BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

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In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whether they denote a real increase in the incidence of the disease or are due merely to improved standards of diagnosis. Some believe that the latter factor can be regarded as wholly, or at least mainly, responsible—for example, Willis (1948), Clemmesen and Busk (1947), and Steiner (1944). On the other hand, Kennaway and Kennaway (1947) and Stocks (1947) have given good reasons for believing that the rise is at least partly real. The latter, for instance, has pointed out that "the increase of certified respiratory cancer mortality during the past 20 years has been as rapid in country districts as in the cities with the best diagnostic facilities, a fact which does not support the view that such increase merely reflects improved diagnosis of cases previously certified as bronchitis or other respiratory affections." He also draws attention to differences in mortality between some of the large cities of England and Wales, differences which it is difficult to explain in terms of diagnostic standards.

The large and continued increase in the recorded deaths even within the last five years, both in the national figures and in those from teaching hospitals, also makes it hard to believe that improved diagnosis is entirely responsible. In short, there is sufficient reason to reject that factor as the whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 56 were heavy smokers, and, in contrast, among 86 "healthy men of the same age groups" there were 14 non-smokers and only 31 heavy smokers. Similarly, in America, Schrek and his co-workers (1950) reported that 14.6% of 82 male patients with cancer of the lung were non-smokers, against 23.9% of 522 male patients admitted with cancer of sites other than the upper respiratory and digestive tracts. In this country, Thelwall Jones (1949—personal communication) found 8 non-smokers in 82 patients with proved carcinoma of the lung, compared with 11 in a corresponding group of patients with diseases other than cancer; this difference is slight, but it is more striking that there were 28 heavy smokers in the cancer group, against 14 in the comparative group.

Clearly none of these small-scale inquiries can be accepted as conclusive, but they all point in the same direction. Their evidence has now been borne out by the results of a large-scale inquiry undertaken in the U.S.A. by Wynder and Graham (1950).

Wynder and Graham found that of 605 men with epidermoid, undifferentiated, or histologically unclassified types of bronchial carcinoma only 1.3% were "non-smokers"—that is, had averaged less than one cigarette a day for the last 20 years—whereas 51.2% of them had smoked more than 20 cigarettes a day over the same

period. In contrast, they estimated from the experience of 882 other male patients that 14.6% of general hospital patients of the same age composition as the bronchial carcinoma cases are "non-smokers" and only 19.1% smoke more than 20 cigarettes a day. They found a similar contrast between the 25 women with epidermoid and undifferentiated bronchial carcinoma and the other female patients, but no such association with smoking could be found in the small group of patients with adenocarcinoma.

Present Investigation

The present investigation was planned in 1947, to be carried out on a sufficiently large scale to determine whether patients with carcinoma of the lung differed materially from other persons in respect of their smoking habits or in some other way which might be related to the atmospheric pollution theory. Patients with carcinoma of the stomach, colon, or rectum were also incorporated in the inquiry, as one of the contrasting groups, and special attention was therefore given at the same time to factors which might bear upon the aetiology of these forms of malignant disease. A separate report will be made upon these inquiries. The present study is confined to the question of smoking in relation to carcinoma of the lung.

The method of the investigation was as follows: Twenty London hospitals were asked to co-operate by notifying all patients admitted to them with carcinoma of the lung, stomach, colon, or rectum. For the most part these hospitals were initially confined to one region of London (the north-west), to allow ease of travelling, but others were subsequently added to increase the scope of the inquiry. A list of those taking part is given at the end of the paper. The method of notification varied; in some it was made by the admitting clerk on the basis of the admission diagnosis, in others by the house-physician when a reasonably confident clinical diagnosis had been made, and in yet others by the cancer registrar or the radiotherapy department. None of these methods is likely to have resulted in complete notification, but there is no reason to suppose that those who escaped notification were a selected group—that is, selected in such a way as to bias the inquiry—as the points of interest in the investigation were either not known or known only in broad outline by those responsible for notifying.

On receipt of the notification an almoner, engaged wholly on research, visited the hospital to interview the patient, using a set questionary. During the inquiry four almoners were employed and all the patients were interviewed by one or other of them. As well, however, as interviewing the notified patients with cancer of one of the four specified sites, the almoners were required to make similar inquiries of a group of "non-cancer control" patients. These patients were not notified, but for each lung-carcinoma patient visited at a hospital the almoners were instructed to interview a patient of the same sex, within the same five-year age group, and in the same hospital at or about the same time. (Where more than one suitable patient was available the choice fell upon the first one in the ward lists considered by the ward sister to be fit for interview.)

At two specialized hospitals (Brompton Hospital and Harefield Hospital) it was not always possible to secure a control patient by this method, and in such cases a control patient was taken from one of the two neighbouring hospitals, the Royal Cancer and Mount Vernon Hospitals. Even with this relaxation of the rule control cases were deficient at the Brompton Hospital and the numbers had to be made up by using the records of patients who had been interviewed as cancer patients, either there or at the Royal Cancer Hospital, but in whom cancer was finally excluded. Because of these differences in technique the records obtained from these hospitals were analysed separately. As, however, the results were in accordance with those found at the other hospitals, all the records are presented here as a single series.

In view of the method of notification used it could not be expected that the diagnosis then given would invariably be accurate. The diagnosis of each patient was checked, therefore, after discharge from or death in hospital, and this check was made in all but nine instances (0.4% of the total). In these few cases (three of carcinoma of the lung, two of carcinoma of the stomach, two of carcinoma of the rectum, and two non-cancer) no records of any sort could be traced, and they have had to be classified according to the information available at the time of their interview. As a general rule the hospital diagnosis on discharge was accepted as the final diagnosis, but occasionally later evidence became available—for example, by histological examination at necropsy—which contradicted that diagnosis. In these instances a change was made and the diagnosis based upon the best evidence.

The Data

Between April, 1948, and October, 1949, the notifications of cancer cases numbered 2,370. It was not, however, possible to interview all these patients. To begin with, it had been decided beforehand that no one of 75 years of age or more should be included in the inquiry, since it was unlikely that reliable histories could be obtained from the very old. There were 150 such patients. In a further 80 cases the diagnosis was incorrect and had been changed before the almoner paid her visit. Deducting these two groups leaves 2,140 patients who should have been interviewed. Of these, 408 could not be interviewed for the following reasons: already discharged 189, too ill 116, dead 67, too deaf 24, unable to speak English clearly 11, while in one case the almoner abandoned the interview as the patient's replies appeared wholly unreliable. No patient refused to be interviewed.

The proportion not seen is high, but there is no apparent reason why it should bias the results. It was in the main due to the time that inevitably elapsed between the date of notification and the date of the almoner's visit. The remaining 1,732 patients, presumed at the interview to be suffering from carcinoma of the lung, stomach, or large bowel, and the 743 general medical and surgical patients originally interviewed as controls, constitute the subjects of the investigation. The numbers falling in each disease group—that is, after consulting the hospital discharge diagnoses—are shown in Table I. The carcinoma cases are here divided into two groups: Group A consisting of cases in which the diagnoses were confirmed by necropsy, biopsy, or exploratory operation, and Group B of the remainder.

TABLE I.—*Number of Patients Interviewed in Each Disease Group, Subdivided According to Certainty of Diagnosis*

Disease Group	No. of Cases		
	Group A. Diagnosis Confirmed at Necropsy, etc.	Group B. Other Criteria of Diagnosis	Total
Carcinoma of lung	489	220	709
,, ,, stomach	178	28	206
,, ,, colon and rectum	412	19	431
Other malignant diseases	—	—	81
Diseases other than cancer (controls)	—	—	709
Other cases	—	—	335
Excluded	—	—	4
All cases	—	—	2,475

The 81 patients classified in Table I as having "other malignant diseases" were interviewed as cases of carcinoma of the lung, stomach, or large bowel, or as non-cancer controls. On the subsequent checking of the diagnosis either they were found to have primary carcinoma in some site other than one of those under special investigation or histological examination showed that the growth was not, in fact, carcinoma—for example, sarcoma, reticulo-endothelioma, etc. The 335 "other cases" either were interviewed as cases of carcinoma of the lung, stomach, or large bowel and were subsequently found not to be cases of malignant disease or, having been interviewed as non-cancer controls, they became redundant when the cases of carcinoma of the lung with which they were paired were found not to be carcinoma of the lung. The four "excluded" cases were excluded on grounds of doubt about their true category. Two were diagnosed at hospital as primary carcinoma of the lung, but there was reason to suppose that the growths might have been secondary to carcinoma of the breast and to carcinoma of the cervix uteri respectively; the other two showed evidence of primary carcinoma in two of the sites under special investigation—that is, lung and colon, and stomach and colon.

The 709 control patients with diseases other than cancer form a group which was, as previously stated, deliberately selected to be closely comparable in age and sex with the carcinoma of the lung patients. Comparisons between these two groups are shown in Table II.

TABLE II.—*Comparison Between Lung-carcinoma Patients and Non-cancer Patients Selected as Controls, With Regard to Sex, Age, Social Class, and Place of Residence*

Age	No. of Lung-carcinoma Patients		No. of Non-cancer Control Patients	
	M	F	M	F
25– ..	2	1	2	1
30– ..	6	0	6	0
35– ..	18	3	18	3
40– ..	36	4	36	4
45– ..	87	10	87	10
50– ..	130	11	130	11
55– ..	145	9	145	9
60– ..	109	9	109	9
65– ..	88	9	89*	9
70–74..	28	4	27*	4
All ages	649	60	649	60

Social Class (Registrar-General's Categories. Men Only)	No. of Lung-carcinoma Patients	No. of Non-cancer Patients
I and II ..	77	87
III	388	396
IV and V ..	184	166
All classes ..	649	649
Place of residence		
County of London	330	377
Outer London	203	231
Other county borough ..	23	16
Urban district	95	54
Rural district ..	43	27
Abroad or in Services ..	15	4
Total (M + F)..	709	709

* One control patient was selected, in error, from the wrong age group.

It will be seen that the lung-carcinoma patients and the control group of non-cancer patients are exactly comparable with regard to sex and age, but that there are some differences with regard to social class and place of residence. The difference in social class distribution is small and is no more than might easily be due to chance ($\chi^2=1.61$; $n=2$; $0.30<P<0.50$). The difference in place of residence is, however, large ($\chi^2=31.49$; $n=5$; $P<0.001$), and Table II shows that a higher proportion of the lung patients were resident outside London at the time of their admission to hospital. This difference can be explained on the grounds that people with cancer came to London from other parts of the country for treatment at special centres. When a comparison is made between the 98 lung-carcinoma patients and the 98 controls who were seen at district hospitals in London—that is, those regional board hospitals which do not have special surgical thoracic or radiotherapeutic centres—the difference disappears. Of these 98 patients with carcinoma of the lung, 56 lived in the County of London, 42 in outer London, and none elsewhere; of their non-cancer controls the corresponding numbers were 60, 38, and 0, clearly an insignificant difference.

It is evident, therefore, that the control group of patients with diseases other than cancer is strictly comparable with the group of lung-carcinoma patients in important respects but differs slightly with regard to the parts of England from which the patients were drawn. It is unlikely that this difference will invalidate comparisons, but it must be kept in mind; fortunately, it can be eliminated, if necessary, by confining comparisons to the smaller group of patients seen in the district hospitals.

Assessment of Smoking Habits

The assessment of the relation between tobacco-smoking and disease is complicated by the fact that smoking habits change. A man who has been a light smoker for years may become a heavy smoker; a heavy smoker may cut down his consumption or give up smoking—and, indeed, may do so repeatedly. An acute respiratory disease may force the sufferer to stop smoking, or he may be advised to stop for one of many pathological conditions. In 1947 a further complication was introduced by the Chancellor of the Exchequer, the duty on tobacco being raised to such an extent that many people made large cuts in the amount of tobacco they smoked—often to restore them partially or completely in the succeeding months. Fortunately the interviewing of patients was not begun till a year after the last major change was made in the tobacco duty; in any case the effect was minimized by interviewing the control patients *pari passu* with the lung-carcinoma patients, so that the change in price is likely to have affected all groups similarly.

The difficulties of a varying consumption can be largely overcome if a more detailed smoking history is taken than is customary in the course of an ordinary medical examination—for example, one man who was described in the hospital notes as being a non-smoker admitted to the almoner that he had been a very heavy smoker until a few years previously. In this investigation, therefore, the patients were closely questioned and 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 varying proportions smoked in pipes and cigarettes; and (*f*) whether or not they inhaled.

To record and subsequently to tabulate these details it was necessary to define what was meant by a smoker. Did the term, for example, include the woman who took one cigarette annually after her Christmas dinner, or the man of 50 who as a youth smoked a couple of cigarettes to see whether he liked it and decided he did not? If so, it is doubtful whether anyone at all could be described as a non-smoker. A smoker was therefore defined in this inquiry as a person who had smoked as much as one cigarette a day for as long as one year, and any less consistent amount was ignored. The histories obtained were, of course, a function of the patient's memory and veracity. To assess their reliability 50 unselected control patients with diseases other than cancer were interviewed a second time six months or more after their initial interview. Table III shows the comparison between the two answers obtained

TABLE III.—*Amount of Tobacco Smoked Daily Before Present Illness as Recorded at Two Interviews With the Same Patients at an Interval of Six Months or More*

First Interview No. of Persons Smoking	Second Interview. No. of Persons Smoking						
	0	1 cig.–	5 cigs.–	15 cigs.–	25 cigs.–	50 cigs.+	Total
0	8	1					9
1 cig.– ..		4	1				5
5 cigs.– ..		1	13	3			17
15 cigs – ..			4	9	1		14
25 cigs.– ..				1	3	0	4
50 cigs.+ ..					1	0	1
Total ..	8	6	18	13	5	0	50

to the question "How much did you smoke before the onset of your present illness?"

The answers to the other questions on smoking habits showed a variability comparable to that shown in Table III. It may be concluded, therefore, that, while the detailed smoking histories obtained by this investigation are not, as would be expected, strictly accurate, they are reliable enough to indicate general trends and to substantiate material differences between groups.

Smokers and Non-smokers

The simplest comparison that can be made to show whether there is any association at all between smoking and carcinoma of the lung is that between the proportion of lung-carcinoma patients who have been smokers and the proportion of smokers in the comparable group of subjects without carcinoma of the lung. Such a comparison is shown in Table IV.

TABLE IV.—*Proportion of Smokers and Non-smokers in Lung-carcinoma Patients and in Control Patients with Diseases Other Than Cancer*

Disease Group	No. of Non-smokers	No. of Smokers	Probability Test
Males: Lung-carcinoma patients (649)	2 (0·3%)	647	P (exact method) = 0·00000064
Control patients with diseases other than cancer (649) ..	27 (4·2%)	622	
Females: Lung-carcinoma patients (60)	19 (31·7%)	41	$\chi^2 = 5·76$; n = 1 0·01 < P < 0·02
Control patients with diseases other than cancer (60) ..	32 (53·3%)	28	

It will be seen that the vast majority of men have been smokers at some period of their lives, but also that the very small proportion of those with carcinoma of the lung who have been non-smokers (0.3%) is most significantly less than the corresponding proportion in the control group of other patients (4.2%). As was to be expected, smoking is shown to be a much less common habit among women; but here again the habit was significantly more frequent among those with carcinoma of the lung. Only 31.7% of the lung-carcinoma group were non-smokers, compared with 53.3% in the control group.

Amount of Smoking

In the simple comparison of Table IV all smokers have been classified together, irrespective of the amount they smoked. In Table V they have been subdivided according to the amount they smoked immediately before the onset of the illness which brought them into hospital. (If they had given up smoking before then, they have been classified according to the amount smoked immediately prior to giving it up.) This classification is described subsequently as "the most recent amount smoked."

TABLE V.—*Most Recent Amount of Tobacco* Consumed Regularly by Smokers Before the Onset of Present Illness; Lung-carcinoma Patients and Control Patients with Diseases Other Than Cancer*

Disease Group	No. Smoking Daily					Probability Test
	1 Cig.–*	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+	
Males: Lung-carcinoma patients (647)	33 (5·1%)	250 (38·6%)	196 (30·3%)	136 (21·0%)	32 (5·0%)	$\chi^2 = 36·95$; n = 4; P < 0·001
Control patients with diseases other than cancer (622)..	55 (8·8%)	293 (47·1%)	190 (30·5%)	71 (11·4%)	13 (2·1%)	
Females: Lung-carcinoma patients (41)..	7 (17·1%)	19 (46·3%)	9 (22·0%)	6 (14·6%)	0 (0·0%)	$\chi^2 = 5·72$; n = 2; 0·05 < P < 0·10 (Women smoking 15 or more cigarettes a day grouped together)
Control patients with diseases other than cancer (28) ..	12 (42·9%)	10 (35·7%)	6 (21·4%)	0 (0·0%)	0 (0·0%)	

* 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.

From Table V it will be seen that, apart from the general excess of smokers found (in Table IV) in lung-carcinoma patients, there is in this group a significantly higher proportion of heavier smokers and a correspondingly lower proportion of lighter smokers than in the comparative group of other patients. For instance, in the lung-carcinoma group 26.0% of the male patients fall in the two groups of highest consumption (25 cigarettes a day or more), while in the control group of other male patients only 13.5% are found there. The same trend is observable for women, but the numbers involved are small and the difference here between the carcinoma group and their control patients is not quite technically significant. If, however, the female lung-carcinoma patients are compared with the total

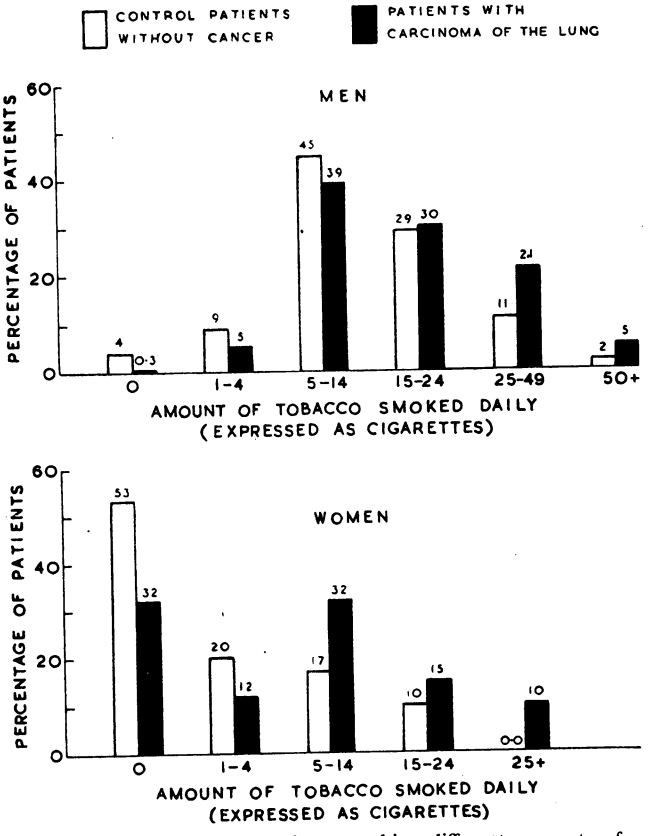

FIG. 1.—Percentage of patients smoking different amounts of tobacco daily.

TABLE VI.—*Maximum Amount of Tobacco Ever Consumed Regularly by Smokers; Lung-carcinoma Patients and Control Patients with Diseases Other Than Cancer*

Disease Group	No. Smoking as a Daily Maximum					Probability Test
	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.–	50 Cigs.+	
Males:						
Lung-carcinoma patients (647)	24 (3·7%)	208 (32·1%)	196 (30·3%)	174 (26·9%)	45 (7·0%)	$\chi^2=23·16$; n=4; P<0·001
Control patients with diseases other than cancer (622)..	38 (6·1%)	242 (38·9%)	201 (32·3%)	118 (19·0%)	23 (3·7%)	
Females:						
Lung-carcinoma patients (41)..	6 (14·6%)	15 (36·6%)	12 (29·3%)	8 (19·5%)	0 (0·0%)	$\chi^2=7·58$; n=2; 0·02<P<0·05 (Women smoking 15 or more cigarettes a day grouped together)
Control patients with diseases other than cancer (28) ..	12 (42·9%)	9 (32·1%)	6 (21·4%)	0 (0·0%)	1 (3·6%)	

TABLE VII.—*Estimate of Total Amount of Tobacco Ever Consumed by Smokers; Lung-carcinoma Patients and Control Patients with Diseases Other Than Cancer*

Disease Group	No. Who have Smoked Altogether					Probability Test
	365 Cigs.–	50,000 Cigs.–	150,000 Cigs.–	250,000 Cigs.–	500,000 Cigs.+	
Males:						
Lung-carcinoma patients (647)	19 (2·9%)	145 (22·4%)	183 (28·3%)	225 (34·8%)	75 (11·6%)	$\chi^2=30·60$; n=4; P<0·001
Control patients with diseases other than cancer (622)..	36 (5·8%)	190 (30·5%)	182 (29·3%)	179 (28·9%)	35 (5·6%)	
Females:						
Lung-carcinoma patients (41)..	10 (24·4%)	19 (46·3%)	5 (12·2%)	7 (17·1%)	0 (0·0%)	$\chi^2=12·97$; n=2; 0·001< P < 0·01 (Women smoking 15 or more cigarettes a day grouped together)
Control patients with diseases other than cancer (28) ..	19 (67·9%)	5 (17·9%)	3 (10·7%)	1 (3·6%)	0 (0·0%)	

number of women interviewed—that is, bringing in the other cancer groups interviewed and making appropriate allowance for age differences between them—then the significance of the trend in their case also is established ($\chi^2=13.23$; n=2; P approximately 0.001).

The results given in Tables IV and V are shown together graphically in Fig. 1. (The percentages in the figure are not all exactly the same as those in the tables. In the figure the percentages are based on the total number of patients in each disease group, smokers and non-smokers alike; in Table V they are percentages of smokers alone.)

Smoking History

Going one stage further, it has been noted earlier that the amount smoked daily at any one period does not, of course, necessarily give a fair representation of the individual's smoking history. This has been overcome to some extent in the previous tables by classifying a patient as a non-smoker only if he has never smoked regularly, by classifying him according to the amount he last smoked regularly if he had given up smoking, and by ignoring changes in smoking habits which had taken place subsequent to the illness which brought the patient into hospital. Other methods of analysis have also been adopted. Thus Table VI shows the results in the two main groups when a comparison is made between the maximum amounts ever smoked regularly, and Table VII shows a comparison between the estimated total amounts of tobacco smoked throughout the patients' whole lives. The estimates of the total amount smoked (expressed as cigarettes) have been made by multiplying the daily amount of tobacco smoked by the number of days that the patient has been in the habit of smoking and making allowance for the major recorded changes in the smoking history. Such estimates may, needless to say, be only very rough approximations to the truth, but they are, it is thought, accurate enough to reveal broad differences between the groups.

The results in Tables V, VI, and VII are, it will be seen, closely similar. Whichever measure of smoking is taken, the same result is obtained—namely, a significant and clear relationship between smoking and carcinoma of the lung. It might perhaps have been expected that the more refined concepts—the maximum amount ever smoked and the total amount ever smoked—would have shown a closer relationship than the most recent amount smoked before the onset of the present illness. It must be supposed, however, that any greater efficiency that might be introduced by the use of these measures is counterbalanced by the inaccuracy which results from requiring the patient to remember habits of many years past. It seems, therefore, that we may reasonably adopt "the most recent amount smoked" in subsequent tables as the simplest characteristic to describe a patient's smoking experience.

Comparisons of the age at which patients began to smoke, the number of years they have smoked, and the number of years they have given up smoking are shown in Table VIII.

It will be seen that the lung-carcinoma patients showed a slight tendency to start smoking earlier in life, to continue longer, and to be less inclined to stop, but the differentiation is certainly not sharp and the difference is technically significant only with respect to length of time stopped.

Cigarettes and Pipes

So far no distinction has been made between cigarette and pipe smokers, and it is natural to ask whether both methods of smoking tobacco are equally related to carcinoma of the lung. Again the difficulty arises that a man who describes himself as a pipe smoker may have smoked cigarettes until shortly before interrogation, or, alternatively, he may have had his teeth extracted and substituted cigarettes for his pipe. To overcome this, we have excluded

TABLE VIII.—*Age of Starting to Smoke, Number of Years Smoked, and Number of Years Stopped Smoking in Lung-carcinoma Patients and Control Patients with Diseases Other Than Cancer (Male and Female)*

Age at Starting	Lung-carcinoma Patients		Control Patients		No. of Years Smoking	Lung-carcinoma Patients		Control Patients		No. of Years Stopped	Lung-carcinoma Patients		Control Patients	
	No.	%	No.	%		No.	%	No.	%		No.	%	No.	%
Under 20 ..	541	78·6	488	75·1	1–	14	5·1	18	7·7	0	649	94·3	590	90·8
20–	118	17·2	129	19·8	10–	21		32		1–	30	4·4	37	5·7
30–	17	4·2	22	5·1	20–	351	51·0	338	52·0	10–	4	1·3	14	3·5
40+	12		11		40+	302	43·9	262	40·3	20+	5		9	
All ages ..	688		650		Total	688		650		Total	688		650	
$\chi^2=2·40$; n=2; 0·30<P<0·50					$\chi^2=4·65$; n=2; 0·05<P<0·10					$\chi^2=8·59$; n=2; 0·01<P<0·02				

all the men who gave a history of having ever consistently smoked both pipes and cigarettes and have compared the proportions of " pure pipe " and " pure cigarette " smokers among the lung-carcinoma and non-cancer control patients. The results are as follows: of the 525 lung-carcinoma patients who had smoked either pipes or cigarettes but not both 5.7% were pipe smokers and 94.3% were cigarette smokers; of 507 control patients with other diseases 9.7% were pipe smokers and 90.3% were cigarette smokers. The lower proportion of pipe smokers, and the corresponding excess of cigarette smokers, in the lung-carcinoma group is unlikely to be due to chance ($\chi^2=5.70$; $n=1$; $0.01<P<0.02$).

It therefore seems that pipe smoking is less closely related to carcinoma of the lung than cigarette smoking. On the other hand, it has been shown in Table V that light smoking is less closely related to carcinoma of the lung than heavy smoking, so that the result might be explained merely on the grounds that pipe smokers tend to smoke less tobacco.

In fact, pipe smokers do consume, on the average, less tobacco than cigarette smokers, but this is unlikely to be the whole explanation of the relative deficiency of pipe smokers observed in the carcinoma group. We find a higher proportion of cigarette smokers and a lower proportion of pipe smokers among the lung-carcinoma patients than among the control group of non-cancer patients at each level of consumption of tobacco—that is, at 1–4, 5–14, 15–24, and 25+ cigarettes or their equivalent a day. On the other hand, if we consider the " pure pipe " smokers by themselves and subdivide them according to the amount smoked, then we find a higher proportion of the carcinoma patients than of the control group in the higher smoking categories—that is, smoking more than 6 oz. of tobacco a week. In short, the results of this subdivision are similar to those shown in Table V for all smokers. It seems that the method by which the tobacco is smoked is of importance and that smoking a pipe, though also related to carcinoma of the lung, carries a smaller risk than smoking cigarettes. With the data at our disposal we are unable to determine how great the difference in risk may be.

Inhaling

Another difference between smokers is that some inhale and others do not. All patients who smoked were asked whether or not they inhaled, and the answers given by the lung-carcinoma and non-cancer control patients were as follows: of the 688 lung-carcinoma patients who smoked (men and women) 61.6% said they inhaled and 38.4% said they did not; the corresponding figures for the 650 patients with other diseases were 67.2% inhalers and 32.8% non-inhalers. It would appear that lung-carcinoma patients inhale slightly less often than other patients ($\chi^2=4.58$; $n=1$; $0.02<P<0.05$). However, the difference is not large, and if the lung-carcinoma patients are compared with all the other patients interviewed, and the necessary allowance is made for sex and age, the difference becomes insignificant ($\chi^2=0.19$; $n=1$; $0.50<P<0.70$).

Interpretation of Results

Though from the previous tables there seems to be no doubt that there is a direct association between smoking and carcinoma of the lung it is necessary to consider alternative explanations of the results. Could they be due to an unrepresentative sample of patients with carcinoma of the lung or to a choice of a control series which was not truly comparable? Could they have been produced by an exaggeration of their smoking habits by patients who thought they had an illness which could be attributed to smoking? Could they be produced by bias on the part of the interviewers in taking and interpreting the histories?

Selection of Patients for Interview

The method by which the patients with carcinoma of the lung were obtained has been discussed earlier; there is no reason to suppose that they were anything other than a representative sample of the lung-carcinoma patients attending the selected London hospitals. The control patients, as was shown in Table II, were exactly comparable so far as sex and age were concerned and they were sufficiently comparable with regard to social class for the difference between the two series to be ignored. They were not wholly comparable from the point of view of place of residence. The difference in this respect, however, was that more of the lung-carcinoma patients came from small towns and rural districts, and the figures in this inquiry show that consumption of tobacco per head in these areas is less than in London. Clearly this feature cannot have accounted for the observation that the lung-carcinoma patients smoked more. Further, if the comparison is confined to patients seen in district hospitals—and all of these resided in Greater London—the results are the same (Table IX).

TABLE IX.—*Most Recent Amount Smoked by Lung-carcinoma and Control Patients Seen in District Hospitals (Male and Female)*

Disease Group	No. Smoking Daily				
	0	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+
Lung-carcinoma patients (98) ..	2	12	36	27	21
Control patients with diseases other than cancer (98) ..	9	9	50	19	11

$\chi^2 = 11{\cdot}68$; $n = 4$; $0{\cdot}01<P<0{\cdot}02$

It might possibly be argued that the choice of a control group of patients with various medical and surgical conditions has, of itself, resulted in the selection of subjects with a smoking history less than the average. This would seem very unlikely, as we know of no evidence to suggest that less than average smoking is a characteristic of persons with any one group of diseases, and it certainly could not be held that it is equally a characteristic of persons suffering from all diseases other than carcinoma of the lung. Yet in Table X the smoking habits of the patients in five main groups of diseases are compared, allowing for their sex and age composition, and no significant difference can be demonstrated between them. (We have

TABLE X.—*Most Recent Amount Smoked by all Patients Other Than Those with Carcinoma of Lung, Divided According to Type of Disease (Male and Female)*

Disease Group.	No. Smoking Daily				
	0	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+
Cancer, other than carcinoma of lung (718)	236* *220·0*	78 *85·3*	237 *236·9*	110 *122·8*	57 *53·0*
Respiratory disease, other than cancer (335)	42 *47·0*	33 *29·7*	128 *136·1*	98 *84·1*	34 *38·1*
Cardiovascular disease (166) ..	22 *17·7*	19 *16·7*	64 *73·8*	38 *39·5*	23 *18·3*
Gastro-intestinal disease (328)..	39 *55·7*	31 *32·3*	143 *130·2*	81 *75·8*	34 *34·5*
Other diseases (215)	38 *36·6*	24 *21·1*	91 *86·0*	44 *48·9*	18 *22·1*

$\chi^2 = 20{\cdot}14$; $n = 16$; $0{\cdot}20<P<0{\cdot}30$.

* The roman figures show the actual numbers observed, those in italics are the numbers that would have occurred if the disease group in question had had in each sex and at each age exactly the same smoking habits as all the patients included in the table.

brought into this table all the patients with diseases other than carcinoma of the lung.)

As in other tables where sex and age differences between groups have had to be taken into account, the "expected" numbers have been obtained by taking the actual numbers of patients with each type of disease in each age and sex subgroup, and calculating what proportion of them would fall in each smoking category if they had had exactly the same habits as all the patients included in the Table. In other words, we have computed what ought to be the smoking habits of each disease group if it behaved in each sex and at each age like the total population of patients, and compared them with what, in fact, they were. The relatively large numbers of non-smokers in some of the groups are due to the fact that these disease groups included many old women.

There remains the possibility that the interviewers, in selecting the control patients, took for interview from among the patients available for selection a disproportionate number of light smokers. It is difficult to see how they could have done so, but the point can be tested indirectly by comparing the smoking habits of the patients whom they did select for interview with the habits of the other patients, other than those with carcinoma of the lung, whose names were notified by the hospitals. The comparison is made in Table XI and reveals no appreciable difference between the two groups.

TABLE XI.—*Most Recent Amount Smoked by All Patients Other Than Those with Carcinoma of Lung, Divided According to Whether They Were Notified or Selected for Interview (Male and Female)*

Method of Selection of Patient	No. Smoking Daily				
	0	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+
Notified by hospital (1,032) ..	307*	114	354	179	78
	301·8	*119·0*	*345·2*	*186·1*	*80·0*
Selected by interviewer (730) ..	70	71	309	192	88
	75·2	*66·0*	*317·8*	*184·9*	*86·0*
	$\chi^2 = 2{\cdot}14$; n = 4; $0{\cdot}70 < P < 0{\cdot}80$.				

* See footnote to Table X.

It can therefore be concluded that there is no evidence of any special bias in favour of light smokers in the selection of the control series of patients. In other words, the group of patients interviewed forms, we believe, a satisfactory control series for the lung-carcinoma patients from the point of view of comparison of smoking habits.

Patient's Smoking History

Another possibility to consider is that the lung-carcinoma patients tended to exaggerate their smoking habits. Most of these patients cannot have known that they were suffering from cancer, but they would have known that they had respiratory symptoms, and such knowledge might have influenced their replies to questions about the amount they smoked. However, Table X has already shown that patients with the other respiratory diseases did not give smoking histories appreciably different from those given by the patients with non-respiratory illnesses. There is no reason, therefore, to suppose that exaggeration on the part of the lung-carcinoma patients has been responsible for the results.

The Interviewers

When the investigation was planned it was hoped that the interviewers would know only that they were interviewing patients with cancer of one of several sites (lung, stomach, or large bowel) but not, at the time, the actual site. This, unfortunately, was impracticable; the site would be written on the notification form, or the nurse would refer to the diagnosis in pointing out the patient, or it would become known that only patients with cancer of one of the sites under investigation would be found in one particular ward. Out of 1,732 patients notified and interviewed as cases of cancer, the site of the growth was known to the interviewer at the time of interview in all but 61. Serious consideration must therefore be given to the possibility of interviewers' bias affecting the results (by the interviewers tending to scale up the smoking habits of the lung-carcinoma cases).

Fortunately the material provides a simple method of testing this point. A number of patients were interviewed who, at that time, were thought to have carcinoma of the lung but in whom the diagnosis was subsequently disproved. The smoking habits of these patients, believed by the interviewers to have carcinoma of the lung, can be compared with the habits of the patients who in fact had carcinoma of the lung and also with the habits of all the other patients. The result of making these comparisons is shown in Tables XII and XIII, and it will be seen that the smoking

TABLE XII.—*Most Recent Amount Smoked by Patients with Carcinoma of Lung and by Patients Thought Incorrectly by the Interviewers to be Suffering from Carcinoma of Lung (Male and Female)*

Disease Group	No. Smoking Daily				
	0	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+
Patients with carcinoma of lung (709)	21*	40	269	205	174
	31·7	*48·0*	*276·0*	*201·0*	*152·7*
Patients incorrectly thought to have carcinoma of lung (209)†	35	25	83	50	16
	24·3	*17·0*	*76·0*	*54·0*	*37·3*
	$\chi^2 = 29{\cdot}76$; n = 4; $P < 0{\cdot}001$.				

* See footnote to Table X.
† There is a large number of cases in this group because one hospital notified all cases admitted for bronchoscopy; 147 out of the 209 incorrectly thought to have carcinoma of the lung were interviewed at this hospital.

TABLE XIII.—*Most Recent Amount Smoked by Patients Incorrectly Thought by the Interviewers to be Suffering from Carcinoma of Lung and All Other Patients Not Suffering from Carcinoma of Lung (Male and Female)*

Disease Group	No. Smoking Daily				
	0	1 Cig.–	5 Cigs.–	15 Cigs.–	25 Cigs.+
Patients incorrectly thought to have carcinoma of lung (209)†	35*	25	83	50	16
	36·8	*20·4*	*82·0*	*48·8*	*20·8*
All other patients not suffering from carcinoma of lung (1,553)	342	160	580	321	150
	340·2	*164·6*	*581·0*	*322·2*	*145·2*
	$\chi^2 = 2{\cdot}58$; n = 4; $0{\cdot}50 < P < 0{\cdot}70$.				

* See footnote to Table X. † See footnote to Table XII.

habits of the patients who were incorrectly thought to have carcinoma of the lung at the time of interview are sharply distinguished from the habits of those patients who did in fact have carcinoma of the lung (Table XII), but they do not differ significantly from the habits of the other patients interviewed (Table XIII).

It is therefore clearly not possible to attribute the results of this inquiry to bias on the part of the interviewers, as, had there been any appreciable bias, the smoking habits of the patients thought incorrectly to have carcinoma of the lung would have been recorded as being like those of the true lung-carcinoma subjects and not the same as those without carcinoma of the lung.

We may add that the results cannot be due to different workers interviewing different numbers of patients in the cancer and control groups, for, while the four interviewers

did not see exactly the same proportions of patients in all the groups, the proportions were very close. Moreover, if the patients seen by each of the interviewers are treated as four separate investigations, highly significant differences are found between the lung-carcinoma patients and the other patients interviewed in three instances. In the fourth the difference is in the same direction, but, owing to the small number of patients seen, the results are not technically significant (P lies between 0.10 and 0.05; in this instance the almoner had to stop work because of illness, having seen only 46 patients with carcinoma of the lung).

TABLE XIV.—*Ratios of Patients Interviewed With Carcinoma of Lung and with a Given Daily Consumption of Tobacco to the Estimated Populations in Greater London Smoking the Same Amounts (Male and Female Combined; Ratios per Million)*

Age	Daily Consumption of Tobacco						Total
	0	1–4 Cigs.	5–14 Cigs.	15–24 Cigs.	25–49 Cigs.	50 Cigs.+	
25– ..	*0**	*11*	*2*	*6*	*28*	—	4
35– ..	*2*	*9*	43	41	67	*77*	29
45– ..	*12*	34	178	241	429	667	147
55– ..	14	133	380	463	844	600	244
65–74 ..	21	110	300	510	1,063	*2,000*	186

* Ratios based on less than 5 cases of carcinoma of the lung are given in italics.

Discussion

To summarize, it is not reasonable, in our view, to attribute the results to any special selection of cases or to bias in recording. In other words, it must be concluded that there is a real association between carcinoma of the lung and smoking. Further, the comparison of the smoking habits of patients in different disease groups, shown in Table X, revealed no association between smoking and other respiratory diseases or between smoking and cancer of the other sites (mainly stomach and large bowel). The association therefore seems to be specific to carcinoma of the lung. 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.

The effect of smoking varies, as would be expected, with the amount smoked. The extent of the variation could be estimated by comparing the numbers of patients interviewed who had carcinoma of the lung with the corresponding numbers of people in the population, in the same age groups, who smoke the same amounts of tobacco. Our figures, however, are not representative of the whole country, and this may be of some importance, as countrymen smoke, on the average, less than city dwellers. Moreover, as was shown earlier, the carcinoma and the control patients were not comparable with regard to their places of residence. The difficulty can be overcome by confining the comparison to the inhabitants of Greater London.

If it be assumed that the patients without carcinoma of the lung who lived in Greater London at the time of their interview are typical of the inhabitants of Greater London with regard to their smoking habits, then the number of people in London smoking different amounts of tobacco can be estimated. Ratios can then be obtained between the numbers of patients seen with carcinoma of the lung and the estimated populations at risk who have smoked comparable amounts of tobacco. This has been done for each age group, and the results are shown in Table XIV. It must be stressed that the ratios shown in this table are not measures of the actual risks of developing carcinoma of the lung, but are put forward very tentatively as proportional to these risks.

Thus Table XIV shows clearly, and for each age group, the conclusion previously reached—that the risk of developing carcinoma of the lung increases steadily as the amount smoked increases. If the risk among non-smokers is taken as unity and the resulting ratios in the three age groups in which a large number of patients were interviewed (ages 45 to 74) are averaged, the relative risks become 6, 19, 26, 49, and 65 when the number of cigarettes smoked a day are 3, 10, 20, 35, and, say, 60—that is, the mid-points of each smoking group. In other words, on the admittedly speculative assumptions we have made, the risk seems to vary in approximately simple proportion with the amount smoked.

One anomalous result of our inquiry appears to relate to inhaling. It would be natural to suppose that if smoking were harmful it would be more harmful if the smoke were inhaled. In fact, whether the patient inhaled or not did not seem to make any difference. It is possible that the patients were not fully aware of the meaning of the term and answered incorrectly, but the interviewers were not of that opinion. In the present state of knowledge it is more reasonable to accept the finding and wait until the size of the smoke particle which carries the carcinogen is determined. Until this is known nothing can be stated about the effect which any alteration in the rate and depth of respiration may have on the extent and site of deposition of the carcinogen (Davies, 1949).

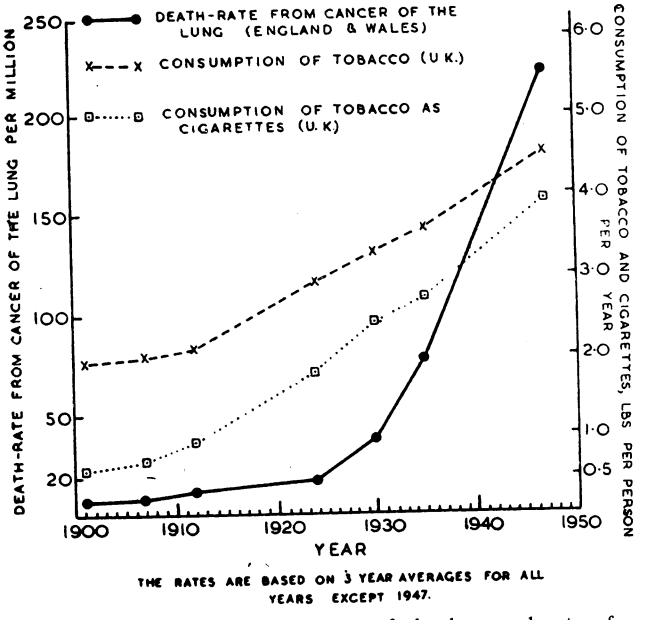

FIG. 2.—Death rate from cancer of the lung and rate of consumption of tobacco and cigarettes.

How, in conclusion, do these results fit in with other known facts about smoking and carcinoma of the lung? Both the consumption of tobacco and the number of deaths attributed to cancer of the lung are known to have increased, and to have increased largely, in many countries

this century. The trends in this country are given in Fig. 2, and show that over the last 25 years the increase in deaths attributed to cancer of the lung has been much greater than the increase in tobacco consumption. This might well be because the increased number of deaths in the latter years is partly an apparent increase, due to improved diagnosis; in other words, it is not wholly a reflection of increased prevalence of cancer of the lung. On the other hand, it is possible that the carcinogenic agent is introduced during the cultivation or preparation of tobacco for consumption and that changes in the methods of cultivation and preparation have occurred as well as changes in consumption. However that may be, it is clearly not possible to deduce a simple time relationship in this country between the consumption of tobacco and the number of deaths attributed to cancer of the lung.

The greater prevalence of carcinoma of the lung in men compared with women leads naturally to the suggestion that smoking may be a cause, since smoking is predominantly a male habit. Although increasing numbers of women are beginning to smoke, the great majority of women now of the cancer age have either never smoked or have only recently started to do so. It is therefore tempting to ascribe the high sex ratio to the greater consumption of tobacco by men. If this were true it would be expected that the incidence of carcinoma of the lung would be the same among non-smokers in both sexes. In this series, 2 out of 649 men and 19 out of 60 women with carcinoma of the lung were non-smokers.

To calculate the incidence rates among non-smokers of either sex it is necessary to estimate the number of non-smokers in the population from which the patients were drawn. For reasons given earlier this cannot be done, but an estimate can be obtained of the expected sex ratio of cases occurring among non-smokers in the Greater London area. From the experience of the patients without carcinoma of the lung who lived in Greater London at the time of their interview it can be calculated that there were, in 1948, 175,000 men and 1,582,000 women in London between the ages of 25 and 75 who had never been smokers according to our definition of the term. Taking these figures, subdivided by age, in association with the age distribution of the 16 cases of carcinoma of the lung observed among non-smokers living in Greater London, it can be calculated that, if the incidence of the disease were equal among non-smokers of both sexes, one case should have occurred in a man and 15 in women. In fact, the observed ratio was 0 to 16.

This finding is consistent with the theory that the risk of developing carcinoma of the lung is the same in both men and women, apart from the influence of smoking. It is not, however, possible to demonstrate with the data at our disposal that different amounts of smoking are sufficient to account for the overall sex ratio.

As to the nature of the carcinogen we have no evidence. The only carcinogenic substance which has been found in tobacco smoke is arsenic (Daff and Kennaway, 1950), but the evidence that arsenic can produce carcinoma of the lung is suggestive rather than conclusive (Hill and Faning, 1948). Should arsenic prove to be the carcinogen, the possibility arises that it is not the tobacco itself which is dangerous. Insecticides containing arsenic have been used for the protection of the growing crop since the end of the last century and might conceivably be the source of the responsible factor. This, too, might account for the observation that deaths from cancer of the lung have increased more rapidly than the consumption of tobacco.

Summary

The great increase in the number of deaths attributed to cancer of the lung in the last 25 years justifies the search for a cause in the environment. An investigation was therefore carried out into the possible association of carcinoma of the lung with smoking, exposure to car and fuel fumes, occupation, etc. The preliminary findings with regard to smoking are reported.

The material for the investigation was obtained from twenty hospitals in the London region which notified patients with cancer of the lung, stomach, and large bowel. Almoners then visited and interviewed each patient. The patients with carcinoma of the stomach and large bowel served for comparison and, in addition, the almoners interviewed a non-cancer control group of general hospital patients, chosen so as to be of the same sex and age as the lung-carcinoma patients.

Altogether 649 men and 60 women with carcinoma of the lung were interviewed. Of the men 0.3% and of the women 31.7% were non-smokers (as defined in the text). The corresponding figures for the non-cancer control groups were: men 4.2%, women 53.3%.

Among the smokers a relatively high proportion of the patients with carcinoma of the lung fell in the heavier smoking categories. For example, 26.0% of the male and 14.6% of the female lung-carcinoma patients who smoked gave as their most recent smoking habits prior to their illness the equivalent of 25 or more cigarettes a day, while only 13.5% of the male and none of the female non-cancer control patients smoked as much. Similar differences were found when comparisons were made between the maximum amounts ever smoked and the estimated total amounts ever smoked.

Cigarette smoking was more closely related to carcinoma of the lung than pipe smoking. No distinct association was found with inhaling.

Taken as a whole, the lung-carcinoma patients had begun to smoke earlier and had continued for longer than the controls, but the differences were very small and not statistically significant. Rather fewer lung-carcinoma patients had given up smoking.

Consideration has been given to the possibility that the results could have been produced by the selection of an unsuitable group of control patients, by patients with respiratory disease exaggerating their smoking habits, or by bias on the part of the interviewers. Reasons are given for excluding all these possibilities, and it is concluded that smoking is an important factor in the cause of carcinoma of the lung.

From consideration of the smoking histories given by the patients without cancer of the lung a tentative estimate was made of the number of people who smoked different amounts of tobacco in Greater London, and hence the relative risks of developing the disease among different grades of smokers were calculated. The figures obtained are admittedly speculative, but suggest that, above the age of 45, the risk of developing the disease increases in simple proportion with the amount smoked, and that it may be approximately 50 times as great among those who smoke 25 or more cigarettes a day as among non-smokers.

The observed sex ratio among non-smokers (based, it must be stressed, on very few cases) can be readily accounted for if the true incidence among non-smokers is equal in both sexes.

It is not possible to deduce a simple time relationship between the increased consumption of tobacco and the increased number of deaths attributed to cancer of the lung. This may be because part of the increase is apparent—that is, due to improved diagnosis—but it may also be because the carcinogen in tobacco smoke is introduced into the tobacco during its cultivation or preparation. Greater changes may have taken place in the methods involved in these processes than in the actual amount of tobacco consumed.

Co-operating Hospitals.—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', St. Mary's, St. Thomas's, University College, Whittington.

We are indebted to the staffs of the above-named hospitals for having allowed us to interview their patients and to have access to the hospital notes; also to the individual members of the staffs, both medical and lay, who notified the cases and collected the notes for examination. The work could not have been carried out without their co-operation. Sir Ernest Kennaway and Dr. Percy Stocks took part in a conference called by the Medical Research Council, at which this investigation was initiated, and we have been fortunate in having their helpful advice throughout its course. Professor W. D. Newcomb has advised us on individual problems of pathology. We are most grateful for this assistance. Finally, we wish to thank Miss Marna Buckatzsch, Miss Beryl Iago, Miss Keena Jones, and Miss Rosemary Thomson, who interviewed the patients and helped with the analysis of the results; and Dr. J. T. Boyd for assistance in the calculations.

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REGIME FOR TREATMENT OF SEVERE AND ACUTE LIVER DISEASE

BY

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In spite of increasing biochemical knowledge on the subject of liver necrosis, the high mortality rate of severe liver disease of acute onset remains a therapeutic challenge. Once coma has occurred a fatal outcome is probable; a recovery is always an event of note.

It is, however, a remarkable fact that even patients suffering from massive necrosis may linger on for a number of days. This is in marked contrast to the short period of survival of animals after hepatectomy. Moreover, in so-called "acute yellow atrophy" several of the liver's functions may remain apparently normal until death. Even the fasting blood-sugar level may remain within normal limits. This must surely mean that enough liver tissue survives to carry out certain highly important metabolic processes. There is also reason to believe that the histological picture of massive necrosis is not unrelated to post-mortem autolysis, and that much more liver tissue survives during life than is apparent after death (van Beek and Haex, 1943).

These facts are of great importance. If practically all the liver were necrotic during life, then treatment would obviously be useless. On the other hand, if large numbers of liver cells were diseased but not dead the possibility would remain that the process was reversible, and that a successful treatment might eventually be discovered. In the hope that the latter state of affairs actually occurs, I have been attempting over a number of years to treat these cases on biochemical principles.

Earlier Work

Some three years ago treatment was begun in a series of six patients in coma from acute liver disease (Latner and Mowbray—paper in preparation). By daily intravenous administration, each patient received 1 to 3 g. of cystine in addition to glucose and plasma. The importance of this amino-acid in the prevention of experimental necrosis had already been demonstrated (Glynn *et al.*, 1945). All these cases presented the clinical picture of "acute yellow atrophy" and all had a fatal outcome.

A gross amino-aciduria has been demonstrated in severe liver disease by paper chromatography (Dent, 1949). In view of the known increase in the amino-acid content of the blood, including the thioamino-acids, Dent has suggested that the necrotic liver cannot utilize them and they could not therefore be of much use in curative treatment.

There was some possibility that a reflex circulatory upset affecting the liver might prevent the cystine reaching the liver cells. With this possibility in view, tetraethylammonium bromide was administered to our sixth case as soon as it became obvious that there was no response to cystine. The downhill progress of the patient was in no way affected.

These discouraging results made it obvious that we were thinking along incorrect lines. The diseased liver cell required cystine to prevent necrosis but could not utilize it adequately from external sources. The problem, therefore, was to render the cells less sensitive to cystine deficiency, so that they could utilize their own cystine until such time as recovery was complete enough to allow them to use the amino-acids of surrounding tissue fluid. From this point of view the role assigned to tocopherol in the production of experimental hepatic necrosis (Schwarz, 1944; György, 1947; Himsworth and Lindan, 1949) assumes great importance. This vitamin has therefore been included in the regime of treatment described below.

The intracellular oxidative processes of the liver and other organs also require other vitamins. In their absence toxic products accumulate which could easily be a factor in the final death of liver cells. The successful application of massive doses of the vitamin-B group in the cholaemia of cirrhosis has already been reported (Patek *et al.*, 1948). This form of therapy was therefore also included in the regime.

Recent knowledge of the state of dynamic equilibrium of the body proteins also has a bearing on this problem. It seems likely that proteins are not only destroyed by wear and tear but are continuously being broken down and resynthesized at a remarkably rapid rate. This protein turnover can be demonstrated with radioactive tracers. One would not be far wrong in stating that every protein in the body was in a state of dynamic equilibrium with all other proteins (Whipple, 1948). The liver has been described as the master organ for protein metabolism. The diminution of the plasma proteins in severe disease of this organ could profoundly upset the normal equilibrium of the tissue proteins and so lead to metabolic upsets. The resulting toxic metabolites could act unfavourably on already damaged liver cells. It therefore becomes of great importance to administer plasma protein in severe liver disease, and for this reason it has been included in the regime.

Vitamins of the B group have been administered along with a dextrose solution in normal saline. The saline vehicle has been used because of the remarkable tendency for these patients to develop low plasma-chloride levels, probably related to vomiting and possibly to associated renal failure.