a smaller risk than smoking cigarettes (see also section on estimated risks).

Cigarette-holders.—A possible explanation of this lower risk of pipe-smoking is that the pipe-stem acts as a partial filter of a carcinogenic agent. If that were so, we might expect that fewer of the patients with carcinoma of the lung had used cigarette-holders. We sought information on this point in the latter stages of the inquiry—from the last 523 pairs of male lung-carcinoma and control patients to be interviewed. Judged by the proportions of non-smokers and pure pipe-smokers in the two groups, these last patients seem to be a representative sample of the total. Table VII shows results obtained from them. Few

TABLE VII.—*Use of Cigarette-holders: Male Lung-carcinoma and Matched Control Patients. (Information Obtained During the Last Part of the Investigation Only)*

Disease Group	Non-smokers	Never Smoked Cigarettes	Cigarette-smokers. Holders Used			Total Cigarette-smokers
			Never	Occasionally	Regularly	
523 lung-carcinoma patients	4	15	479	15	10	504
523 control patients	26	30	413	27	27	467

patients had ever used holders, but the proportion of cigarette-smokers who had done so was significantly smaller in the group with carcinoma of the lung (5%) than in the control patients (12%) ($\chi^2=14.74$, n=2, P<0.001).

This difference might merely be due to an association between using a holder and light smoking, but the available evidence suggests not. Among the 54 cigarette-smokers in the control group who had used holders five (9%) smoked an average of fewer than 15 cigarettes a day and six (11%) smoked an average of 25 or more; the corresponding figures for the 413 cigarette-smokers who had not used holders were 32 (8%) and 55 (13%). Further evidence that an association with light smoking cannot account for the relative deficiency of users of cigarette-

holders in the lung-carcinoma group is the finding that the proportion who had used holders was lower at each level of tobacco consumption—namely:

	Percentage of Cigarette-smokers who had ever used Holders at Each Average Daily Consumption Level			
	Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.+
Male lung-carcinoma patients who smoked cigarettes	5·9%	4·0%	6·0%	4·5%
Male control patients with other diseases who smoked cigarettes	13·5%	12·6%	10·4%	9·8%

Types of Cigarettes.—Cigarette-smokers were asked whether they bought manufactured cigarettes or bought tobacco and rolled their own. Of the 1,297 male lung-carcinoma 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%. Evidently there is no specific association of manufactured, as opposed to hand-rolled, cigarettes and carcinoma of the lung. It can also be concluded that the different risks associated with cigarette- and pipe-smoking are unlikely to be the result of the different types of tobacco consumed, as a number of men who roll their cigarettes use pipe tobacco.

In view of the presence of arsenic in American tobacco and its almost complete absence from Oriental tobacco (Daff and Kennaway, 1950) it was clearly of interest to determine whether there was any difference in the proportions of American and "Turkish" tobacco smokers in the lung-carcinoma and control groups. The results of such inquiry were inconclusive because nearly all smokers had habitually smoked "Virginian." In fact, only one smoker was found who had never regularly smoked it (a man of 70, under treatment for an enlarged prostate). Of the 504 male lung-carcinoma patients who had smoked cigarettes only 3.8% said that they had, at some period, regularly smoked Turkish tobacco; among the 467 control patients the figure was 4.5%. The difference is statistically insignificant.

During the last part of the investigation inquiries were also made about the brands of cigarettes smoked and the use of filter-tipped cigarettes. The results (Table VIII) show that none of the four main brands recorded was more closely associated with carcinoma of the lung than another. The proportions are remarkably similar in the two groups of patients. On the other hand, very few of the men with lung carcinoma had ever regularly used filter-tipped cigarettes

TABLE VIII.—*Brands of Cigarettes Smoked and Use of Filter-tipped Cigarettes: Male Lung-carcinoma and Matched Control Patients. (Information Obtained During the Last Part of the Investigation Only)*

Type of Smoker	Lung-carcinoma Patients	Control Patients
Cigarette-smokers, smoking manufactured cigarettes—		
Brand mainly smoked:		
Brand A	72 (18·2%)	70 (19·4%)
,, B	11 (2·8%)	14 (3·9%)
,, C	123 (31·1%)	107 (29·6%)
,, D	21 (5·3%)	15 (4·2%)
Other brands	36 (9·0%)	39 (10·8%)
Mixed ,, ...	133 (33·6%)	116 (32·1%)
All brands	396 (100·0%)	361 (100·0%)
Brand not stated (present smokers of hand-rolled cigarettes or pipes) ..	108	106
All cigarette-smokers ..	504	467
Cigarette-smokers, filter-tipped cigarettes:		
Ever smoked regularly*	3	15
Never ,, ,, ...	501	452
All cigarette-smokers ..	504	467

* For one or more years.

—3 in 504 compared with 15 in the 467 controls. The difference is significant ($\chi^2=7.74$, n=1, P<0.01), but with so few observations the conclusions to be drawn must be highly speculative. The explanation may be that filter-tipped cigarettes are smoked predominantly by light smokers, but we have insufficient data to test that possibility.

Use of Petrol Lighters.—In the two groups of 523 male patients last interviewed inquiry was made into the use of petrol lighters. Of the 504 male patients with carcinoma of the lung who smoked cigarettes, 42.9% reported that at some period they had regularly used petrol lighters; of the 468 similar control patients, the proportion was 41.3%. The difference is negligible, and the evidence is against the hypothesis—often put forward—that petrol lighters are the responsible carcinogenic agent.

Use of Tobacco for Chewing and as Snuff.—Although extraneous substances will be brought into contact with the bronchial mucosa more readily by smoking than by chewing or by snuff, it is possible that particles of tobacco are inspired into the bronchial tree by these latter means and that these uncombusted particles are carcinogenic. The possibility is suggested by the frequent occurrence of cancer of the buccal cavity in Eastern countries where the inhabitants have the habit of chewing quids of tobacco mixed with flavouring agents.

Questions about chewing tobacco and the use of snuff were asked of 1,209 male patients with lung carcinoma and of the 1,209 corresponding control patients.* The results show (Table IX) that fewer patients with lung carcinoma

TABLE IX.—*Use of Tobacco for Chewing and as Snuff: Male Lung-carcinoma and Matched Control Patients. (Information Obtained During Part of the Investigation Only)*

Disease Group	Tobacco Never Chewed	Tobacco Chewed				Total who had Chewed Tobacco
		Occasionally		Regularly		
		Less than 10 Yrs.	10 Yrs.+	Less than 10 Yrs.	10 Yrs.+	
1,209 lung-carcinoma patients..	1,169	8	4	11	17	40
1,209 control patients ..	1,145	6	9	17	32	64
	Tobacco Never Taken as Snuff	Tobacco Taken as Snuff				Total who had Taken Tobacco as Snuff
1,209 lung-carcinoma patients..	1,176	8	7	10	8	33
1,209 control patients ..	1,166	11	5	16	11	43

Significance tests of differences between lung-carcinoma and control patients:
Chewing: $\chi^2=5·79$, n=1, $0·01<P<0·02$.
Snuff-taking: $\chi^2=1·36$, n=1, $0·20<P<0·30$.

had chewed tobacco (40, or 3.3%, against 64, or 5.3%) and slightly fewer had ever taken snuff (33, or 2.7%, against 43, or 3.6%); the differences are small though statistically significant for chewing. That this latter difference is likely to be real is borne out by the fact that it is more marked for those who had chewed regularly (28 to 49) than for those who had done so occasionally (12 to 15), and most marked for those who had chewed regularly for more than 10 years (17 to 32). The number of patients who were still in the habit of chewing was too small for it to be possible to assess the amount they smoked in comparison with others. It may be that there were fewer lung-carcinoma patients who had chewed tobacco because men who chew will smoke less.

*After the completion of the first part of the investigation these questions were temporarily omitted from the questionary, and 148 male patients with lung carcinoma interviewed outside London and their corresponding control patients were not asked whether they chewed tobacco or used snuff.

Nature of the Carcinoma in Relation to Smoking

Histological Type

According to Wynder and Graham (1950), adenocarcinoma of the lung is less closely related to smoking than the other histological types of lung carcinoma. Primary adenocarcinoma of the lung is an uncommon condition, but of particular interest, in relation to smoking, in that it has invariably been reported as being relatively commoner in women than in men. In the present series, all patients with a histologically confirmed diagnosis (approximately 70% in each sex) have been divided according to type, with the following results:

	Histological Type				
	Epidermoid	Oat-cell or Anaplastic	Adeno-carcinoma	Unclassified	No Histological Confirmation
1,357 men ..	475 (52%)	303 (33%)	33 (4%)	105 (11%)	441
108 women	18 (23%)	38 (48%)	10 (13%)	13 (16%)	29

In Table X the numbers of men and women smoking different amounts of tobacco are shown separately for each histological type of growth and are compared with the numbers expected from the experience of all male and all female patients in whom the diagnosis was confirmed histologically. There is no statistically significant difference between the amounts smoked by patients in the different histological groups in either sex. The number of proved cases of adenocarcinoma is, however, too small (43) to conclude that no difference exists. There were, in fact, relatively more non-smokers and very light smokers (average consumption less than five cigarettes a day) among the patients with adenocarcinoma in both sexes, and it is possible that larger numbers would have supported Wynder and Graham's findings.

Table X also shows that it is not possible to detect any difference, in amount smoked, between the cases diagnosed clinically and those in whom the diagnoses were histologically confirmed. This result suggests that the "clinical" diagnoses were generally accurate—which is not surprising, since they were based on findings at thoracotomy or at necropsy in 93 (19.8%), on direct observation of the tumour bronchoscopically in a further 96 (20.4%), while in many of the remainder bronchoscopic examination suggested the presence of a carcinoma though no tumour was seen.

Site of Tumour

The site of origin of a tumour within the lung may be of interest, since it is possible that aetiological agents might reach the main bronchi but not the bronchioles and alveoli. In the present series 1,154 (90.4%) were considered to have arisen centrally and 122 (9.6%) peripherally (in 189 it was not possible to decide).

Analysis of the smoking habits of the patients in these two groups reveals no difference between them in the amounts smoked but a slight difference in the prevalence of inhaling. (See Table XI. The comparison here does not allow for differences in age distribution of the patients with central and peripheral growths, but these differences are small and do not materially affect the results.) It will be seen that a slightly higher proportion of the males with peripheral growths inhaled regularly (62.6%) compared with

TABLE X.—*Average Amount of Tobacco Smoked Daily Over the 10 Years Preceding the Onset of the Present Illness, Divided According to Histological Type: Lung-carcinoma Patients*

Histological Type	No. of Non-smokers	Average Amount Smoked Daily over 10 Years. Number Smoking:			
		Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.+
A			*Men*		
Epidermoid carcinoma (475)	1 (2·4)*	14 (19·3)	169 (166·9)	175 (172·4)	116 (114·1)
Oat-cell or anaplastic carcinoma (303)	2 (1·8)	12 (11·2)	110 (106·7)	105 (111·4)	74 (72·0)
Adenocarcinoma (33)	2 (0·2)	2 (0·9)	7 (11·5)	16 (12·3)	6 (8·2)
Type unclassified (105)	0 (0·6)	8 (4·7)	36 (37·0)	38 (38·0)	23 (24·8)
B					
Histological evidence obtained (916) ..	5 (4·9)	36 (34·5)	322 (328·5)	334 (322·4)	219 (225·8)
No histological evidence (441)	2 (2·1)	19 (20·5)	167 (160·5)	141 (152·6)	112 (105·2)
C			*Women*		
Epidermoid carcinoma (18)	11 (8·6)	1 (1·9)	4 (4·3)	1 (1·6)	1 (1·6)
Oat-cell or anaplastic carcinoma (38) ..	12 (11·2)	6 (5·1)	9 (10·0)	7 (7·4)	4 (4·3)
Adenocarcinoma (10)	5 (3·8)	2 (1·2)	1 (2·7)	0 (1·4)	2 (1·0)
Type unclassified (13)	1 (5·5)	2 (1·8)	5 (3·0)	4 (1·6)	1 (1·1)
D					
Histological evidence obtained (79) ..	29 (28·7)	10 (11·1)	20 (18·4)	12 (10·9)	8 (10·1)
No histological evidence (29)	11 (11·3)	5 (3·9)	5 (6·6)	2 (3·2)	6 (4·0)

* The figures in parentheses are the numbers that would have occurred if the patients in the histological group in question had had, at each age, exactly the same smoking habits as all the patients with which the group is being compared. That is, in part A of the table, all male patients with histological evidence of the growth; in part B, all male patients; in part C, all female patients with histological evidence of the growth; in part D, all female patients.

TABLE XI.—*Prevalence of Inhaling: Patients with Carcinoma of the Lung Arising Centrally and Peripherally and Corresponding Matched Control Patients*

Disease Group	No. of Smokers Inhaling			Total No. of Smokers	No. of Non-smokers
	Regularly	Occasionally	Never		
Male lung-carcinoma patients with:					
1,070 central growths	558 (52·4%)	126 (11·8%)	380 (35·7%)	1,064 (99·9%)	6
116 peripheral growths	72 (62·6%)	13 (11·3%)	30 (26·1%)	115 (100%)	1
Male control patients corresponding to lung-carcinoma patients with:					
1,070 central growths	583 (57·1%)	116 (11·4%)	322 (31·5%)	1,021 (100%)	49
116 peripheral growths	63 (53·3%)	12 (10·5%)	39 (34·2%)	114 (100%)	2
Female lung-carcinoma patients with:					
84 central growths	24	6	17	47	37
6 peripheral growths	1	1	3	5	1
Female control patients corresponding to lung-carcinoma patients with:					
84 central growths	14	5	20	39	45
6 peripheral growths	0	0	1	1	5

Significance tests. Prevalence of inhaling (regular plus occasional):
Male lung-carcinoma patients, central compared with peripheral growths: $\chi^2=4{\cdot}24$, $n=1$, $0{\cdot}02<P<0{\cdot}05$.
Male patients, patients with central growths compared with corresponding controls: $\chi^2=4{\cdot}07$, $n=1$, $0{\cdot}02<P<0{\cdot}05$
Male patients, patients with peripheral growths compared with corresponding controls: $\chi^2=1{\cdot}79$, $n=1$, $0{\cdot}10<P<0{\cdot}20$.

the men with central growths (52.4%)—a statistically significant difference (0.05 level). The patients in each group can also be compared with their own matched controls. It is then found that the males with central growths include rather fewer regular inhalers than their controls (52.4 to 57.1%), while the group with peripheral growths contain rather more (62.6 to 53.3%). The difference is statistically significant in the former case but not in the latter, where the observations are too few to eliminate chance as an explanation. With the women the numbers are too small to warrant consideration.

Estimated Risks

Amount of Smoking

To measure approximately the relative risks associated with different levels of smoking we need to know (*a*) the number of people smoking different amounts of tobacco in each age group—that is, the numbers "at risk"—and (*b*) the number of people smoking different amounts in each age group who died from carcinoma of the lung. It would then be possible, because of the very high fatality of the disease, to equate the calculated death rates to the risks of developing it.

The present investigation cannot provide estimates of these figures for the whole country, since the patients interviewed were drawn mainly from Greater London, and smoking habits and the lung-cancer death rate both vary between countryside and town. For example, in 1949 the report of the Registrar-General shows that the recorded death rates from lung cancer in men were 597, 521, 398, and 292 per million in, respectively, Greater London, county boroughs outside Greater London, other urban districts, and rural districts.

For the Greater London area alone we may, however, proceed on three assumptions—namely, (*a*) that the smoking habits reported by the control patients without carcinoma of the lung who lived in Greater London at the time of their interview are, at each age and in each sex, typical of the inhabitants of Greater London generally; (*b*) that the smoking habits reported by the patients with carcinoma of the lung, also living in Greater London at the time of their interview, are typical of the inhabitants who died of the disease during the period of the survey; and (*c*) that the deaths attributed by the Registrar-General to lung cancer both in men and in women provide a reasonable estimate of the actual numbers of deaths due to carcinoma of the lung. On these assumptions, which are bold but, we think, not wholly unreasonable, we can calculate, for the one region, death rates for each level of tobacco consumption.

The population of Greater London given by the Registrar-General for June 30, 1950, has been taken as the population at risk. The numbers of persons within this population smoking different amounts of tobacco have been estimated from the data for each sex and for each of the age groups 25–44, 45–64, and 65–74.

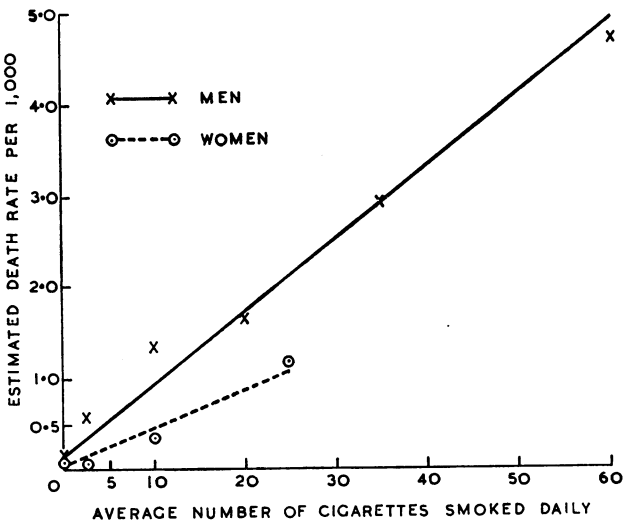
Thus at ages 45–64 we had 932 male patients resident in Greater London with diseases other than lung carcinoma; 4.1% were non-smokers, 9.3% had smoked an average over the preceding 10 years of fewer than five cigarettes (or their equivalent) a day, 42.6% an average of 5–14 a day, 29.9% an average of 15–24 a day, 12.8% an average of 25–49 a day, and 1.3% an average of 50 or more a day. The male population of Greater London at ages 45–64 was 937,000, and this population has been given the above proportions of non-smokers and smokers of different amounts. (In making these estimates we ignore the lung-carcinoma patients in the total population, but their proportion is too small to make any material difference.) In the same way the numbers of persons of each sex and age dying from lung cancers in Greater London in 1950 have been divided up on the basis of the smoking habits of the lung-carcinoma patients who were interviewed.

The death rates thus obtained (Table XII) increase with both age and amount smoked. They pass from a negligible figure for male non-smokers aged 25–44 to a level of the order of 1 in 100 per year among men aged 65–74 who have smoked an average of 25 cigarettes or more a day for the preceding 10 years. The greatest number of our subjects were aged 45–64, and the rates for this group should therefore be the most reliable. In the Chart these are shown graphically against the amounts smoked. It appears, on the assumptions made, that the death rate increases in approximately simple proportion with the amount smoked. Among women the death rate seems to rise more slowly, but the numbers are smaller and considerably less reliable.

TABLE XII.—*Estimated Annual Death Rates from Lung Cancer per 1,000 Men and per 1,000 Women Living in Greater London; by Age Group and Average Amount of Tobacco Smoked Daily in Preceding 10 Years**

Sex and Age	Annual Death Rate per 1,000 Persons						No. of Lung-carcinoma Patients Interviewed
	Non-smokers	Average Amount Smoked Daily in Preceding Ten Years					
		Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+	
Men							
25– ..	*0·00*†	*0·03*	0·13	0·12	0·17	*0·52*	61
45– ..	*0·14*	0·59	1·35	1·67	2·95	4·74	539
65–74 ..	*0·00*	2·38	2·66	3·88	6·95	*10·24*	130
Women							
25– ..	*0·006*	*0·04*	*0·03*	*0·13*		—	9
65– ..	0·09	*0·06*	0·34	1·19		—	39
45–74 ..	0·32	*0·70*	*0·59*	*2·37*		—	13

* The reasons for the adoption of this measure of smoking habits is explained in the text (see section on amount smoked).
† Rates based on observation of fewer than five cases of carcinoma of the lung are given in italics.



Estimated annual death rates from lung cancer in Greater London for men and for women aged 45–64, in relation to the average amount of tobacco smoked daily (measured in terms of cigarettes) in the preceding 10 years.

Cigarettes or Pipe

On the same assumptions, that our data are representative of Greater London, it is also possible to estimate mortality rates for each type of smoker—that is, cigarettes only, cigarettes and pipe, pipe only. As previously shown, the pure pipe-smokers are few and we can therefore calculate rates only for the one broad age group 45–74. The results are:

	Estimated Annual Mortality Rates from Lung Cancer per 1,000 Men Aged 45–74. Average Amount Smoked Daily for Preceding 10 Years in Terms of Cigarettes*				
	Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+
Pure cigarette-smokers ..	1·11	1·71	2·16	3·50	7·37
Smokers of cigarettes and pipe	0·87	1·67	1·98	3·35	*2·24*†
Pure pipe-smokers	*0·95*†	1·35	*0·79*†	*2·08*†	—
All smokers ..	1·04	1·66	2·05	3·42	5·42

* See footnote to Table III. † Based on fewer than 5 cases.

At each smoking level the estimated death rate of pipe-smokers is less than that of cigarette-smokers, and the difference increases with heavier smoking. In three of the four groups the death rate of those smoking cigarettes and pipe is intermediate. With the amount of data at our disposal and the assumptions made in calculating these rates we would be reluctant to draw any precise conclusion on the relative level of the risks. But it certainly appears that the risks are less in pipe-smokers than in cigarette-smokers, and perhaps to the greatest extent in the heavier-smoking categories.

Town and Country

There seem to be differences in smoking habits between townsmen and countrymen (briefly referred to above), and our data may be used to see whether they can wholly, or partially, account for the reported different mortality rates from carcinoma of the lung—though they are insufficient to give more than an approximate answer. The patients interviewed in this inquiry lived in different parts of the country. Grouping them according to place of residence, we can roughly estimate the smoking habits of persons living in Greater London, county boroughs, urban districts, and rural districts. There were, however, relatively few patients living in the country, and a special survey was therefore made (in February, 1950) of the smoking habits of 531 other patients, aged 25–74, admitted to hospitals in rural areas of Dorset and Wiltshire.

To facilitate comparisons the male inhabitants of England and Wales between the ages of 25 and 74 have been taken as a standard population, and the smoking habits in this population have been estimated from the incidence rates of smoking actually observed in the age groups in each of the four areas (Table XIII). It appears that as the place of residence becomes more highly urbanized the proportion of non-smokers and of pure pipe-smokers decreases and the proportion of heavier smokers and pure cigarette-smokers increases. Thus the changes are in the direction which would lead to a higher death rate from carcinoma of the lung in the towns. Whether they can account for the observed differences in mortality is difficult to say. On the assumption that the estimated death rates of Table XII should prevail equally in all areas, it would seem that the recorded differences in mortality between town and country are greater than could be attributed wholly to the differences in smoking habits. In other words, the differences in smoking habits shown in Table XIII are not sufficient to lead to a rural mortality rate which is only about half that of the large towns.

TABLE XIII.—*Smoking Habits of Male Patients Living in Different Parts of the Country; Divided According to Density of Population. (Standardized to age distribution of population of England and Wales, aged 25–74)*

Area of Residence	Percentage of Non-smokers	Percentage Smoking Daily Average of				Percentage of			No. of Patients Interviewed
		Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.+	Pure Cigarette-smokers	Cigarette and Pipe-smokers	Pure Pipe-smokers	
Greater London ..	5·1	8·3	38·3	33·7	14·6	74·2	16·0	4·8	1,393
County borough ..	6·8	6·6	42·7	34·0	9·9	66·3	22·8	4·1	240
Other urban district ..	8·4	13·3	37·1	32·3	8·9	59·9	23·9	7·8	439
Rural district	10·4	13·7	40·8	27·6	7·7	58·4	21·5	9·8	327

Other Aetiological Factors

The inquiry here reported was designed to throw light on any aetiological agent in carcinoma of the lung—for example, on substances which pollute the atmosphere. The questions on smoking were merely one facet of the investigation. We now turn to other aspects.

Occupation and Social Class

Occupational histories were taken from all patients, but these reveal no gross association between any type of occupation and lung carcinoma which might indicate an aetiological agent of general significance—for example, persons occupationally exposed to motor fumes or road dust do not appear more frequently in the lung-carcinoma group. The results will be published in full later.

Social class has already been considered (Table II); it showed no significant difference between the male patients with lung carcinoma and their controls. This observation is in keeping with the Registrar-General's 1930–2 decennial supplement on occupational mortality, though in the present inquiry the lack of association may be overemphasized from the fact that our control patients were usually, and deliberately, taken from the same hospitals as the patients with carcinoma of the lung. This designed equality in some respects may give an overestimated equality in social class.

Place of Residence

The Registrar-General's evidence that cancer of the lung is more frequent in the large towns than in the smaller towns and countryside suggests that a higher proportion of our lung-carcinoma patients would be expected to have been living in Greater London and the county boroughs. In fact, as shown in Table II, this was not the case. If, however, the patients' places of residence are analysed separately, for those interviewed in Greater London and those interviewed in the provinces, a different picture is obtained (Table XIV).

Of patients interviewed in Greater London, fewer with lung carcinoma lived there (76%) compared with the controls (87%); more lived in each of the other types of area. Of patients interviewed in the provinces, more with lung carcinoma lived in the county boroughs (45% against 38%) and fewer lived in rural districts (22% against 28%).

The differences in Greater London can reasonably be explained on the grounds that patients with cancer living outside London tend, more than patients with other diseases, to come to London for treatment. In the provinces, however, the control patients with other diseases were interviewed in hospitals which were deliberately chosen because, like the thoracic units, they also served as regional centres. Consequently there should not be on demographic grounds any deficiency among them of patients living in the smaller towns or in the countryside. It would be reasonable to suspect that any difference between the places of residence

TABLE XIV.—*Place of Residence: Lung-carcinoma and Matched Control Patients, Subdivided by Place of Interview*

Place of Residence	Place of Interview			
	Greater London		Provinces	
	Lung-carcinoma Patients	Control Patients	Lung-carcinoma Patients	Control Patients
Greater London	791	900	0	0
Other county boroughs ..	31	16	194	165
Other urban districts ..	133	71	142	142
Rural districts	62	42	93	122
Abroad	18	6	1	1
All places	1,035	1,035	430	430

Difference between places of residence:
Patients interviewed in Greater London: $\chi^2=40{\cdot}50$, n=4, $P<0{\cdot}001$.
Patients interviewed in provinces (excluding patients residing abroad): $\chi^2=6{\cdot}25$, n=2, $0{\cdot}02<P<0{\cdot}05$.

of patients in the lung-carcinoma and control groups would reflect differences in the relative incidence of the conditions in the different areas. The observation in the provinces that a smaller proportion of the lung-carcinoma than of the control patients lived in the country supports, therefore, the contention that lung carcinoma is less common in rural than in urban areas.

Evidence can also be obtained by comparing, for patients living in a given type of area at the time of interview, the proportion who had previously lived for any long time in the countryside (see Table XV). Among the lung-carcinoma patients living in Greater London at the time of interview, 4.3% had previously lived for 10 or more years in a rural district; among control patients living in Greater London

TABLE XV.—*Residence for 10 or More Years in the Countryside: Lung-carcinoma and Matched Control Patients, Subdivided by Place of Residence at the Time of Interview*

Residence at Time of Interview	Lung-carcinoma Patients			Control Patients		
	No. Interviewed	Lived for 10 or More Years in a Rural District		No. Interviewed	Lived for 10 or More Years in a Rural District	
		No.	%		No.	%
Greater London..	791	34	4·3	900	62	6·9
Other county boroughs ..	225	13	5·8	181	12	6·6
Other urban districts	275	37	13·5	213	32	15·0
Rural districts ..	155	136	87·7	164	149	90·9
Abroad	19	1	—	7	0	—
All places ..	1,465	221	(15·1)	1,465	255	(17·4)

the proportion was 6.9%. For each type of area this proportion is lower among the lung-carcinoma patients. The differences, though slight, are consistent and in conformity with the previous conclusion. They are not, however, statistically significant ($\chi^2=6.45$, n=4, $0.10<P<0.20$).

Residence Near a Gasworks

Gasworkers have been reported as specially liable to carcinoma of the lung (Kennaway and Kennaway, 1947; Doll, 1952), and it was therefore thought possible that residence near a gasworks with inhalation of its fumes might conduce to the disease. All the patients were asked whether they had ever lived near a gasworks and, if so, for how long. The results revealed no difference: 23.0% (337/1,465) of the lung-carcinoma patients and 21.5% (315/1,465) of the control patients had lived near a gasworks for a year or more ($\chi^2=0.95$, n=1, $0.30<P<0.50$). This result agrees with that obtained by McConnell, Gordon, and Jones (1952).

Exposure to Different Forms of Heating

Further information on the possible effects of exposure to coal-gas was sought by asking the form of heating used in the houses in which the patients had lived. This question also related to the possibility that exposure to benzpyrene in the soot of domestic fires might be conducive to the development of carcinoma. Analysis was made of the kinds of heating used in the living-rooms of all the houses in which the patients had resided for three or more years, and the numbers of years were calculated that each patient had been exposed, in his living-room, to a coal fire, a gas fire, an electric fire, an anthracite stove, a radiator, or other form of heating. The results (Table XVI) reveal very little difference in the histories given by the two groups of patients.

Previous Respiratory Illnesses

A large number of the control patients had some respiratory disease, and we clearly cannot assume that the history of previous respiratory illnesses given by these patients would be characteristic of other patients generally. It would not, therefore, be proper to compare the lung-carcinoma patients with the general control groups of patients to determine whether previous respiratory illnesses play any part in the aetiology of carcinoma of the lung. We have accordingly compared lung-carcinoma patients with patients with other forms of cancer (mainly stomach and large bowel, and excluding those in whom the site of origin of the growth was in no doubt and also those with growths elsewhere in the chest, upper respiratory passages, and mouth).

The general cancer group was not selected to be of the same sex and age distribution as the lung-carcinoma group, and it is therefore necessary to allow for sex and age differences between them. For this purpose we have first calculated for *all* the cancer patients put together—lung, stomach, large bowel, etc.—the reported incidence of previous respiratory illness in each sex and 10-year age subgroup. These rates we have then applied to the numbers of patients of corresponding sex and age with (*a*) carcinoma of the lung, and (*b*) other forms of cancer, to calculate how many cases of previous respiratory illness would have occurred in each subgroup if both types of patients had had these same rates of attack. The total number expected for each illness was then readily obtained by summing the numbers in each subgroup. The numbers, "expected" on the basis of equality, can be compared with the histories actually recorded. To avoid bias due to any confusion between an earlier independent respiratory illness (in which our interest lay) and an illness induced by the presence of the tumour, we included in the analysis only such illnesses as had occurred at least five years before the interview. Occasionally illnesses occurring more than five years previously may have been due to a slow-growing tumour, but the number is unlikely, we think, to be important.

Questions were asked about the past occurrence of pneumonia, pulmonary tuberculosis, pleural effusion, chronic bronchitis, asthma, and chronic nasal catarrh. The results (Table XVII) show that the lung-carcinoma patients more frequently had a history of preceding pneumonia or chronic bronchitis, while other respiratory illnesses were referred to with approximately equal frequency by the two groups. The differences in the incidence of pneumonia and chronic bronchitis are statistically significant (particularly the latter), though the actual proportion of lung-carcinoma patients with positive histories is not large (with each disease 17%).

TABLE XVI.—*Exposure to Different Forms of Heating: Lung-carcinoma and Matched Control Patients. (Information obtained during part of the investigation only)*

Type of Heating in Living-room of Patients' Residence	Disease Group	No. of Patients Exposed for Different Durations of Time				Total No. of Patients	Test of Significance of Difference
		Never	1 Yr.–	30 Yrs.–	50 Yrs.+		
Coal fire	Lung carcinoma	9	93	434	735	1,271	$\chi^2=1·01$, n=3, $0·70<P<0·80$
	Other diseases	11	105	429	726	1,271	
Anthracite stove	Lung carcinoma	1,261	6	3	1	1,271	Combining all over 1 yr.:
	Other diseases	1,258	12	1	0	1,271	$\chi^2=0·39$, n=1, $0·50<P<0·70$
Gas fire	Lung carcinoma	1,192	59	13	7	1,271	Combining all over 30 yrs.:
	Other diseases	1,169	74	21	7	1,271	$\chi^2=3·25$, n=2, $0·10<P<0·20$
Electric fire	Lung carcinoma	1,184	62	14	11	1,271	Combining all over 30 yrs.:
	Other diseases	1,172	71	21	7	1,271	$\chi^2=0·84$, n=2, $0·50<P<0·70$
Radiator	Lung carcinoma	1,191	66	8	6	1,271	Combining all over 30 yrs.:
	Other diseases	1,169	85	12	5	1,271	$\chi^2=2·89$, n=2, $0·20<P<0·30$
Other heating	Lung carcinoma	1,192	55	14	10	1,271	Combining all over 30 yrs.:
	Other diseases	1,189	59	16	7	1,271	$\chi^2=0·17$, n=2, $0·90<P<0·95$

TABLE XVII.—*Frequency of Occurrence of Respiratory Illnesses in the Past History; Lung-carcinoma and Other Cancer Patients**

Type of Respiratory Illness	Lung-carcinoma Patients				Other Cancer Patients				Test of Significance of Difference
	No. of Patients	History of Illness 5 or More Years Previously			No. of Patients	History of Illness 5 or More Years Previously			
		Observed		Expected		Observed		Expected	
		No.	%	No.		No.	%	No.	
Asthma	1,465	19	1·3	19·5	853	13	1·5	12·5	$\chi^2=0·033$, n=1, 0·80<P<0·90
Chronic bronchitis	1,465	254	17·3	222·9	853	94	11·3	125·1	$\chi^2=14·13$, n=1, P<0·001
Chronic nasal catarrh	1,465	198	13·5	189·2	853	90	11·0	98·8	$\chi^2=1·35$, n=1, 0·20<P<0·30
Pleural effusion	1,465	25	1·7	25·7	853	14	1·7	13·3	$\chi^2=0·057$, n=1, 0·80<P<0·90
Pneumonia	1,465	250	17·1	224·8	853	83	10·1	108·2	$\chi^2=10·03$, n=1, P<0·01
Pulmonary tuberculosis	1,465	11	0·8	13·1	853	8	1·1	5·9	$\chi^2=1·09$, n=1, 0·20<P<0·30

* Excluding cancer patients notified incorrectly as having lung carcinoma (see Table XIX).

TABLE XVIII.—*Frequency of Occurrence of Previous Pneumonia and Chronic Bronchitis: Lung-carcinoma and Other Cancer Patients,* Subdivided by Age and Sex*

Age	Men								Women							
	Lung-carcinoma Patients				Other Cancer Patients*				Lung-carcinoma Patients				Other Cancer Patients*			
	No. of Patients	History of Illness 5 or More Years Previously			No. of Patients	History of Illness 5 or More Years Previously			No. of Patients	History of Illness 5 or More Years Previously			No. of Patients	History of Illness 5 or More Years Previously		
		Pneumonia		Chronic Bronchitis		Pneumonia		Chronic Bronchitis		Pneumonia		Chronic Bronchitis		Pneumonia		Chronic Bronchitis
		No.	%	No.		No.	%	No.		No.	%	No.		No.	%	No.	%
25–	17	5 } 18		3 } 16	7	0 } 15		0 } 4	3	1 } 22		0 } 17	7	2 } 12		0 } 0	
35–	116	19		18	46	8		2	15	3		3	26	2		0	
45–	493	83	17	72	15	109	15	14	11	10	38	4	11	10	26	81	4	5	5	6
55–	545	103	19	107	20	213	20	9	27	13	34	3	9	7	21	101	5	5	13	13
65–74	186	26	14	30	16	151	18	12	22	15	18	3	17	4	22	112	9	8	14	13
Total	1,357	236	—	230	—	526	61	—	62	—	108	14	—	24	—	327	22	—	32	—

* See footnote to Table XVII.

Detailed figures for the previous occurrence of these two diseases are given in Table XVIII. The lung-carcinoma patients show a uniformly higher incidence of each disease in both sexes and in all age groups, though in men many of the differences are quite small. In neither group, however, does the frequency of a past history of pneumonia increase with age as would naturally be expected. It is not unlikely that some older patients forgot their earlier attacks of pneumonia. This being so, the differences found between the lung-carcinoma and the other cancer patients may merely have arisen because patients with a respiratory disease recall more completely their previous respiratory infections—that is, for the very reason which led us to exclude other respiratory illnesses from the control group. This possibility can, however, be tested by comparing the histories given by patients thought to have carcinoma of the lung when they were interviewed but in whom the diagnosis turned out to be erroneous (Table XIX) with the histories given by the lung-carcinoma patients and by the other cancer patients (Table XVIII).

The incorrectly notified patients gave, in nearly every sex and age group, a history of previous pneumonia and chronic bronchitis of similar frequency to that given by the patients with lung carcinoma and of greater frequency than that of the patients with other forms of cancer. For all sex and age groups taken together the proportions with a positive history were:—pneumonia: incorrectly notified patients 20%, lung-carcinoma patients 17%, other cancer patients 10%; chronic bronchitis: incorrectly notified patients 21%, lung-carcinoma patients 17%, other cancer patients 11%.

When age and sex differences are allowed for (Table XIX) the incorrectly notified patients and the lung-carcinoma patients do not differ significantly, while the differences between the incorrectly notified patients and the group of other cancers are highly significant. It would seem, therefore, that the more frequent history of a preceding attack of pneumonia or of frequent attacks of chronic bronchitis in the lung-carcinoma group may well result from patients with respiratory symptoms recalling their previous attacks of certain common respiratory illnesses more readily than other patients (though it is possible that the lung-cancer and the incorrectly diagnosed groups both have suffered a greater frequency of such attacks in the past). On the present evidence we feel unable to deduce any aetiological relationship between lung carcinoma and previous respiratory illness.

TABLE XIX.—*Frequency of Occurrence of Previous Pneumonia and Chronic Bronchitis: Patients Incorrectly Thought to have Lung-carcinoma, Subdivided by Age and Sex*

Age	Patients Incorrectly Thought to have Lung Carcinoma							
	Men				Women			
	No. of Patients	History of Illness 5 or More Years Previously:			No. of Patients	History of Illness 5 or More Years Previously:		
		Pneumonia		Chronic Bronchitis		Pneumonia		Chronic Bronchitis	
		No.	%	No.		No.	%	No.	%
25–	17	5 } 25		2 } 14	14	1 } 22		5 } 30	
35–	48	11		7	9	4		2	
45–	79	11	14	10	13	25	4	16	5	20
55–	98	25	26	25	26	15	3 } 20		3 } 20	
65–74	25	3	12	9	36	5	1		1	
All ages	267	55	—	53	—	68	13	—	16	—

Comparison with patients proved to have lung carcinoma

Patients incorrectly thought to have lung carcinoma:
No. giving a history of previous pneumonia 68
No. expected to give such a history .. .. 59·9
$\chi^2=1·64$, n=1, P=0·20
No. giving a history of previous chronic bronchitis 69
No. expected to give such a history .. .. 61·99
$\chi^2=1·20$, n=1, 0·20<P<0·30

Comparison with other cancer patients

Patients incorrectly thought to have lung carcinoma:
No. giving a history of previous pneumonia 68
No. expected to give such a history .. .. 48·22
$\chi^2=13·84$, n=1, P<0·001
No. giving a history of previous chronic bronchitis 69
No. expected to give such a history .. .. 44·5
$\chi^2=21·43$, n=1, P<0·001

Validity of the Results

The larger and more detailed data that we have presented here confirm those in our preliminary report, and support our conclusion that there is an association between smoking and carcinoma of the lung. Other explanations of the figures might, however, be possible, and we carefully considered several alternatives in our earlier paper—namely, (*a*) that our group with carcinoma of the lung was unrepresentative of patients with that disease; (*b*) that the patients in the control group were not truly comparable with the lung-carcinoma patients; (*c*) that the method of selection of the control patients had led to the choice of patients who smoked less than the average; (*d*) that the lung-carcinoma patients tended, because of their disease, to exaggerate their smoking habits; (*e*) that the interviewers tended to scale up the smoking habits of the lung-carcinoma patients; and (*f*) that the individual interviewers might have obtained different results and have interviewed different proportions of the patients in the various disease groups.

The main points of the arguments that we put forward against these alternative explanations are illustrated in Table XX, which, utilizing the various groups of control patients, shows the proportions who smoked different amounts of tobacco, standardized according to the age distribution of the population of England and Wales, between the ages of 45 and 74.

In this standardization the incidence rate of smoking in a given age group in a given sample of patients was applied to the number of men—or women—in that age group in England and Wales to give the numbers of smokers in the general population. The summation of the figures thus derived from each separate sex/age group gave the total distribution in the standard population of smokers of different amounts—which were then converted into a percentage distribution as shown in Table XX. The two age groups under 45 years were omitted from the calculations because there were few such patients in some disease groups, and these unreliable figures would have been given undue weight in the process of standardization.

Table XX shows (*a*) that the lung-carcinoma group contains a smaller proportion of non-smokers and light smokers and a higher proportion of heavy smokers than *any* of the other disease groups, and (*b*) that the proportions in the group of patients incorrectly thought to have carcinoma of the lung and in the groups with other respiratory diseases, with cancer in other sites, and with other diseases, are similar. We would, as before, lay special stress upon the group of patients believed by the interviewers to have carcinoma of the lung at the time of interview, but who proved finally not to have that disease. This group reveals a distribution of smoking habits very similar to that shown by the other groups but very different from that of the lung-carcinoma patients.

TABLE XX.—*The Smoking Habits of Patients in Different Disease Groups, Standardized According to the Age Distribution of the Population of England and Wales Aged 45–74, at June 30, 1950*

Disease Group	Percentage of Non-smokers	Percentage Smoking Daily Average of				No. of Patients Interviewed Aged 45–74
		Less than 5 Cigs.	5 Cigs.–	15 Cigs.–	25 Cigs.+	
Men						
Carcinoma of lung ..	0·3	4·6	35·9	35·0	24·3	1,224
Patients incorrectly thought to have carcinoma of lung ..	5·3	9·9	35·5	37·8	11·4	202
Other respiratory diseases	4·9	9·9	38·3	38·7	11·2	301
Other cancers ..	4·6	9·4	47·2	26·0	12·8	473
Other diseases ..	5·6	9·0	44·8	26·9	13·7	875
Women						
Carcinoma of lung ..	40·6	13·7	22·0	9·5	14·2	90
Patients incorrectly thought to have carcinoma of lung ..	66·9	16·4	12·7	4·2	0·0	45
Other respiratory diseases	66·5	22·4	0·0	11·1	0·0	25
Other cancers ..	68·4	14·3	11·0	5·0	1·3	294
Other diseases ..	55·9	22·1	17·5	3·6	0·9	157

These observations make it unreasonable, we suggest, (*a*) to attribute the results to exaggeration by the lung-carcinoma patients, since patients with other respiratory diseases would presumably be equally inclined to exaggerate their smoking histories; (*b*) to attribute the results to bias on the part of the interviewers, since patients who were believed by them to have lung carcinoma but who were finally proved not to would have been recorded, had there been bias, as having smoking habits similar to the patients proved to have lung carcinoma; (*c*) to attribute the results to some special selection of control patients who were, on the average, light smokers, since there is no important difference between patients without carcinoma of the lung who were *notified* to us—that is, the incorrectly diagnosed group and the greater part of the other cancer group—and patients who were *selected* as controls by the interviewers on the basis laid down (that is, the respiratory disease group and the great majority of the "other diseases" group).

The further extensive data collected since the publication of our first report have proved to be essentially similar to the earlier data, and we have obtained no subsequent information to throw doubt on the validity of the conclusion that there is a real association between smoking and carcinoma of the lung.

Some figures for the smoking habits of the general population of Great Britain in 1951 have been obtained, for other purposes, by the Social Survey of the Central Office of Information, and it is of interest to see how these compare with the habits recorded by our hospital patients. The survey of the general population was made in May, 1951, and was based upon interviews made by trained investigators with a representative random sample of the civilian population of Great Britain aged 21 years and over. The names of persons to be interviewed were selected at random from local records in a representative sample of about 100 urban and rural local authority areas of different types throughout Great Britain. The sample thus adequately represented the population in respect of sex, age, and all other relevant factors. The questions about smoking were part of an extensive investigation concerned mainly with other subjects; they were, however, drawn up in such a way as to permit the replies to be compared with those of our inquiry.

To avoid difficulties of geographical variations in smoking habits we have limited the comparison to patients and individuals in the Social Survey sample who were resident in Greater London—from which the greater part of our data came. To eliminate differences due to variation in smoking habits with age we have taken the age distribution of the Social Survey sample as a standard and adjusted the patients to that age distribution before calculating the percentage distribution of the different grades of smokers (by, as usual, applying the incidence rates of smoking in the patients at each given age to the Social Survey population of that age and summing for the age groups). Persons of 75 and over were excluded. Table XXI shows that the percentages of non-smokers and light smokers among women agree closely, but it appears on the whole that somewhat heavier smoking habits have been recorded amongst the patients than in the sample of the general public.

Differences in the dates of the interviews (April, 1949, to February, 1952, in the one case, May, 1951, in the other) are unlikely to have influenced the results appreciably, as the national consumption of tobacco varied very little over that period. It may be argued that the differences indicate an association between smoking and many separate diseases; they may, on the other hand, result from the different methods of interviewing and from the different groups of interviewers employed. The comparison certainly provides no evidence that the association we have

TABLE XXI.—*Comparison Between Smoking Habits of Patients Without Carcinoma of the Lung, Interviewed in the Investigation, and of the General Public, Interviewed by the Social Survey Investigators; Residents in Greater London Only*

Subjects	Percentage of Non-smokers	Most Recent Amount Smoked. Percentage Smoking: 1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+	No. Interviewed
Men						
Patients with diseases other than lung carcinoma	7·0	4·2	43·3	32·1	13·4	1,390*
Sample of general public (Social Survey)..	12·1	7·0	44·2	28·1	8·5	199
Women						
Patients with diseases other than lung carcinoma	54·7	13·0	21·6	8·2	2·5	456
Sample of general public (Social Survey) ..	52·9	16·9	24·3	4·7	1·2	255

* This number is three less than that shown in Table XIII, because the patients interviewed in the special investigation in rural hospitals are not included.

observed between smoking and carcinoma of the lung can be attributed to a selective choice, for comparison with the lung-carcinoma patients, of other patients who tended to be light smokers.

Discussion

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

Investigations in Germany (Müller, 1939; Schairer and Schöniger, 1943) and in the U.S.A. (Schrek, Baker, Ballard, and Dolgoff, 1950; Wynder and Graham, 1950; Levin, Goldstein, and Gerhardt, 1950; Mills and Porter, 1950) have led to very similar conclusions. In Britain, McConnell, Gordon, and Jones (1952) found no difference between the proportions of "non-smokers" in 100 lung-carcinoma patients and in 200 control patients (collected at a later date). On the other hand, they showed a considerable difference among cigarette-smokers between the proportions smoking the larger quantities: 44.1% of the lung-carcinoma group had smoked more than 20 cigarettes a day against 23.2% of the controls.

The present analysis of nearly 1,500 cases, or more than double the number dealt with in our preliminary report, supports the conclusion then reached and has revealed no alternative explanation—for example, in the use of petrol lighters.

It has been suggested that subjects with a particular physical constitution may be prone to develop (*a*) the habit of smoking and (*b*) carcinoma of the lung, and that the association might therefore be indirect rather than causal (Parnell, 1951). We know of no evidence of such a physical constitution characteristic of patients with lung carcinoma. If it does exist we should still have to find some environmental factor to account for the increased incidence of the disease in recent years.

To say that smoking is a factor in the production of carcinoma of the lung is not, of course, to say that it contributes to the development of *all* cases of the disease. All observers agree that the disease occurs in non-smokers, and in the present series there were 34 such cases confidently diagnosed and histologically proved. These 5 men and 29 women said that they had never smoked at all or had smoked so little as never to have consumed as much as one cigarette a day for as long as one year. Such patients in the ordinary course of their lives must have inspired air containing tobacco smoke, and it is not possible to say whether the disease would occur in its complete absence. The reasonable presumption is that it would. Experience of cancer in other sites (for example, cancer of the skin) indicates that it is unlikely for one environmental agent to be the effective cause in all cases.

Whether smoking is the sole cause of the *increase* in the disease in recent years is another matter. There is no evidence to show whether there has been an increased incidence among non-smokers. It is certain, we think, that some, if not much, of the increase is spurious and merely the result of improved diagnosis. Rigdon and Kirchoff (1952) have pointed out that in the U.S.A. the death rate attributed to lung cancer in the different States is positively correlated with the number of physicians per 1,000 inhabitants, and it can be shown, from their figures, that this is true independently of the correlation with cigarette consumption—which is also related to the number of physicians per 1,000 inhabitants. The extent to which the increase is real does not, however, affect the present evidence from which the association between smoking and lung carcinoma is deduced. It would be material if it were proved that there had, in fact, been *no* true increase of the disease following a great increase in the consumption of tobacco; but that, in our opinion, is as far from having been proved as that the recorded increase is all real. The position, then, as we see it, is (*a*) that an association has been demonstrated—here and elsewhere—between tobacco-smoking and carcinoma of the lung; (*b*) that, independently of this evidence, there has been a recorded increase over the years in the number of deaths attributed to the disease and an increase has also occurred in the consumption of tobacco, and particularly of cigarettes; (*c*) that the increase in the number of deaths recorded is relatively greater than the increase in the consumption of tobacco, but the actual relation between the real increase in the number of deaths and the increase in the consumption of tobacco is entirely a matter of conjecture.

Needless to say, environmental factors other than tobacco may be responsible for part of the presumed increase. The part played by any such factors cannot, however, be deduced merely from a contemporaneous increase in their incidence and in the death rate from lung cancer—that is, on the basis of a correlation in time: a direct association between the disease and exposure to them must be demonstrated. In the present investigation some additional, but not very strong, evidence was obtained that lung carcinoma is commoner in urban than in rural areas, but otherwise we found no major or clear association apart from that with the consumption of tobacco.

We should perhaps point out that we made no inquiries which would throw light upon a relationship between the development of lung carcinoma and an attack of influenza during the pandemic of 1918–19—a relationship from time to time suggested in the literature (see *Lancet*, 1951, **2**, 737). It would be difficult to gather sufficiently accurate information on such a disease after the passage of so many years. We may note (*a*) that no appreciable increase in lung cancer has occurred in Iceland (Dungal, 1950), though the influenza pandemic was severe there, and (*b*) that, in Britain, influenza in 1918–19 affected both sexes almost equally (as judged by mortality), while deaths from lung cancer occur predominantly in men.

Year	Influenza (Death Rate per Million) M	F	Year	Lung Cancer (Death Rate per Million) M	F
1918	3,360	2,967	1948	422	83
1919	1,350	1,101	1949	453	86

All methods of smoking tobacco do not, according to our results, carry equal risks. As in our previous report, smoking a pipe appears to be less closely associated with the disease than smoking cigarettes. In the present observations we have found that, contrasted with other patients, rather fewer of the patients with carcinoma of the lung have used a cigarette-holder or smoked filter-tipped cigarettes. These observations are of interest, though it is impossible to draw any firm conclusions from them since so few people have limited themselves throughout their lives to one method of smoking. It must also be remembered that any smoking technique which is differentially associated with a tendency to light smoking will necessarily, according to our figures, appear to be less closely related to lung carcinoma. Nevertheless, it seems possible, from these results, that pipes, cigarette-holders, and filter tips may, to some unknown extent, each partly separate out an active agent before it reaches the respiratory tract.

On the other hand, the observation that patients who recognize that they inhale are found no more frequently in the lung-carcinoma group than in the control group appears somewhat paradoxical. We pointed out, however, in our preliminary report that until the size of the particles carrying the carcinogen is determined nothing can be stated about the effect which differences in depth of respiration may have on the extent and site of deposition of the carcinogen. From the present extended observations it seems that patients with growths of central origin inhale less frequently than normal (though the difference is very small), while patients with peripheral growths may inhale rather more frequently. Such a finding could be expected if smoke when not "inhaled" were to penetrate mainly to the large bronchi while inhaling spread the deposition of smoke particles more evenly throughout the bronchial tree.

From the evidence collected about each patient's smoking habits it has been possible to compute some estimates of the risks of dying from carcinoma of the lung in different age groups at different levels of tobacco consumption. These estimates, we would emphasize, are speculative and dependent on the validity of three assumptions: namely, first, that the smoking habits of the lung-carcinoma patients interviewed in this inquiry and resident in Greater London are representative of the habits of all persons dying of the disease in Greater London in 1950; secondly, that the smoking habits of the patients with other diseases interviewed in this inquiry and residents of Greater London are representative of the habits of the general population of Greater London in 1950; and, thirdly, that the actual numbers of deaths from carcinoma of the lung in each sex in Greater London were close to the numbers recorded by the Registrar-General. The only one of these assumptions upon which we have a check is the second. Observations on smoking habits made by the Social Survey upon a cross-section of inhabitants of Greater London do not differ radically from the observations based upon our patients, though they reveal rather fewer heavy smokers than we have found. Keeping these assumptions in mind, our estimates indicate that the risk of dying of lung carcinoma increases with age, as is of course known, and in approximately simple arithmetical proportion with the amount smoked.

A test of the truth of this conclusion is to see whether it accords with the observed incidences of lung carcinoma and of tobacco consumption in different sections of the community and in different parts of the world. In this country there is a pronounced difference in the smoking habits of men and women; it appears inadequate to account for the whole excess of cases which occur in men, as is shown by the different death rates estimated for each sex at each level of tobacco consumption (Table XII and the Figure, based upon it). On the other hand, the sex ratio of the relatively few cases observed in non-smokers is not incompatible with a similar incidence in men and women in the absence of smoking—it could not be identical because of risks associated with certain industrial occupations. There is also an appreciable difference in smoking habits between men living in town and country, which should lead to a higher death rate in the towns, but not to the extent that is actually observed.

It may be that other factors also operate to produce these different death rates in men and in women, in towns and in the countryside. On the other hand, the relationship between smoking and lung carcinoma is quite likely to be more complex than that depicted in Table XII. For example, common observation would suggest that some women—especially the light smokers among them—tend to hold their cigarettes in their mouths less continuously than men and not to smoke them to the end. An equal number of cigarettes a day may not therefore be the same thing, from the point of view of cancer risk, when smoked by men and by women. Again, differences in consumption of cigarettes in town and country may have been more pronounced 10 or 20 years ago than they are to-day. We have no information to guide us.

Stocks (1952) has, however, shown a distinct relation between the size of a town—assessed by the number of occupied dwellings—and the mortality from lung cancer. It would seem likely that some agent other than tobacco (present perhaps in domestic chimney smoke or in the exhaust fumes of cars) is at least partly responsible for the excess mortality in towns.

Comparisons between the recorded death rates at different epochs and in different countries present many difficulties in interpretation. Varying standards of diagnosis of the cause of death, differences in methods of preparation and consumption of tobacco, changes in consumption over the last 50 years, may all introduce gross errors. Nevertheless, some correlation between national figures for cigarette consumption and the death rate from lung cancer would be expected, though in view of the uncertainties of the data the correlation is unlikely to be high. Studying the incidence of lung cancer in some European countries, Daff, Doll, and Kennaway (1951) conclude: "The consumption of tobacco per head has been for the last 10 years rather higher in Switzerland than in the United Kingdom, and in Norway has been about one-half that in the other two countries, while the crude death rates at the beginning and end of the period were roughly in the proportion of 10 (England and Wales) to 5 (Switzerland) and 2 (Norway). Cigarette consumption was approximately in the proportion of 4 (England and Wales) to 2 (Switzerland) and 1 (Norway), and was more in accord with the relative death rates. The increase in the number of deaths has been about the same (twofold) in all three countries, but the increase in consumption of tobacco and cigarettes has been less. The differences in the incidence of cancer of the lung are therefore quite different in extent from those in the quantity of tobacco consumed; they are more like (though still different from) those in the quantity of cigarettes consumed. The study of the relation between the national consumption of tobacco and the national incidence of cancer of the lung has scarcely begun."

No responsible agent in tobacco smoke has been detected. The suggestion that arsenic, introduced by insecticides sprayed on the growing crop, might be a factor would seem to be discountenanced by the absence of arsenic from Turkish tobacco and the high proportion of lung carcinoma found at necropsy in Istanbul (Daff, Doll, and Kennaway, 1951; Saglam, 1944). Benzpyrene has not been detected in cigarette smoke (Waller, 1952). Long-continued exposure of mice to atmospheres containing tobacco smoke has failed to produce lung cancer (Campbell, 1936; Lorenz, Stewart, Daniel, and Nelson, 1943), but it may be of significance, in view of our findings, that the smoke was brought to the mice through long tubes. In contrast, tumours of the skin of mice can be produced by the application of tars obtained from tobacco burnt at temperatures which occur in normal smoking (Lamb and Sanders, 1932; Flory, 1941). Goulden, Kennaway, and Urquhart (1952) have pointed out that carcinogenic agents

in tobacco smoke and in town dust might supplement one another, and have summarized the available data about the additive effects of two carcinogens. An agent in tobacco smoke might be by itself only weakly, if at all, carcinogenic, but might act as a co-carcinogen in the presence of, for example, the benzpyrene in urban atmospheres.

Summary

In an investigation designed to throw light on the aetiology of carcinoma of the lung nearly 5,000 hospital patients have been interviewed by four specially appointed almoners. The interviews took place in the years 1948 to 1952 in hospitals in London, Bristol, Cambridge, Leeds, Newcastle-upon-Tyne, and (for a limited purpose) in the rural areas of Dorset and Wiltshire. The questions asked covered a very wide range, including the occupational histories of the patients, where they had lived and the forms of domestic heating in their homes, their previous attacks of respiratory illnesses, their habits with regard to smoking, and, for other purposes, some particulars of their dietary habits and use of purgatives.

Preliminary figures on tobacco-smoking were published in a previous paper (Doll and Hill, 1950). The present paper gives corresponding data for the whole of the material collected as well as the analysis of other questions included in the inquiry. The main comparisons are between 1,465 patients with carcinoma of the lung and an equal number of "matched control" patients with other diseases, each of these being carefully chosen so as to be of the same age, the same sex, and, so far as possible, in the same hospital at the same time as a lung-carcinoma patient.

There is no appreciable difference between the two groups in the number of persons belonging to the Registrar-General's five social classes, and no association has been found between any type of occupation and lung carcinoma which would suggest the presence of an aetiological agent likely to be of general significance.

With regard to the possible effects of fumes in the atmosphere, both within and without the home, there is no significant difference between the groups. Of the lung-carcinoma patients 23.0%, and of the control patients 21.5%, had lived near a gasworks for a year or more. Their use of coal, gas, or electric fires or other forms of heating in the living-rooms of their homes did not differ appreciably.

In conformity with the national death rates rather fewer of the lung-carcinoma patients lived, or had lived, in the countryside and more, correspondingly, in the towns.

The lung-carcinoma group in comparison with patients with other forms of cancer more often gave a history of a previous attack of pneumonia and of chronic bronchitis. Detailed analysis of the data suggests, however, that this difference may be due merely to the lung-carcinoma patients, with their respiratory symptoms, recalling more readily than other persons their previous attacks of respiratory illness. The data are not accurate enough for an aetiological relationship to be postulated.

Of the 1,357 men with carcinoma of the lung 7, or 0.5%, were non-smokers (as defined in the text); of the 108 women there were 40, or 37.0%. The corresponding figures for their paired controls were 61 men (4.5%) and 59 women (54.6%). Of the men with lung carcinoma 25.0% reported that they had been smoking, before the onset of their illness, an average of 25 or more cigarettes a day (or the equivalent in pipe tobacco). The corresponding figure for the male control patients was only 13.4%. For women these proportions were 11.1% for the carcinoma group and 0.9% for the controls.

For men these differences are present consistently in each of the five areas of inquiry. For women they are present in London but not in the 28 patients observed in the provincial towns, where only one woman with the heavier smoking habits was found.

Estimated death rates for Greater London (on assumptions stated in the text) indicate that the mortality from carcinoma of the lung may increase in approximately simple proportion with the amount smoked. Amongst men of ages 45–64 the death rate in non-smokers is negligible, while in the heavier-smoking categories it is estimated to reach 3 to 5 deaths per annum per 1,000 living.

Regular users of petrol lighters were found with equal frequency in patients with lung carcinoma and in the control patients with other diseases (42.9% and 41.3%); the proportions who said they inhaled were similar (64.6% and 66.6%); and so were the proportions of cigarette-smokers who had smoked mainly hand-rolled cigarettes (20.7% and 19.1%). On the other hand, rather fewer of the cigarette-smoking patients with lung carcinoma had ever used a cigarette-holder regularly (5% against 12% of the controls), and only 3 out of 504 had smoked filter-tipped cigarettes, compared with 15 out of 467 controls. The observations in these respects are too few for a definite conclusion, but conceivably they may have a bearing on the appreciably lower risks reported here for pipe-smokers compared with cigarette-smokers. Each of these methods of smoking might partly separate out an active agent before it reached the respiratory tract.

The validity of these various results is studied, and it is concluded that the association between smoking and carcinoma of the lung is real. It is not argued that tobacco smoke contributes to the development of all cases of the disease—a most unlikely event. It is not argued that it is the sole cause of the increased death rate of recent years nor that it can wholly explain the different mortality rates between town and country.

ACKNOWLEDGMENTS

The following hospitals co-operated in the investigation:

Bristol.—Frenchay (departments of plastic and jaw surgery, neurological surgery, and thoracic surgery).

Cambridge.—Addenbrooke's (radiotherapeutic centre) and Papworth Hall.

Leeds.—General Infirmary (thoracic department).

London.—Brompton, Central Middlesex, Fulham, Hackney, Hammersmith, Harefield, Lambeth, Lewisham, Middlesex, Mount Vernon and the Radium Institute, New End, Royal Cancer, Royal Free, St. Bartholomew's, St. Charles's, St. James's, St. Mary's, St. Thomas's, University College, and Whittington.

Newcastle-upon-Tyne.—General Infirmary (department of neurological surgery) and Shotley Bridge General (departments of plastic surgery, radiotherapy, and thoracic surgery).

Wiltshire and Dorset (in the survey of habits of rural patients only).—Blandford, Bridport General, Dorset County, Odstock, Poole General, Portwey (Weymouth), Salisbury General, Swanage, Victoria (Wimborne), Westminster Memorial (Shaftesbury), Weymouth and District, and Yeatman Memorial (Sherborne).

We are indebted to the medical staffs of these hospitals for allowing us to interview their patients and to have access to the hospital notes; also to the individual members of the staffs, medical and lay, who notified the cases and collected the case-notes for examination. The work could not have been carried out without their co-operation.

We are most grateful for advice on the interpretation of pathological specimens to Professor W. G. Barnard, Drs. A. B. Bratton and J. W. Clegg, Professor W. D. Newcomb, Drs. D. M. Pryce, R. J. Sandry, A. C. Thackray, K. Weavers, and R. R. Wilson; and for assistance in determining the final diagnoses in the patients interviewed to Dr. A. Adelstein, Mr. G. P. Alexander, Mr. P. R. Allison, Mr. R. C. Bell, Mr. R. Belsey, Dr. J. R. Bignall, Dr. D. M. J. Burns, Mr. R. Dobson, Dr. J. Faulkner, Mr. G. M. FitzGibbon, Mr. G. K. Harrison, Mr. G. A. Hendry, Mr. F. I. Herbert, Mr. E. Hoffman, Mr. G. A. Mason, Professor J. S. Mitchell, Mr. K. Price, Dr. G. O. Richardson, Mr. C. A. Ross, Mr. W. M. Ross, Mr. G. F. Rowbotham, Dr. K. R. Stokes, and Dr. G. Strang.

Sir Ernest Kennaway and Dr. Percy Stocks took part in a conference called by the Medical Research Council, at which the investigation was initiated, and we have been fortunate in having their helpful advice throughout its course. Dr. John Knowelden and Dr. Ian Sutherland kindly read our draft report, and we have benefited by their criticisms.

We are also grateful to Dr. W. P. D. Logan, chief medical statistician of the General Register Office, to the Government Social Survey, and to the Statistics Division of the Board of Trade for the provision of data, and to the Statistical Department of the Ministry of Labour for preparing the punched cards used in the mechanical analysis of the results.

Finally, we wish to thank Miss Marna Buckatzsch, Miss Beryl Iago, Miss Keena Jones, and Miss Rosemary Thomson, who interviewed the patients and, together with Mrs. Joan Bodington, analysed the results. They worked untiringly, and at all hours, and the main burden of the work fell on their shoulders.

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The centenary of the birth of Antoine Henri Becquerel, the French physicist, falls on December 15. Like his father and grandfather before him, he occupied the chair of physics at the Musée d'Histoire Naturelle, Paris, to which he was appointed in 1892. Three years later he became professor of physics at the Ecole Polytechnique. In 1896 he made the discovery that uranium ores at ordinary temperatures emit an invisible radiation similar in several respects to *x* rays, and capable of fogging a photographic plate after passing through metal plates. Pierre and Marie Curie investigated this radiation and showed it to be an atomic phenomenon. They named it radioactivity. The discovery of radium by the Curies followed in 1898, and they shared the Nobel Prize for Physics with Becquerel in 1903. Becquerel also made important contributions to the knowledge of magnetism, polarization of light, phosphorescence, and absorption of light in crystals. He died at Croisic, Brittany, on August 25, 1908.

PSYCHIATRIC DISORDERS IN LATER LIFE*

BY

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"Grow old along with me !
The best is yet to be,
The last of life, for which the first was made:"

As Robert Browning's words imply, it is probable that psychogenic factors causing simple anxiety and hysterical reactions play less part in later life than they do at earlier ages. But, as Sir Humphry Rolleston remarked, quoting another authority: "Whatever may be said in favour of it, old age is a losing game." There is the high incidence of cerebral vascular disease, and intracranial tumours occur with some frequency. Affective disturbances are common. But I should like to refer chiefly to the two principal organic syndromes seen in later life: the syndrome of acute clouding of consciousness, delirium, or confusion, and that of presenile dementia. There is particularly the relation of the former to biochemical and toxic factors and of the latter to intracranial disease.

1. Biochemical and Toxic Causes of Psychiatric Symptoms in Later Life

Great as are the differences between the age periods of growth and decline, both the very young and the very old show an undue mental instability in response to disturbances in their body chemistry. Thus, an elderly person who exhibits at the most only slight mental signs of ageing, may, through the fortuitous introduction of a biochemical or toxic factor, develop acute mental symptoms indicative of clouding of consciousness. In increasing order of severity these are: (1) Simple impairment of attention, registration, and recall, often associated with a facile or euphoric affect and push of talk. (2) Perseveration showing itself in the spontaneous behaviour, in the speech, and in the response to simple requests. (3) Disorientation in time, place, and for persons, usually at some stage with confabulation. In many instances, concrete orientation may be correct or the time sense only lost, but further testing will reveal evidence of abstract disorientation. (4) In more severe cases there are grossly defective grasp and delirium with noisy and irrational behaviour.

Recognized causes of such (usually reversible) effects are toxaemia from fever or urinary infection; the incautious use of bromides, morphine, barbiturates, or other drugs; and vitamin deficiency. Other causes which, although known, are less generally appreciated include dehydration, alkalosis, anoxia, and hypoglycaemia.

Dehydration

If a sufficient fluid intake is not secured dehydration will arise in any feverish condition or after a surgical operation (such as prostatectomy) requiring general anaesthesia. The statement that the patient has "passed urine" has little weight in this respect unless it is known that the output is adequate and the specific gravity satisfactory. The after-care of old people undergoing operation for cataract also deserves note. Hallucinations and disorientation or acute delirium may occur as the result of a combination of unfavourable circumstances such as recumbency, bandaging

*Read in opening a discussion in the Section of Psychiatry at the Joint Annual Meeting of the British Medical Association and Irish Medical Association, Dublin, 1952.