BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 9 1957

SOME QUESTIONS ON CANCER OF THE LUNG, LARYNX, AND URINARY TRACT*

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The study of cancer as it occurs in man must be carried on empirically while others attack the fundamental question, "How, and why, does a cell divide?" The distribution of cancer in man, and all factors which might affect this distribution, must be examined systematically.

Some Characters of Cancer in Man

These characters are: (1) *sex incidence*; (2) *prevalence*—increasing, decreasing, or stationary; (3) *social gradient*—rise or fall, or neither, in relation to the Registrar-General's Social Classes I to V; (4) *urban-rural rates*—urban +, rural +, or neither.

Sexes must always be considered separately. They may or may not be found to behave in the same way. Figures for the total incidence of any one form of cancer are of little if any value.

The reason for any difference in these characters can be the subject of inquiry. It may not be possible to prove what the reason is, because: (1) one cannot experiment on man; (2) the time lag of such effects is very largely unknown; and (3) social conditions and atmospheric pollution are continually changing.

Thus about 150 years ago the Industrial Revolution began to change England from an agricultural to an industrial country, and about 1850, in the districts most affected by this change and in others to the east of them, about 50 species of *Lepidoptera* began to change their protective colour from lighter to darker shades as the lichens on the blackened bark of trees were killed by the sulphur dioxide and other constituents of town

smoke (Fig. A). Now atmospheric pollution is decreasing with more efficient combustion of coal and the increased use of gas and electricity for heating. (Kettlewell, 1955a, Fig. 1.)

Sexual Incidence of Cancer of Lung

Doll (1953) concluded that the incidence of cancer of the lung was about the same in non-smokers of either sex. But no inferences can be drawn from the incidence of cancer of the lung upon smokers of one sex with regard to the other sex, as is very often done, because we simply do not know whether any intrinsic sexual factor is concerned. The kind of wholly impossible experiment which is required is to set up populations of, say, 10,000 persons of each sex, of the same age distribution, who will smoke 30 cigarettes daily for 30 years. Our present knowledge does not allow any forecast of the resulting sexual incidence of cancer of the lung.

The Registrar-General's figures (Table I) show that the immense increase in deaths from cancer of the lung in the 12 years 1943 to 1954 has not been accompanied by any change in the ratio of the death rates of the two sexes (1:5.8 in the first half and 1:5.9 in the second half of the period). This fact suggests that the agent causing this rise has changed uniformly. The data from Japan (Stocks, 1956) provide an interesting comparison (see Table VII).

Incidence of Cancer in Town and Country* and in Smokers and Non-Smokers

A comparative study, of the incidence of all forms of cancer in town- and in country-dwellers, and in smokers and in non-smokers, in both sexes is needed urgently. The two problems are very much of the same nature and require

*Since this paper was written the Registrar-General's *Statistical Review of England and Wales* (1953, Text) has been issued, which contains a very large amount of data on this subject.

*These notes are based upon data used in May, 1956, for the Richardson Lecture at the Massachusetts General Hospital and for talks given at the Sloan-Kettering Institute for Cancer Research, and in Professor W. U. Gardner's Department of Anatomy at Yale, with the addition of material obtained from Dr. E. Cuyler Hammond and Dr. Oscar Auerbach. It is a great pleasure to acknowledge my debt to all who did so much to make this visit enjoyable and valuable in every way.

FIG. A.—Left: Black and light forms of the peppered moth on an oak trunk in an industrial area. The normal protective colouring of the latter is clearly no longer effective. Right: The black and light forms of the same moth resting on a lichened oak trunk; the black form is now the more conspicuous (Kettlewell, 1955b). (Reproduced, by permission, from *Discovery*.)

TABLE I.—*Cancer of the Trachea, Bronchus, and Lung. England and Wales, 1943–54 (Registrar-General, Statistical Review, 1953–54, Tables, Part I, Medical)*

	Males			Females		
	Deaths	Rates per Million Living	Increase in Mean Rate	Deaths	Rate per Million Living	Increase in Mean Rate
1943	4,943	303		1,166	54	
1944	5,331	329		1,237	57	
1945	5,805	354		1,356	62	
1946	6,607	355		1,437	65	
1947	7,581	387		1,623	73	
1948	8,403	413		1,759	79	
Mean of first 6 years	6,445	375.0		1,430	65.0	
1949	9,130	444		1,845	82	
1950	10,254	485		1,987	87	
1951	11,166	530		2,081	91	
1952	11,981	568		2,237	98	
1953	12,881	607		2,251	98	
1954	13,995	658		2,336	101	
Mean of second 6 years	11,568	548.7	46.3%	2,123	92.8	42.8%

Ratio of mean rates, female to male: first 6 years, 1: 5.8; second 6 years, 1: 5.9.

the same kind of investigation. Tobacco and coal are both plant products, one of which is about 300 million years older than the other.

Thus when one is exposed to the irritating atmosphere of a fog a good deal of mucus upon which particles have been arrested passes back from the nose into the pharynx, and comes up from the bronchial passages into the mouth, and this material, if not expectorated, is swallowed. Is it quite harmless to the alimentary canal? Similarly, the subject of "smoker's throat" may swallow a good deal of mucus when smoking.

Urban Factors

A number of investigations have shown, with varying degrees of distinctness, a higher incidence of various forms of cancer among town-dwellers. In seeking for a reason, the fact that better methods of diagnosis are more accessible in towns is always easy to invoke and difficult to assess. Any numerical estimate of the effect of improved diagnosis can only be arbitrary. Thus Kreyberg (1954) considers that in Norway a four-and-a-half-fold increase in lung cancer in females is due to better diagnosis, while a sevenfold increase in men is a real one.

Where the respiratory tract is concerned one must of course consider atmospheric pollution and exposure to soot containing at least two carcinogens—namely, 3:4-benzopyrene and arsenic—and doubtless others not yet identified. But do these factors penetrate to and affect any other parts of the body? Some data showing the very large range of atmospheric pollution in various towns and countries are given in Table II.

Thirty years ago my wife and I showed that cancer of the scrotum is rare in agricultural workers and is almost

TABLE II.—*Some Examples of Atmospheric Pollution. (Published and Other Data from H.M. Fuel Research Station: J. M. Campbell, R. L. Cooper, F. Goulden, E. L. Kennaway, M. E. Urquhart, and R. E. Waller)*

	Smoke (mg./100 m. ³)	3:4- Benzopyrene (μg./100 m. ³)	Arsenic (As ₂ O ₃) (μg./100 m. ³)
Sheffield, February, 1948	44–173	6 to 33	
Salford, November to March		15 to 30	
London { January		14.7	7.7–9.6
(County Hall) { June		2.6	2.0
Sheffield { 1950, January		7.8	7.0–9.4
{ 1949, June		2.0	
Mean of { London (Beckton)		7.1	13.2
year { Bristol		1.3	3.7
7 English towns, { Winter	36.5 *		
mean { Summer	18.4		
Oslo, Whole year	1.3–5.7	2.5	1.9–3.1
Copenhagen, Mean of 4 stations, Winter	4.9	1.45	1.8
Iceland { Reykjavik, Whole year	0.9–1.5	0.23	0 to 0.7
{ Akureyri { Winter	0.8		0 to 1.7
{ Summer	0.5	0.049–0.057	

unknown in those social classes who wash most (Kennaway, 1925; Kennaway and Kennaway, 1946), and the suggestion was made that "it would seem possible that cancer of the scrotum is influenced by exposure to coal-smoke—in other words, possibly all town-dwellers are in some very slight degree liable to 'chimneysweep's cancer.'" Probably various carcinogens, with the exception of sunlight, are more abundant in towns, and their actions may summate, a process about which we know very little; one of the latest contributions on this question is that of Cloudman *et al.* (1955).

When comparing various batches of data about atmospheric pollution one must bear in mind that the materials concerned may not be the same in different countries or even in different towns in the same country. Thus the suspended matter of Liverpool might have a carcinogenic effect which summates with that of tobacco (Stocks and Campbell, 1955), while the corresponding material of Oslo might not do so (Kreyberg, 1954).

A very valuable source of data on this question is available in the official figures for mortality and morbidity from Norway, Denmark, and Finland, which are classified under urban and rural districts, and in the two last-named the figures for the capital† also are given separately. The populations of these three countries are of the order of one-eleventh of that of England and Wales, and present a more manageable problem.

The first evidence brought forward suggesting that urban conditions induced cancer of the lung and larynx was perhaps that showing the low incidence upon male outdoor workers. Calculations based on the Registrar-General's figures showed (Table III) that a group of open-air occu-

TABLE III.—*Cancer of Lung and Larynx in Out-of-Door Occupations, England and Wales (Kennaway and Kennaway, 1936, 1947)*

Occupation	Ratio of Registered to 100 Calculated Deaths			
	Cancer of Lung		Cancer of Larynx	
	1921–32	1933–8	1921–32	1933–8
Gardeners	58	61	75	79
Farm bailiffs and foremen	26	22	44	30
Agricultural labourers, including shepherds	34	26	41	60
Farmers	53	32	40	41

TABLE IV.—*Open-air Occupations, England and Wales, 1951 (Registrar-General)*

Standard Mortality Ratio. Males aged 20–64

Cancer	Social Class IV Partly Skilled	
	Agricultural Workers	Others
Larynx	13*	115*
Lung, bronchus, trachea	62	97

* Based upon fewer than 10 deaths.

pations (gardeners, farmers, agricultural labourers, including shepherds, and farm bailiffs and foremen), which included about 954,000 men, had low ratios for cancer of the lung (22 to 61) and of the larynx (29 to 79). The highest figures in each case are given by gardeners, of whom many live in or near large towns.

[Some evidence that the same character of open-air occupations persists in recent years is given by the smaller numbers derived from the 1951 Census 1% Sample Tables (Table IV).]

These results led to further investigation comparing the whole population of England and Wales of both sexes (Curwen, Kennaway, and Kennaway, 1954). This showed that the standard mortality ratio for cancer of the lung in both sexes, and of the larynx in males, falls with decreasing urbanization, as is shown in Fig. 1 by the series—county boroughs (mostly towns with a population of 100,000 or more), urban districts (other towns), and rural districts (the

†An important instance of the value of such data is given below, in the section on Cancer of the Urinary Tract.

FIG. 1.—Urban and rural incidence of cancer of the lung and larynx. England and Wales (Curwen *et al.*, 1954). Reproduced, by permission, from the *British Journal of Cancer*.

rest of the country). The gradient is less steep for cancer of the lung in women, and cancer of the larynx in women shows exactly the reverse relationship. This peculiar behaviour of cancer of the female larynx has at present no explanation, although one might suspect a diet consisting too largely of white bread and tea.

When considering urban factors in relation to cancer one must of course seek for other conditions besides atmospheric pollution by smoke from various sources. There may be differences in the diet, both solid and liquid, of town and country dwellers, and radioactivity increases in any enclosed place owing to emanation from walls. Thus Dawson (1952) observed that: "In the laboratory there was usually twice the activity found at the open-air site on the roof. At Chiswick, ventilating the room lowered the activity by as much as one-half, whilst in the coal-cellar the activity was 14 times greater than at the site in the garden. In the Post Office air-raid shelter the ventilation was as restricted as any found in habitable buildings; the activity was 120 times as high as at the open-air site."

Smokers and Non-Smokers

The classification of persons affected by cancer of the lung into smokers and non-smokers is easy, but the matter is not so simple. A person who is going to develop cancer of the lung whether he smokes or not, may be a smoker, and a heavy smoker. Possibly with further knowledge we may be able to identify such cases by the histological type of the tumour. Some possible categories of persons affected by cancer of the lung are shown in Table V.

TABLE V.—Classification of Some Persons Developing Cancer of Lung

Carcinogen:		1. Non-smoker.
Intrinsic		2. Smoker who would have developed cancer of lung if non-smoker.
		3. Smoker not exposed to atmospheric pollution.
Extrinsic	Tobacco	4. Smoker exposed to atmospheric pollution.
	Atmospheric pollution	5. Non-smoker exposed to atmospheric pollution.

The relation of atmospheric pollution and tobacco, together, to the causation of cancer of the lung is the subject of considerable difference of opinion. The summation of carcinogenic action is a subject about which we have much to learn, even under the comparatively simple conditions of experiments upon animals. Data on a very wide range of atmospheric pollution are now available (Table II) thanks to the co-operation of Professor Niels Dungal, of Reykjavik, Professor Leiv Kreyberg, of Oslo, and Dr. Johannes Clemmesen, of Copenhagen. When such data can be correlated with those for smoking habits and for cancer of the lung it may be possible to decide this question. If such summation occurs, a smoker in, for instance, Reykjavik should be able to smoke more cigarettes with

impunity than if he were in Sheffield or Salford. Stocks and Campbell (1955) show the interesting inferences which can be drawn if this process of summation is accepted.

The simple adding together of amounts of materials—for example, arsenic or 3:4-benzpyrene inspired with town air, and with tobacco smoke, is misleading, because the greater part of the former is taken in through the nose, which arrests 80% of particles larger than 2.5μ (Davies, 1949), while tobacco smoke evades this filter altogether.*

Scar-Cancers of the Lung: Possible Importance of Cholesterol

The cancers of the lung associated with scars (*Narbenkrebs*) and with deposits of cholesterol described by the German pathologists Rösle (1953) and Lüders and Themel (1954) have been investigated in this country by Raeburn (1956), who states: "Further cases of lung cancer associated with scarring have been studied in detail. The scars are of various aetiology—collapse pneumonia, tuberculosis, and even foreign body. The common factor is proliferation of bronchial epithelium within the fibrous framework of the scarred area. Twelve cases of cancer in association with tuberculosis are receiving separate attention. These scars are rich in cholesterol."

This proximity of cholesterol to malignant growth is of great interest in view of the discovery by Hieger† (1949) of the carcinogenic power of cholesterol, which is not diminished by drastic purification (Schwenk process). Of course, the juxtaposition of these crystals and a carcinoma is very far from proving that one is the cause of the other, but what more evidence can one expect from histological appearances?

The Process of Smoking a Cigarette

The physical and chemical changes which take place when a cigarette is smoked are complex, and the conditions under which they occur are unlike those present

FIG. 2.—Diagram of a cigarette.

in most other combustions. The changes include: (1) oxidation, (2) pyrolytic condensations producing polycyclic compounds, (3) volatilization repeatedly, and (4) condensation repeatedly.

Commins, Cooper, and Lindsey (1954) threaded a thermocouple through a cigarette and observed the readings as the burning zone approached. They found that the maximum temperature ranges from 650 to 700° in the centre, to 900° at the surface, where the oxidation is most rapid. The temperature drops very rapidly behind the burning area—for example, from 770° to 100° in 3.5 mm. (Harlow, 1956). Hence a continuous process of volatilization and condensation takes place in a "leap-frog" manner as the cigarette is smoked.

For the present purpose, nothing matters but what emerges at the stump, and in this respect there may well be a considerable difference between smoking, say, 66% and 80% of the cigarette (Fig. 2).

*The first smokers of tobacco seen by Europeans (two companions of Columbus in Cuba in 1492) inspired the smoke of cigars through the nostrils; but their example was not followed (Koskowski, 1955).

†The work of Dr. Hieger and Professor L. F. Fieser on the carcinogenic action of cholesterol was the subject of a talk which I gave at the Sloan-Kettering Institute for Cancer Research, and in Professor W. U. Gardner's Department of Anatomy at Yale, in May, 1956, and is dealt with at length in Chapter 3, entitled "The Carcinogenic Effect of Cholesterol," of a book *Cancer* (in the press).

The investigation shown in Fig. 3 is very elementary, but we seem to have few data of this kind. Cigarettes of two well-known British brands were weighed, and smoked in the ordinary way by one or other of two habitual smokers who dropped the ash, and stump, into weighing-bottles. The mean figures show that the ash and stump

FIG. 3.—Ash and Stump of cigarettes.
C=Cigarette. S=Stump. A=Ash.

1,000 smokes to a butt length less than 23 mm. A length of 23 mm. is 29% of 70 mm., which is the length of an English cigarette of a very popular brand; hence almost always less than 71% of the length of the cigarette is smoked, as compared with 80% which is commonly smoked in this country (Fig. 3), and was adopted by Commins *et al.* (1954) in their method of artificial smoking. Anyone from this country who observes ash-trays in the United States will note the difference in the length of the cigarette ends.

Work of Dr. E. L. Wynder on the Carcinogenic Action of Cigarette Smoke

The emphasis laid upon the collected negative results of painting experiments from various laboratories, and the more or less explicit suggestion that these discredit Wynder's results (see, for instance, *Nature*, 1956), suggest that, in this instance, where smoking is concerned, the comparison of evidence from man and from animals may not always be conducted with complete impartiality. We do not smoke chromium compounds and no one doubts that these are carcinogenic to the human lung on the ground that we have no confirmatory evidence from animals. Positive results, if obtained by legitimate methods, must take precedence of negative results.

Recently I had the opportunity of seeing, and handling, Dr. Wynder's mice, which showed no sign of undue injury to the skin; and, in any case, no process of simple ulceration of the skin of the mouse, or of any other tissue, will give carcinoma in 44% of cases (Wynder *et al.*, 1953). To anyone who has any experience of such work with mice it is clear that the material used is carcinogenic under these conditions. The suggestion has been made that Wynder's mice are "hypersensitive"; one might just as well assert that other mice are "hyposensitive."

Negative results of smoke-inhalation experiments on rodents seem to me to be of no significance, because the animals, presumably, unlike smokers, keep their mouths shut and pass the smoke over their turbinates, which, in the rabbit at any rate, are more complex than our own.

Comparison of Cigars and Cigarettes

A cigar consists of intact portions of tobacco leaf arranged more or less concentrically, while a cigarette is made up of more finely divided material packed together; the conditions for combustion, and therefore its products, are different, quite apart from any difference due to the quality of the tobacco. The smoke from a cigar gives an

alkaline condensate, and that from a cigarette an acid one. The very large difference between cigar smokers and cigarette smokers in regard to cancer of the lung which is shown by Dr. Hammond's figures (see below) suggests that if one could ascertain the cause of it one might attempt to construct something which would embody this quality of a cigar in something sufficiently like a cigarette to be adapted for smoking during short periods, which character is the chief advantage of the cigarette over the cigar. One could then offer smokers a precaution which would not involve "giving up smoking." A cigar is comparatively large and expensive, and hence the economical smoker wishes to smoke one as completely as possible.

A valuable piece of evidence on smoking habits in the U.S.A. is given by Harlow (1956) in his study of temperatures in a cigarette. He says: "In our experience, not one cigarette smoker in

1,000 smokes to a butt length less than 23 mm. A length of 23 mm. is 29% of 70 mm., which is the length of an English cigarette of a very popular brand; hence almost always less than 71% of the length of the cigarette is smoked, as compared with 80% which is commonly smoked in this country (Fig. 3), and was adopted by Commins *et al.* (1954) in their method of artificial smoking. Anyone from this country who observes ash-trays in the United States will note the difference in the length of the cigarette ends.

Dr. Lindsey, at the Sir John Cass College, and Mr. J. M. Campbell, in Professor Blacklock's department at St. Bartholomew's Hospital, are examining cigar smoke, and will compare their results with the considerable experience which they have gained in the study of cigarette smoke.

I asked Dr. Hammond what kind of cigar would be smoked by persons who furnish the bulk of his statistical material. He writes: "I went to a cigar store located on a street which is near the dividing line between a rich residential district and a poor residential district. The customers appear to be largely middle class or lower middle class, but many are labourers and some are rich men. They sell a very large number of different brands, with prices ranging from \$0.04 to \$1.25 per cigar. I asked the owner to sell me one each of his best-selling cigars." Dr. Hammond has very kindly sent to us samples of 18 of these brands.

In this country at the present time a person who smokes a cigarette uses 1 g. of tobacco, costing perhaps about 2½d., in 10 to 15 minutes. One of the smallest cigars on sale here, weighing 2 g., costs 8½d.—that is, nearly twice as much per gramme; we have not as yet any figure for an average time taken to smoke such cigars. The cigarillos commonly smoked by women in Denmark weigh about 1.8 g.; some of the smallest cigars smoked in the U.S.A. weigh 3 to 3.4 g. and cost 4 to 5 cents.

Dr. Hammond has kindly obtained for me the figures of the U.S. Internal Revenue Service for the retail price range of cigars sold in the U.S. in 1955:

Retail Price Range	%
Not over 2½ cents	0.48
Over 2½ to 4 "	3.68
" 4 to 6 "	39.04
" 6 to 8 "	9.64
Subtotal: Up to 8 cents	52.84
Over 8 to 15 cents	40.79
" 15 to 20 "	3.28
Over 20 cents	3.09
Subtotal: Over 8 cents	47.16
Total—all classes	100.00

Thus 89% of the cigars sold cost from 4 to 15 cents (3½d. to 1s. 1d.).

Cigarette Smoking and Cancer of Lung

Statistical Inquiries.—No attempt is made here to summarize the very numerous papers of recent years on the relation of cigarette smoking and cancer of the lung. Such investigations may be either retrospective, dealing wholly with data from the past; or, prospective, in which current events are followed. Hammond, in a personal communication in 1956, referred to 17 studies of the first class from five countries. The prospective class is represented by the inquiry among medical practitioners in Great Britain by Doll and Bradford Hill (1954, 1956), and by the geographical survey of Stocks and Campbell (1955), which is also retrospective. The prospective scheme of the American Cancer Society, designed by the statistician Dr. E. Cuyler Hammond, is chosen for brief mention here because it is an extremely interesting example of organization on a very large scale.

Inquiry by American Cancer Society planned by Dr. E. Cuyler Hammond

This investigation by means of a questionnaire is in progress in nine States of the Union in 394 counties, urban

and rural, selected chiefly because they have well-organized units of the American Cancer Society. Female volunteers, 22,000 in number, were asked (1) to give a copy of the questionnaire "to white men aged 50 to 69 years whom they knew well enough to be able to trace for the next several years"; and (2) to secure the filling up of a follow-up form yearly on November 1. The progress of the inquiry may be summarized as follows:

Questionnaires suitable for study collected between January and May 31, 1952				..	..	190,134.
Of these persons, on October 31, 1954	{	Alive	..	..	179,973	} 188,078
		Dead	..	..	8,105	
		Not traced	..	..	2,056	
		Death certificates	..	..	8,019	
Deaths attributed to cancer of the lung				..	..	288
Regular cigarette smokers at some time				..	..	107,978
Currently smoking a pack or more of cigarettes a day				..	..	25,561

Some early results are as follows:

Ratios of Mortality from Lung Cancer

Regular Cigarette Smokers	1/11/52 to 31/10/53	1/11/53 to 31/10/54
No*	1.0	1.0
Yes	7.3	7.3
Pack-a-day or more	14.1	15.6

* Includes pipe and cigar smokers and occasional cigarette smokers.

Number of Deaths and Annual Death Rate from Lung Cancer per 100,000

Smokers	All 245 Cases Reported		Well-established Diagnosis, Excluding Adenocarcinoma (161 Cases)	
	Deaths	Death Rate	Deaths	Death Rate
Never	9	14.0	2	3.1
Occasional	2	8.4	2	8.4
Cigar only	5	16.5	4	13.3
Pipe only	9	35.2	6	24.1
Cigarette only	151	141.6	97	87.2
Cigarette and other	69	81.9	50	57.7

Cigarette Smoking Habits in 1952	Annual Death Rate from Lung Cancer per 100,000	
	All Cases	Well-established Cases Excluding Adenocarcinoma
Never smoked regularly	12.6	4.5
Ex-regular smokers { None	39.1	31.6
	71.0	71.0
	101.3	67.3
Packs { 1	101.7	61.1
	208.4	119.0
	340.7	278.7
	340.7	278.7

In the well-established series the incidence of lung cancer upon heavy cigarette smokers is 62 times greater than that upon those who had never smoked regularly.

	Cities 50,000+	10,000-50,000	Suburb or Town	Rural
Cigarette smokers per 100 of male population	62.6	60.1	56.9	50.3
Lung cancer death rate { Standardized for age	82.5	67.8	74.6	50.5
	78.7	70.3	78.7	60.0

The urban-rural difference is distinct when all diagnosed cases of lung cancer are taken together, but is much less so among well-established cases in cigarette smokers after exclusion of adenocarcinoma.

The death rates in these tables of the American Cancer Society are standardized for the white male population of the U.S.A. in 1953.

Work of Dr. Oscar Auerbach

At the Veterans' Hospital, East Orange, New Jersey, Dr. Oscar Auerbach and seven other workers (1955, 1957) are investigating "the anatomical approach to the study of smoking and bronchiogenic carcinoma."

As soon as possible after death the trachea and lungs, fixed in formalin, are divided in the coronal plane so as to separate the cartilaginous from the muscular part of the trachea, and the posterior portion is rejected; the bronchial tree is separated by blunt dissection, carried sometimes to within 1 cm. of the pleura, and divided transversely into blocks, usually 208 in number (Fig. 4), and from one to five sections from each block are examined for (1) basal-cell hyperplasia, (2) stratification, (3) squamous metaplasia, and (4) carcinoma-in-situ.*

The results obtained in 28,638 slides from 117 out of the first 150 cases (all white males, of whom more than two-thirds were aged from 50 to 70 years) show (1) a remarkable parallelism between the smoking habits of the deceased and the four changes named above; and (2) carcinoma-in-situ in unexpected numbers, and over a wide area, including the trachea, a discovery which is of obvious surgical importance and complicates the already difficult problem of localization. Cases of "recurrence" after operation may actually be due to growth developing from another centre of carcinoma-in-situ. One now has to explain not only the development of carcinoma-in-situ at many different points but also the prevention of further growth at the great majority of these.

The histological examination of each slide was carried out by from two to five persons who were "ignorant of the smoking histories and the clinico-pathological data." Unfortunately the cases of carcinoma of the lung did not include a single non-smoker; all were "moderate to heavy smokers." Cigar smokers and pipe smokers and ex-cigarette smokers were excluded from the three classes of smokers.

The results of this investigation are presented in an unusual manner (Table VI). The percentage of slides from

TABLE VI.—Histological Changes in the Respiratory Tract in Relation to Cigarette Smoking (Auerbach et al., 1955)

Histological Changes	Deaths from Causes other than Cancer of Lung		Deaths from Cancer of Lung	
	Per Cent. of Slides			
	Never Smoked Regularly	Less than 1 Pack Daily	1 Pack or More Daily	
Basal-cell hyperplasia { Three or more cell rows	18.6	22.0	36.1	43.5
hyperplasia { Five or more cell rows	2.9	5.6	10.8	15.0
Stratification	4.2	7.1	10.4	13.4
Squamous metaplasia	1.9	6.3	9.5	11.7
Carcinoma- <i>in-situ</i>	1.0	4.1	6.0	6.3
No. of cases	16	20	47	34
				Total 117

the respiratory tract which show each one of the four changes named above is recorded separately for each of three classes of smokers, and for cases of cancer of the lung. "In subjects who died of bronchogenic carcinoma, basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma-in-situ were diffusely distributed throughout the epithelium of the bronchial tree in both lungs as well as the trachea." Details of the extent to which these changes occur in the trachea would be of great interest, as carcinoma of the trachea is very rare.

Future Course of Research on Cancer of Lung

The study of the aetiology of cancer of the lung is complicated by several factors: (1) Cancer of the lung has several different histological forms which may differ in aetiology, and these distinctions are lost in figures for total incidence. (2) We do not know which, if any, forms of atmospheric pollution can summate with tobacco smoke as carcinogens. A carcinoma of the lung in a smoker might perhaps be due to the combined action of radio-

*Could not some more appropriate name be found for "carcinoma-in-situ," which tissue lacks the essential invasive property of carcinoma? "In situ" contributes nothing of value to the term; everything at rest is *in situ*. One might suggest "pre-carcinoma."

activity and of several constituents of both atmospheric pollution and tobacco smoke. (3) The recent work of, for example, Salaman and Roe (1956) and Gellhorn *et al.* (1956) shows the complex state of our knowledge of initiators and promoters of malignant growth. (4) The significance of carcinoma-*in-situ*, which, according to Auerbach, occurs on a very large scale, is most difficult to assess, as it is in other forms of cancer (cervix, prostate). (5) Lungs of persons of known smoking history, for chemical and histological research, are difficult to obtain here either from operation or from necropsy.

Cancer of Larynx

The statistical study of cancer of the larynx is made difficult by several factors. (1) Cancer of the larynx in men and that in women are to a large extent different diseases, as the so-called "extrinsic cancer of the larynx" is much more common in women; it is not a cancer of the larynx at all, and would be much better described by some other name (see discussion by Lederman, 1954). (2) The evidence of death certificates does not allow a reliable separation of cases of intrinsic and extrinsic cancer of the larynx. (3) The improvements in surgical and radiological treatment of cancer of the larynx may have reached a stage when the number of deaths is not a reliable measure of the incidence of the disease. Hence cancer registration is required. This system is in operation in Denmark, Finland,

and Norway, and in such countries, with populations of not much more than four million, the establishment of registration is easier than it is in England and Wales, with a population of 44 millions. However, our General Register Office already registers about 70% of the cases of cancer in England and Wales, and the Anna Fuller Fund has given us a grant for a Fellowship to be devoted to the study of the new material obtained by registration.

FIG. 5.—Deaths from cancer of the lung and larynx. Males. England and Wales. 1921-51 (Curwen *et al.*, 1954). (Reproduced, by permission, from the *British Journal of Cancer*.)

FIG. 4.—Schematic diagram of the tracheobronchial tree showing the distribution of the 208 blocks. (Auerbach *et al.*, 1956.)

Cancer of the Larynx and Tobacco

We do not know if there is any association in this country between cancer of the larynx and smoking. Whatever factor is affecting the incidence of cancer of the lung in men does not appear to be affecting cancer of the larynx (Fig. 5), but, as we are not certain about the total of the latter, the question is not settled. Wynder (1955) finds that in the U.S.A. "pipe and cigar smoking are more closely associated with cancer of the larynx than with cancer of the lung" (Wynder, 1955, p. 111; Wynder *et al.*, 1956).

FIG. 6.—Crude death rates per million living. Cancer of the larynx. England and Wales (Registrar-General, 1953-4).

A dissociation of the incidence of cancer of the lung and of the larynx, similar to that shown in Fig. 5, appears in the very valuable study of cancer in Japan by Stocks (1956). In comparing Japan with England and Wales he says: "For the larynx the figures are similar in the two countries up to age 70, but for lung cancer registered mortality of men in Japan is less than one-tenth of the English rates at most ages, and amongst women the ratio is between one-half and one-third" (Table VII). Data about the smoking habits of the Japanese would be of great value.

TABLE VII.—Age-Specific Death Rates from Cancer Per Million in Japan (1952) and in England and Wales (1952-4) (Stocks, 1956)

Age Group	Males				Females			
	Larynx		Lung		Larynx		Lung	
	Japan	E. & W.	Japan	E. & W.	Japan	E. & W.	Japan	E. & W.
0-	0.1	0.1	0.7	2.1	0.1	0.1	0.7	0.6
25-	0.5	0.2	5	26	1.1	0.8	2.4	10
35-	1.2	1.8	6	97	0.8	2.2	3.5	26
40-	6	5	21	249	0.8	3.3	11	52
45-	18	13	43	577	8	7	18	89
50-	32	33	70	1,259	11	13	40	138
55-	57	75	114	2,002	15	17	40	201
60-	85	101	181	2,543	28	19	65	287
65-	151	156	236	2,922	32	24	80	384
70-	146	225	219	2,592	34	32	93	379
75-	125	294	190	2,072	42	33	70	445
80+	83	357	110	1,267	33	39	18	362

Prevalence.—The Registrar-General (*Statistical Review*, 1952, Text, p. 158) states that: "Above 75 there has been no change in the male rate, but both the equivalent average death rate (0-64), and the rates between ages 45 and 75 have fallen by about 40% since 1936, while the female rates have remained constant." (Fig. 6. These figures of course refer to death rates.)

Alcohol and Cancer of Larynx

Men concerned in the sale of alcoholic drinks are especially liable to cancer of the larynx (Kennaway and Kennaway, 1936, 1947), while cancer of the lung appears to be unaffected.

TABLE VIII.—Ratio of Registered to 100 Calculated Deaths From Cancer of Lung and Larynx in Occupations Concerned With the Sale of Alcoholic Drinks. England and Wales

	Lung		Larynx	
	1921-32	1933-8	1921-32	1933-8
Barmen	104	122	469	275
Cellarmen	92	87	319	502
Licensed victuallers ..	128	124	185	199

Social Incidence of Cancer of Larynx

In 1921-3 and 1930-2 cancer of the larynx in males showed a very distinct social gradient, the incidence being highest in the poorer classes (Table IX). In 1950 this gradient had disappeared, and in this respect cancer of the larynx provides a very distinct contrast to cancer of the stomach, in which the gradient has remained the same throughout the whole period. The decreased strength and increased cost of alcoholic drinks during the 16 years

TABLE IX.—Standard Mortality Ratio. Males Aged 20-64 According to Social Class. England and Wales (Registrar-General, 1951 Census. One Per Cent. Sample Tables, Occupational Mortality, Part I)

Cancer	Social Class				
	I	II	III	IV	V
	Professional	Intermediate	Skilled	Partly Skilled	Unskilled
Larynx:					
1921-3	72	96	93	96	135
1930-2 (aged 35-65) ..	60	81	98	90	143
1950	113†	70	110	93	115*
Lung, bronchus, trachea:					
1921-3	100	109	97	79	124
1930-2	107	95	100	92	114
1950	80	79	108	89	116
Oesophagus:					
1921-3	76	91	104	88	130
1950	150*	85	97	94	120
Stomach:					
1921-3	60	82	100	106	130
1930-2 (aged 35-65) ..	55	83	98	112	122
1950	57	67	100	114	132

* Based upon fewer than 50 deaths. † Based upon fewer than 10 deaths.

TABLE X.—Cancer of the Bladder and Kidney, England and Wales, 1944-54 (Registrar-General's Statistical Review, 1953-4. Table. Part I. Medical)

	Bladder						Kidney					
	Male			Female			Male			Female		
	Deaths	Rates per Million	Increase %	Deaths	Rates per Million	Increase %	Deaths	Rates per Million	Increase %	Deaths	Rates per Million	Increase %
1944	1,234	76		573	27		395	24		347	16	
1945	1,339	82		611	28		419	26		303	14	
1946	1,375	74		670	30		434	23		343	16	
1947	1,417	72		651	29		492	25		350	16	
1948	1,540	76		712	32		529	26		381	17	
Mean		76.0			29.2			24.8			15.8	
1949	1,617	79		701	31		562	27		384	17	
1950	1,676	79		773	34		597	28		366	16	
1951	1,787	85		738	32		597	28		430	19	
1952	1,890	90		742	32		638	30		471	21	
1953	1,824	86		801	35		655	31		443	19	
1954	1,861	87		847	37		676	32		455	20	
Mean		84.3	11.0		33.5	14.7		29.3	18.1		18.7	18.1

since 1939 must be considered in relation to the change in the mortality from, and social distribution of, cancer of the larynx. Television might in time have a similar effect, owing to lessened consumption of alcohol, but the results could hardly be apparent as yet.* Cancer of the oesophagus, of which the incidence is certainly high upon occupations concerned with the consumption of alcohol, shows a similar diminution in social gradient.

Cancer of Bladder and Kidney

An increase in cancer of the bladder in recent years has occurred both in Denmark (Clemmesen and Nielsen, 1956) and in England and Wales (Registrar-General, 1954, 1955) (see annotation, this *Journal*, January 26, 1957, p. 218)

Clemmesen and Nielsen say: "... there has been a steady increase in the number of cases notified for papillomata and carcinomata of the urinary bladder among men in the capital. In provincial towns and rural areas a less pronounced increase occurred during the years 1951 to 1953, the significance of which is doubtful, so far. No increase in incidence was observed for tumours of the bladder among women nor for malignant neoplasms of the kidney."

The Registrar-General's figures, on the other hand, show an increase in both sexes in cancer of the bladder and of the kidney in the eleven years 1944-54 (Table X). The percentage increase in the death rates for cancer of the bladder is somewhat greater in women than in men, and for cancer of the kidney it is equal in the two sexes.

Possible Effects of Tobacco upon the Urinary Tract

The importance of a search for carcinogenic effects of tobacco other than those upon the mouth and respiratory tract has been emphasized in a recent paper (Kennaway, 1955) in which attention is drawn to the antidiuretic action (Walker, 1949) which must facilitate any such carcinogenic effect. The quantity of compounds absorbed from tobacco smoke is made plain by the very numerous investigations of their effects upon the circulatory system (see, for instance, Wynder, 1955, Chapters 2 and 3).

Steele, Koch, and Steiner (1951) obtained fibrosarcoma in about 19% of mice after subcutaneous injection of an extract (butyl alcohol, after extraction with benzene) of human urine, presumably from unselected persons. Dr. A. J. Lindsey allows me to say that he is examining, at the Sir John Cass College, the urine of smokers and of non-smokers for compounds which he and his fellow-workers (Commins *et al.*, 1954; Cooper and Lindsey, 1955) and J. A. Campbell in this laboratory have identified in cigarette smoke.

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*The number of television licences in England and Wales rose from 18,730 in May, 1947, to 2,957,000 at the end of 1954.

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BENACTYZINE AS AN AID IN TREATMENT OF ANXIETY STATES

PRELIMINARY REPORT

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Benactyzine hydrochloride has been found to reduce or modify stress-induced behaviour in animals (Jacobsen and Sonne, 1955; Jacobsen and Skaarup, 1955a, 1955b). It has also been found to diminish the autonomic responses of human beings to emotionally disturbing experiences (Jacobsen *et al.*, 1955). Favourable results have been reported in Denmark with clinical use of the drug for the treatment of psychiatric cases (Jensen, 1955; Ostenfeld, 1955), and it has recently been introduced into the United Kingdom. Beresford Davies (1956) reports its use in a group of 110 patients suffering from psychiatric conditions, with favourable results in 67 patients. Further trials have been reported by Raymond and Lucas (1956) and Seager and Leitch (1956).

In recent years a variety of new drugs—the so-called "tranquillizers"—have been introduced in psychiatric practice, some of which are now being prescribed very extensively—so extensively, in fact, that the American Psychiatric Association has issued a warning against their indiscriminate use, and hospital management committees in this country have expressed concern at the high cost incurred by their use in mental hospitals. For some of these drugs the value in specific conditions has been thoroughly assessed—for instance, in the case of reserpine or chlorpromazine employed for the treatment of chronic disturbed hospitalized schizophrenics. But the widespread use of drugs of this type for the treatment of psychoneuroses in general practice rests on no such secure evidence.

If the preliminary findings of the clinical use of benactyzine prove valid it appears likely that its application may lie mainly in the treatment of certain types of psychoneurotic patients, in which case its chief use would be found in general practice and in psychiatric out-patient clinics. It seems therefore to be of particular