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LUNG CANCER DEATH RATES AMONG NON-SMOKERS AND PIPE AND CIGARETTE SMOKERS

AN EVALUATION IN RELATION TO AIR POLLUTION BY BENZPYRENE AND OTHER SUBSTANCES

BY

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The rapid increase in death rates from lung cancer during the last twenty years has led to a search for possible environmental causes, and two sources of carcinogenic material have been suggested—namely, cigarette smoke and the smoke present in the atmosphere. The data so far accumulated from independent sources concerning these factors have suggested that each contributes in some way to the initiation of cancer of the lung and bronchus.

In 1947 the Medical Research Council planned a statistical study of smoking habits in this connexion, and the evidence which appeared three years later (Doll and Hill, 1950) showed a pronounced statistical association between smoking and lung cancer. This was substantiated by similar evidence from the United States of America (Wynder and Graham, 1950) and other countries, and a considerable literature has resulted. The statistical evidence received support by the isolation of a carcinogen, 3 : 4-benzpyrene, from cigarette smoke (Cooper, Lindsey, and Waller, 1954; Cooper and Lindsey, 1955; Seelkopf, 1955), and the production of tumours in mice by using a cigarette-smoke condensate has been reported (Wynder *et al.*, 1953). Nevertheless it has always been obvious that smoking could not account for all cases of lung cancer, though it has not been possible to make a reliable assessment of the proportion so caused.

Meanwhile a number of workers had demonstrated the differences between death rates in town and country (Stocks, 1936, 1939, 1947, 1952, 1955; Kennaway and Kennaway, 1947; Curwen, Kennaway, and Kennaway, 1954), and in 1947 one of us suggested that "either smokiness of the atmosphere is an important factor in itself in producing cancer of the lung, or sunshine is an important factor in preventing its incidence." Following closely upon these observations came reports of the detection of benzpyrene in domestic soot (Goulden and Tipler, 1949) and later in samples of atmospheric smoke (Waller, 1952; Cooper, 1954), but so far the data available for comparison of the benzpyrene content of town and country air have been scanty. In 1954, however, an apparent relationship was demonstrated between the carbon content of lungs and duration of life in large towns (Blacklock, Kennaway, Lewis, and Urquhart, 1954).

In this paper an attempt has been made to evaluate the effects of tobacco smoking and air pollution by benzpyrene acting together upon the male population of a particular region presenting great contrasts in respect of urbanization and smoking habits. It is an interim communication, and the conclusions to which it points are in no sense final, but the reasons for issuing it now are explained.

Sources of Data for Present Study

In 1952 the Cheshire and North Wales Branch of the British Empire Cancer Campaign, with the most helpful co-operation of the Medical Officers of Health and Regional Hospital Boards concerned and of the Clinical and Pathological Register for Cancer in the Liverpool Region, began to collect the past environmental histories of residents in North Wales and Liverpool Hospital Region who were diagnosed as suffering from, or certified as dying with, any form of malignant neoplasm. Starting from July 1 of that year, notifications have been received in respect of the deaths, and if no history has been obtained during life it is sought from near relatives through the agency of the medical officers of health and their health visitors. Supplementary information regarding the basis of diagnosis and duration of symptoms is sought from the certifying doctor, or from the records of the clinical register or hospital if there had been a hospital admission, and all records relating to an individual are brought together by means of a card index. The environmental history is taken on a standard schedule covering residences, occupations, work-places, travel to work, sources of water, milk, and vegetables, diet, methods of heating, cooking, and lighting, and other matters over a period of 20 years prior to the onset of symptoms. Full information is sought also on tobacco smoking and the marital history throughout the whole of life. During the first two years of the inquiry some 10,000 deaths of residents in the area, which were considered to be due to or to have been associated with cancer, occurred, and environmental histories were obtained in respect of about 90%.

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Starting early in 1953, precisely the same questions were asked of adult patients admitted to the hospitals at Bangor, Llandudno, Wrexham, and Chester, and to Broadgreen Hospital in Liverpool, this being done as a matter of regular routine by whole-time recorders appointed to the hospital staffs. The aim was to obtain, so far as possible, an environmental history from every adult in-patient regardless of cause of admission, so as to provide an unselected series of men and women who were not suffering from any form of cancer at any desired age, in addition to the histories of the cancer patients. When time did not permit of every patient without cancer being questioned, those omitted were not selected in any way which could introduce a bias in respect of past history. In the first two years some 12,000 histories, including tobacco smoking, were obtained from patients without cancer by this procedure. It is not known, and cannot be ascertained, to what extent, if at all, in-patients at general hospitals differ in respect of their past smoking habits from the whole population of the same age in the area served by the hospital. For some diseases some hospital bias doubtless exists, but for patients without cancer *in toto*, even if such bias is appreciable, it may be assumed to be of the same kind in different general hospitals. Consequently it should not affect the conclusions drawn in this study, which depend upon comparative rather than absolute estimates of the distributions of smokers and non-smokers in the areas served by the hospitals. Knowing the census populations of these areas by sex and age, and the proportions at each age in various smoking categories, the actual populations in those categories can be estimated.

In 1954 arrangements were made with the Medical Research Council and Department of Scientific and Industrial Research for the supply and installation of 10 air filters of a new design at 10 places in the research area and for analyses in respect of total smoke, trace elements, 3 : 4-benzpyrene, and other polycyclic hydrocarbons contained in the air. The filters are provided by the Fuel Research Station at East Greenwich, and are located usually at health offices, the weekly change of filter papers and reading of the air-meter being carried out by those who are kindly housing the instruments. From October 13, 1954, the filters worked continuously, apart from an occasional breakdown, and analyses for the first six months have by now been made of total smoke at the Fuel Research Station, and of the hydrocarbons at the Pathological Department of St. Bartholomew's Hospital by one of us (J. M. C.). Monthly measurements of sulphur dioxide in the air at the same places are being made by lead peroxide cylinders provided by the Department of Scientific and Industrial Research, the analyses being carried out by the city analyst at Liverpool.

Purpose of this Preliminary Report

The purposes of this paper are : (1) to compare the death rates from lung cancer in the two-year period from mid-1952 to mid-1954 amongst men between the ages of 45 and 75 who had been non-smokers, pipe smokers, light, moderate, and heavy cigarette smokers, and who were resident in three areas differing greatly in respect of their urbanization ; and (2) to report upon the atmospheric content of smoke, sulphur dioxide, 3 : 4-benzpyrene and certain other polycyclic hydrocarbons during six months from October, 1954, to April, 1955, at representative localities within the same three areas and also at some other places in the Merseyside and Deeside region. Such an evaluation is being made now instead of waiting for five-year death rates based on larger numbers, because the two-year rates for men seem to point strongly to certain conclusions which might conceivably help to hasten effective action towards reducing lung cancer incidence, and consequently it was considered that they ought to be put on record for the information of research workers in this field. Certainty about the causation of lung cancer is unlikely to result from any single research, whether chemical, experimental, clinical, or statistical ; most probably conclusions will have to be reached on the grounds of consistency between data and by piecing together evidence from diverse sources rather than by relying upon very high degrees of statistical significance in any one study. In this particular study the advantages of delaying any statement until the five-year survey has been completed might be that death rates of women can then also be examined, analysis by other factors such as occupations will be possible, some irregularities in the rates will probably disappear, and the statistical significance of differences may be enhanced. In circumstances where new evidence is urgently needed these advantages do not seem to justify delay, but it must be emphasized that the conclusions indicated in this interim communication are subject to possible modification in the final analysis.

Urban and Rural Smoking Habits

Men aged 45–74 who were admitted as in-patients and for whom no diagnosis of any form of malignant neoplasm was made before discharge provide the data for assessment of past smoking habits of three age groups, 45–54, 55–64, and 65–74, living in three areas surrounding the hospitals at (R) Bangor and Llandudno, (M) Wrexham and Chester, (U) Liverpool (Broadgreen Hospital). These areas, which offer great contrasts, were defined geographically as (R) the counties of Caernarvon and Anglesey, which are rural with no industrial towns ; (M) the county borough and rural district of Chester, urban and rural districts of Wrexham, urban districts of Wirral, Neston, and Hoole, and rural districts of Hawarden, Runcorn, and Tarvin, a mixed rural and urban area ; (U) the county borough of Liverpool, which is densely urban. The areas are shown on the map in Fig. 1. The

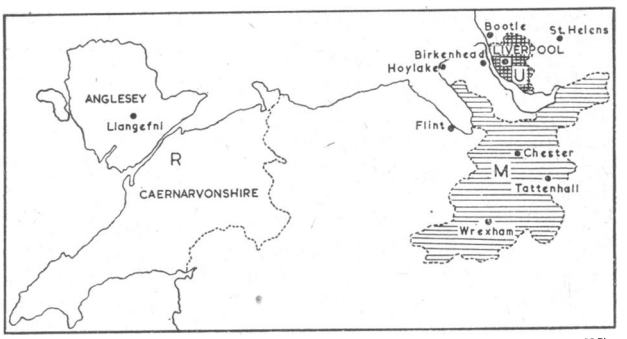


FIG. 1.—Map showing the rural (R), mixed (M), and urban (U) areas, and location of the ten air filters (●).

census populations of men aged 45–54, 55–64, and 65–74 in these areas have been divided into six smoking categories by applying the proportions amongst the non-cancer patients of those ages, whose totals seen at the relevant hospital centres were 802, 1,757, and 969 at ages 45–74 in the R, M, and U areas.

The record of tobacco smoking includes the average weekly number of cigarettes and ounces of pipe tobacco smoked during successive 10-year periods of age, with details also of cigars, tobacco chewing, use of petrol lighter, and ages at starting and ceasing for each of these. If a change took place from cigarette to pipe smoking or vice versa the assignment is to the one for which the weekly amount of tobacco was greatest, counting 25 cigarettes as equivalent to 1 oz. (28 g.) of pipe tobacco. If both cigarettes and pipe were smoked during the same period the assignment is to the cigarette category corresponding to the combined amount of tobacco. Pipe smokers therefore exclude true mixed smokers, and also all who had smoked cigarettes except those who had changed from one to the other with a greater weekly tobacco consumption during the pipe phase. The classification is based on the largest average weekly amount stated for any 10-year age period. Non-smokers are defined as those who have never for any period averaged as much as two cigarettes per week and have not smoked a pipe or cigars or been chewers of tobacco.

The categories used in this study have been condensed to five:

Non-smokers—as defined above
Pipe smokers—as defined above
Cigarette smokers:
Light—maximum 2–99 per week
Moderate—maximum 100–249 per week.
Heavy—maximum 250 or more per week

Table I shows the proportions in each category amongst the male non-cancer patients of each age group in areas R, M, and U, and Table II gives the corresponding populations of the areas estimated by applying those proportions to the census. It is evident from the first table that the urban area has the lowest proportions of non-smokers, pipe smokers, and light cigarette smokers, and the highest proportions of moderate and heavy cigarette smokers. Comparing the mixed with the rural area, the former has higher proportions of non-smokers, moderate and heavy cigarette smokers, and lower proportions of light cigarette smokers. Pipe smoking is much more frequent in the higher age groups in each area, and in the rural area 40% of men aged 65–74 fall into this category.

Urban and Rural Death Rates from Lung Cancer by Smoking Categories

Precisely the same information on past smoking habits was asked for in respect of all residents in the areas R, M, and U who died with cancer of the lung, bronchus, or pleura in the two-year period; and if no record had been obtained during life this was obtained whenever possible from the widow or other relative. Before relating the data thus collected to the population in Table II, two corrections are necessary. In some instances the desired information about smoking could not be obtained because of the failure to interview the relative, sometimes because none were known, sometimes on account of removal out of the research area, or, in rare instances, through refusal or inability to give the information. Since these causes of failure had no possible association with smoking habits and such cases comprised only 1 in 5 of the total, they were distributed over the four categories of smokers in the same proportions as the known cases. None were added to the non-smokers, that category including only persons concerning whom a definite statement had been made that they had never smoked. The second correction is for a tendency to understatement by the widow of the weekly number of cigarettes which had been smoked by her husband. The extent of this tendency was measured by comparing the records of 35 men who had been seen in hospital and had then died before the hospital record had been received and indexed, with the result that the second record was obtained from the widow. Every effort is made to avoid this occurring, but such dual records will be invaluable as data by which to test the consistency and reliability of information on different matters of environmental history. The first 35 cases showed the average weekly number of cigarettes to be 121 according to the men themselves and 106 according to their widows, and in order to correct for this understatement appropriate fractions of the light and moderate cigarette smoking categories were transferred to the next higher group. Table III gives the mean annual death rates obtained by dividing the corrected number of deaths in the two-year period by the corresponding population at risk in Table II and multiplying by 100,000. The rates are also represented pictorially in Fig. 2.

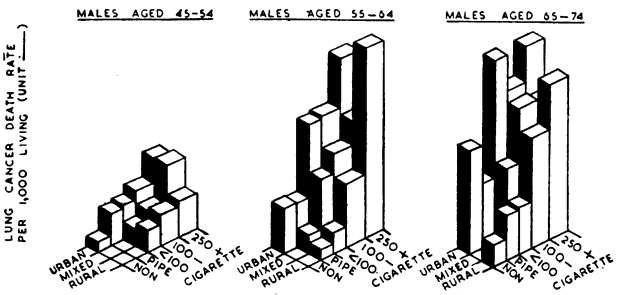


FIG. 2.—Lung cancer mortality by place of residence and type and amount of smoking.

In the rural area of Caernarvon and Anglesey the death rates increase progressively with weekly cigarette consumption at each age, and the standardized death rate (S.D.R.) when plotted on a scale of number of cigarettes forms almost a straight line, the increment of death rate being about 1 per 1,000 for each 13 cigarettes a day. For all pipe smokers the rate corresponds with that of smokers of 25 cigarettes per week, the equivalent of about 1 oz. (28 g.) of tobacco, whereas the average weight of tobacco reported to have been smoked by the group of pipe smokers was about 3 oz. (85 g.). This suggests that in this rural area pipe smoking is only one-third as dangerous as consuming the same amount of tobacco in the form of cigarettes.

In the mixed rural and urban area the death rates of light and moderate cigarette smokers, who there form two-thirds of the male population at ages 45–74, are higher than in the rural area, but this is not true for heavy smokers, nor for pipe smokers aged 65–74.

TABLE I.—*Percentage Distributions According to Past Smoking Habits Among Male Hospital In-patients Without Cancer in Rural, Mixed, and Urban Areas*

Smoking Category	Ages 45–54			Ages 55–64			Ages 65–74		
	Rural	Mixed	Urban	Rural	Mixed	Urban	Rural	Mixed	Urban
Non-smokers	5·9	10·8	3·5	9·9	9·9	4·2	10·2	17·7	3·8
Pipe smokers	9·9	8·5	2·3	16·7	15·8	11·1	40·7	30·1	16·6
Cigarette:									
Light	35·9	26·7	18·4	33·7	29·0	16·7	27·1	21·9	21·0
Moderate	43·9	48·2	65·1	34·9	37·5	57·8	18·6	26·4	50·0
Heavy	4·4	5·7	10·7	4·8	7·8	10·2	3·4	3·9	8·6
Total	100	100	100	100	100	100	100	100	100

TABLE II.—*Estimated Populations of Men of Different Smoking Habits at Risk in Two Years, in Three Regions—Rural, Mixed, and Urban*

Smoking Category	Ages 45–54			Ages 55–64			Ages 65–74		
	Rural	Mixed	Urban	Rural	Mixed	Urban	Rural	Mixed	Urban
Non-smokers	1,351	4,183	3,181	1,897	2,645	2,711	1,417	3,146	1,487
Pipe smokers	2,280	3,327	2,114	3,186	4,232	7,042	5,667	5,352	6,591
Cigarette:									
Light	8,296	10,298	16,751	6,450	7,771	10,665	3,778	3,897	8,292
Moderate	10,135	18,618	59,339	6,679	10,046	36,862	2,598	4,694	19,766
Heavy	1,012	2,202	9,751	910	2,074	6,506	474	703	3,400
Total	23,054	38,628	91,136	19,122	26,768	63,786	13,934	17,792	39,538

Table III.—*Lung Cancer Death Rates (mean annual per 100,000 from mid-1952 to mid-1954) of Men in Rural, Mixed, and Urban Areas Classified According to past Smoking Habits*

Smoking Category	Ages 45–54			Ages 55–64			Ages 65–74			S.D.R. 54–74*		
	Rural	Mixed	Urban	Rural	Mixed	Urban	Rural	Mixed	Urban	Rural	Mixed	Urban
Non-smokers	0	0	31	0	0	147	70	0	336	14	0	131
Pipe smokers	0	0	104	34	59	143	145	26	232	41	25	143
Cigarette:												
Light	69	57	112	70	224	378	154	259	592	87	153	297
Moderate	90	83	138	205	285	386	362	435	473	183	132	287
Heavy	117	214	205	626	362	543	506	412	588	363	303	394
No. of deaths	16	26	124	25	56	232	27	36	183	68	118	539

* Standardized rate based on Liverpool population.

In Liverpool the rates exceeded those in the rural and mixed areas for every group, but the gradient of death rate with rising cigarette consumption is not as steep as in the rural area, nor is it as regular, probably owing to some amount of misfit between the hospital population and deaths. The ratio of rural to urban S.D.R., expressed as a percentage, increases as follows from non-smokers to heavy cigarette smokers:

Non-smokers	11
(Pipe smokers)	(29)
Light cigarette smokers	29
Moderate „ „	64
Heavy „ „	92

This result disposes of the possibility that the urban excess of lung cancer could arise merely from more complete recognition of the disease in towns combined with differences in smoking habits of the populations, since in that event there would be no reason why the ratio should differ according to smoking category. The urban/rural ratio of 9 to 1 for non-smokers is founded on small numbers, and would be subject to a considerable standard error had it not been supported by the trend of the other ratios. Comparing the rates for the three cigarette categories with the weekly numbers of cigarettes, which average about 310, 150, and 62 in the heavy, moderate, and light categories, the percentage rural/urban ratios are 92, 64, and 29, and from these figures, which are based on larger numbers, it is reasonable to expect a ratio about 14% at the zero point.

The differences between the urban and rural standardized death rates are 117 for non-smokers, 102 for pipe smokers, and 104 for moderate cigarette smokers, and this suggests that the Liverpool environment exposes men to a carcinogen which adds about 100 to the death rate per 100,000 from lung cancer, whether they smoke or not, the increment being possibly rather less for heavy cigarette smokers, though that is doubtful. This could happen if urban air contains a carcinogen, which could be the same or different from the one derived from cigarette smoking. In that case it would be expected that the ratio between the urban and rural concentrations of the agent in the air would be about the same as the ratio between the urban and rural death rates among non-smokers, since the average amount inspired in a given time must be proportional to the concentration in the air and the cases of cancer resulting from it would also increase with the concentration.

It may be noted here that, by collecting the smoke produced by mechanical smoking of cigarettes, Cooper and Lindsey (1955) have found that 500 cigarettes produce 4 μg. of 3 : 4-benzpyrene. On this basis the group of light cigarette smokers as defined in this study will, with an average of 62 cigarettes per week, be taking in about 26 μg. per year through smoking, the moderate group (average 150 per week) about 62 μg. and the heavy smokers (average 310 per week) about 130 μg. The mean cigarette consumption in populations of men of the three age groups was 80 per head per week in area A, 88 in area M, and 126 in area U; and the average intake of benzpyrene through smoking on this basis would be 33 μg. per annum in Anglesey and Caernarvonshire, 37 in the mixed area, and 52 in Liverpool. The deaths from lung cancer at the same ages were 1.3, 1.5, and 2.7 per 1,000 in those areas, and this suggests that if benzpyrene is the carcinogen concerned the differences in smoking habits would account for about half of the urban–rural differences in the lung cancer rates. The further possible significance of these figures is discussed in the section on " combined intake."

Contributions of Smoking and " Urban " Factor to the Deaths in Liverpool

By applying the various death rates according to age and smoking category in Table III to the estimated populations at risk in Liverpool, the following totals of deaths from cancer of the lung, bronchus, and pleura would have resulted in the two-year period on different assumptions:

Number of lung cancer deaths among men aged 45–74 in Liverpool in two years from mid-1952 to mid-1954	*539*
If death rates in each smoking category were to remain as in Liverpool and:	
Smoking habits as in rural area	481
All had been non-smokers	256
„ „ „ pipe smokers	271
„ „ „ light cigarette smokers	550
„ „ „ heavy „ „	769
If death rates in each category were as in the rural area and:	
Smoking habits as in Liverpool	315
„ „ „ „ rural area	221
If death rates were as in non-cigarette smokers living in the rural area	63

According to this, abolition of cigarette smoking might be expected eventually to reduce the deaths of men in Liverpool from lung cancer by about one-half, and three-quarters of the remaining half would be due to some local cause only slightly present in the rural area and most likely to be some kind of air pollution.

Chemical Analysis of Suspended Impurity in Rural and Urban Air

The object of the chemical investigation was to determine the concentration of the carcinogen 3 : 4-benzpyrene and other polycyclic hydrocarbons in the suspended impurity of the air at places in North Wales, Cheshire, and Merseyside. This impurity consists of ash, smoke from chimneys and vehicular exhausts, and other windborne dust. The amount of pollution caused by this material suspended in the atmosphere depends on the amount of industry and the number of houses in the area concerned; so sampling stations were set up at 10 sites where very different levels of pollution might be expected. The amounts of hydrocarbons contained in the impurity were extremely small, and spectrophotometry had to be used to identify and determine individual compounds. Anthracene, pyrene, fluoranthene, 3 : 4-benzpyrene, and 1 : 12-benzperylene were determined quantitatively in all samples.

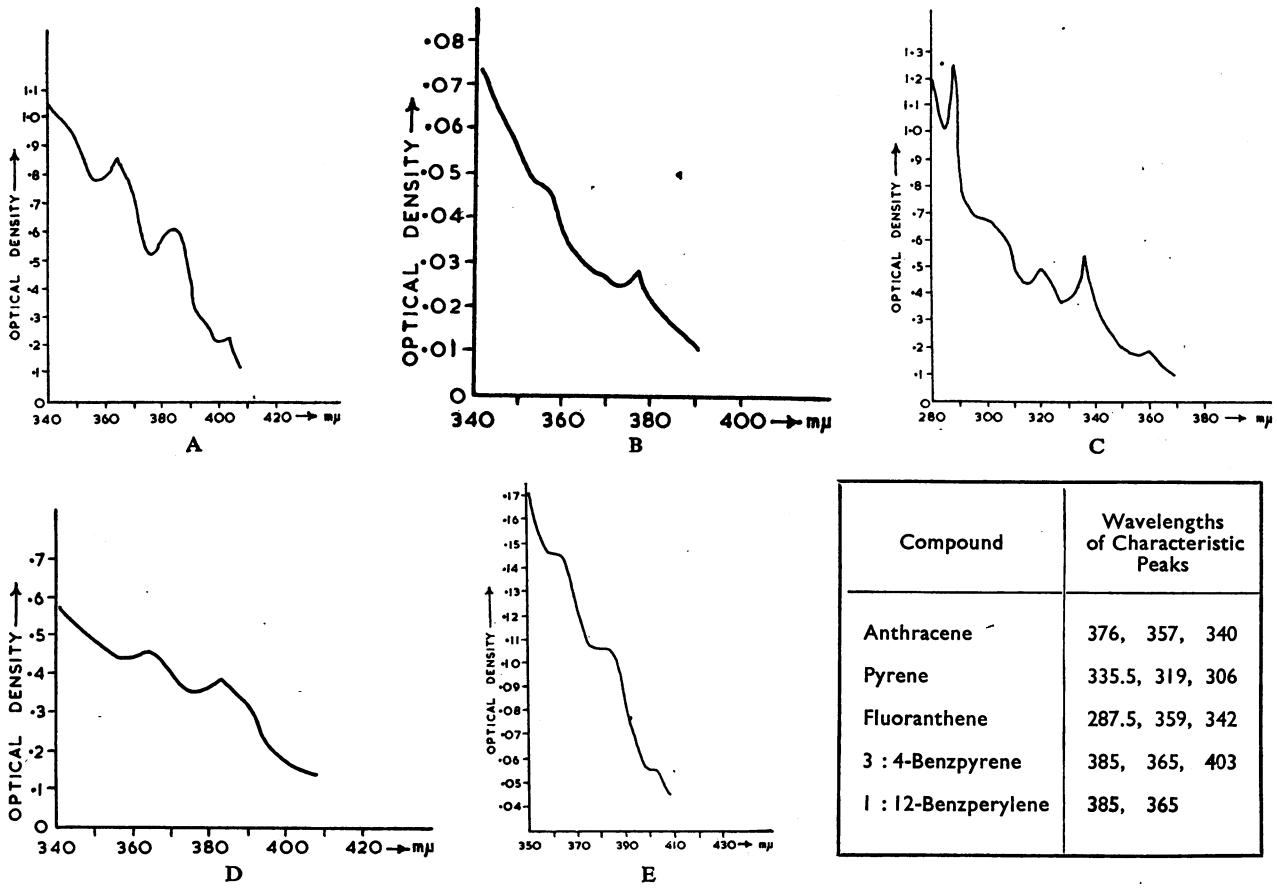
The following analytical technique was used. At each of the 10 sites chosen air was drawn continuously, night and day, through a glass tube leading from outside the building to a Whatman No. 1 filter paper inside the building, at a rate of about 50 cubic feet (1.41 cubic metres) a day. The filter paper was fitted to either a 2-in. (5-cm.) or 4-in. (10-cm.) holder which was connected to an electrically operated pump through a gas-meter, the 4-in. holder being used in large towns and the smaller holder in country districts. At each place the papers were changed weekly, and at the same time the volume of air which had passed through the filter was read from the gas-meter. Each paper had a dark stain caused by the arrested impurity, varying in colour from light grey to black. The weight of material

on each paper was determined at the Fuel Research Station at East Greenwich, either visually by comparing with Owen's standard scale or photometrically by measuring the intensity of reflected light with a standardized photo-electric cell and galvanometer. Both methods have been standardized by direct weighing, so that the weight corresponding with a given shade reading is known. (Department of Scientific and Industrial Research, 1945.)

The filter papers were then cut in halves, one-half being kept for trace-element analysis. The other halves were extracted in a Soxhlet apparatus with acetone until no more fluorescent material was washed out, a process taking about three hours. The acetone was boiled off gently and the residue taken up in cyclohexane, and this solution was chromatographed on a standardized column of alumina, using cyclohexane as an eluent initially and later adding increasing concentrations of benzene. Fractions of about 3 ml. were collected, and each was examined by means of a Unicam S.P.500 spectrophotometer. From a previous study of artificial mixtures, the order in which the hydrocarbons were eluted from the column was known, so each fraction could be examined for the appropriate hydrocarbons by the method of searching for peaks (Wedgwood and Cooper, 1953). Fractions containing individual hydrocarbons were combined and the concentration of each hydrocarbon was determined spectrophotometrically. Finally, the spectrophotometric readings were converted into weights of hydrocarbon and these values expressed as parts per million of deposit and as micrograms per 100 cubic metres of air (μg./100 cubic metres). All glass apparatus used was cleaned in chromic-sulphuric acid mixture and rinsed with cyclohexane, and all solvents used were redistilled twice and residues examined. The alumina was also extracted with cyclohexane and examined after use, and finally a complete experiment was run with blank filter papers. All these tests showed the absence of hydrocarbons in the materials used in the analyses, but the filter papers contained the following weights of compounds expressed as μg. per half-paper: pyrene, 0.003; fluoranthene, 0.002; benzpyrene, 0.004; giving a possible error of less than 3%.

The weights of deposit on the filter papers were found to differ widely according to the locality; for example, in the first week of operation of the filters in October the amounts at five places were as follows: Llangefni, 0.180; Hoylake, 0.327; Flint, 0.721; St. Helens, 1.704; Liverpool, 3.212 mg. There was also considerable variation from week to week in the same locality as well as seasonal change; for example, the amounts of deposit in mg. per cubic metre of air at Liverpool during four weeks from October 13 to November 10 were 0.350, 0.382, 0.522, 0.523, and the six 4-week averages between October 13 and March 30 were 0.413, 0.497, 0.412, 0.342, 0.270, 0.261. Daily and weekly meteorological measurements are being recorded at each filter station for eventual correlation with the analyses.

It was found impracticable to work with less than 5 mg. of the deposit, and consequently, in order to have sufficient material for analysis from the less-polluted areas and to obtain an average value for each locality, the weekly papers were extracted together as follows: for Llangefni, Tattenhall, Chester, Wrexham, Flint, and Hoylake, 13 weeks at a time, and for Liverpool, Bootle, Birkenhead, and St. Helens four weeks at a time. This made 36 estimations in all for the half-year and yielded total deposits ranging from 5.4 mg. in 13 weeks at Llangefni to 24 mg. in 4 weeks at Liverpool. The extracts were each made up to 10 ml., sufficient being then taken to provide an extract representing about 5 mg. of deposit. In this way the chromatographic procedure could be standardized to give identical conditions for each separation.



Compound	Wavelengths of Characteristic Peaks
Anthracene	376, 357, 340
Pyrene	335.5, 319, 306
Fluoranthene	287.5, 359, 342
3 : 4-Benzpyrene	385, 365, 403
1 : 12-Benzperylene	385, 365

FIG. 3.—Spectra of 3:4-benzpyrene and other polycyclic hydrocarbons. (A) Spectrum of 3:4-benzpyrene for combined extracts, showing characteristic peaks. (B) Spectrum of anthracene for combined extracts. (C) Spectrum of pyrene and fluoranthene for combined extracts. (D) Spectrum of 1:12-benzperylene for combined extracts. (E) Spectrum of 3:4-benzpyrene for Birkenhead, weeks 13–16, showing inflexions.

With such small quantities of material, the only means of identification were inflexions at the correct positions in the spectrum, as shown in Fig. 3. When the concentration is increased the inflexions become the peaks of the characteristic spectrum, and to furnish evidence for their identification the fractions containing the separated hydrocarbons from each estimation were combined at the end, concentrated, and the spectrum plotted (see spectra). Finally, the solutions containing these individual hydrocarbons have been kept, and it is hoped to brominate the fractions so that the characteristic spectra of the brominated hydrocarbons may provide further evidence for the identification of each compound (Cooper, Goldup, and Lindsey, 1955).

The results are shown in Table IV in the form of average weights of total smoke and of the hydrocarbons per 100 cubic metres of air during six months, starting from mid-October. Sulphur dioxide indices, obtained by lead peroxide candles exposed in louvered boxes located near to the intake tubes of the air filters, are also included in the table.

TABLE IV.—*Average Concentrations of Smoke, Benzpyrene, Other Polycyclic Hydrocarbons, and Sulphur Dioxide at 10 Localities During Six Months from October 13, 1954*

Location of Filter (See Fig. 2)	Total Smoke (1)	3:4-Benzpyrene (2)	1:12-Benzperylene (2)	Pyrene (2)	Fluoranthene (2)	Anthracene (2)	SO_2 (3)
Areas for this study:							
Rural:							
Llangefni ..	4·9	0·7	0·7	0·3	0·5	0·1	0·3
Mixed:							
Tattenhall(rural)	6·4	1·0	0·9	0·5	0·6	—	0·4
Chester (urban)	21·8	1·9	5·3	0·7	1·5	—	1·1
Wrexham ,,	23·3	5·1	1·8	1·2	1·4	0·4	1·1
Urban: Liverpool	36·3	7·7	6·6	2·3	2·4	0·7	2·8
Urban/rural ratios:							
Liverpool/ Llangefni ..	*7*	*11*	*9*	*7*	*5*	—	*8*
Liverpool/ Tattenhall ..	*6*	*8*	*7*	*5*	*4*	—	*7*
Other localities:							
Flint	15·2	3·3	2·1	0·9	2·2	0·1	0·8
Hoylake	10·0	2·8	1·7	0·7	0·9	0·1	0·9
Birkenhead ..	28·4	5·8	4·9	2·8	3·9	0·5	1·8
Bootle	34·2	8·5	4·1	3·7	4·9	0·9	2·3
St. Helens ..	37·3	7·7	5·3	3·1	3·9	1·2	2·6

Notes.—(1) In mg. per 100 cubic metres; averages for 26 weeks. (2) In μg. per 100 cubic metres; averages for 24 weeks at Liverpool, Birkenhead, Bootle, St. Helens; 26 weeks elsewhere. (3) In mg. of SO_2 per day collected by 100 sq. cm. of lead peroxide during four months, March to June.

The first five stations are located in the rural, mixed, and urban areas used in Tables I–III, and the places were chosen as apparently representative of average conditions in those areas. Llangefni and Tattenhall are of a rural character, Chester and Wrexham are towns of moderate size in fairly open country, though the latter has coal mines in its vicinity, and the Liverpool filter is in the middle of a large densely populated conurbation. The concentrations are seen to rise with increasing urbanization and population density, the only notable irregularity being the contrast between the benzpyrene and benzperylene figures for Chester and Wrexham. For total smoke and pyrene the Liverpool concentrations are about six times as great as in the rural localities, for 3:4-benzpyrene the ratio is around 10 to 1, and for 1:12-benzperylene and sulphur dioxide the ratios are about 8 to 1. These are interesting in view of the 9 to 1 ratio for lung cancer death rates amongst male non-smokers in the urban and rural areas and the known carcinogenic properties of benzpyrene. The benzpyrene content of the smoke deposit in parts per million of the total solid matter showed little excess in Liverpool in comparison with the rural areas, the average figure in six months being 187 p.p.m., compared with 150 at Llangefni and 155 at Tattenhall, but that does not affect the hypothesis that benzpyrene may be the important agent, since it is the total intake of the hydrocarbon which would be expected to show a proportionality with the death rate. Since 1:12-benzperylene is suspected to have weak carcinogenic properties its possible agency should not be overlooked, but there is no good reason at present for suspecting the other substances. It has been found, however, that exhaust fumes from diesel engines, when operating inefficiently or accelerating, contain considerable amounts of benzpyrene, benzperylene, and pyrene, and that the mixture is capable of producing skin cancers in mice (Kotin, Falk, and Thomas, 1955).

Although current death rates have not yet been ascertained for the other places in Table IV, the comparative mortality ratios of males for lung cancer in 1947–51, standardized on the North Wales population, were as follows: Bootle, 289; Liverpool, 238; Birkenhead, 187; St. Helens, 173. For the first three of these towns the benzpyrene concentrations of 8.5, 7.7, and 5.8 show some correspondence, but the St. Helens figure of 7.7 would lead to the expectation of a higher rate than was observed in those years. It must be borne in mind, however, that present smoke analyses will sometimes fail to indicate correctly the relative conditions in towns 10 to 20 years ago which led to changes in the lung now producing deaths.

Combined Intake of Benzpyrene from Air and Smoking

From Cooper and Lindsey's finding that 4 μg. of 3:4-benzpyrene can be extracted from the smoke of 500 cigarettes, together with the amounts of that substance in air as determined by almost the same technique and given in Table IV, it is possible to estimate what would be the total intake per year by men of different smoking categories living in the rural and urban areas on various assumptions regarding the amount which actually reaches the lungs. During normal respiration some filtration takes place in the nose, and this may prevent much of the suspended matter reaching the bronchi. Also, it is not known at present to what extent the air inside factories, offices, and houses contains the suspended matter present in the outside air with its complement of benzpyrene. During sleep in average housing conditions little suspended matter may be reaching the lungs, whereas in some dusty work-places the amount may be increased rather than reduced. All that can be done is to calculate the amount of benzpyrene inspired on the assumption that a man is breathing the outside air all the time, and that all of it is reaching the lungs; add trial fractions of this to the calculated intake from cigarettes, and then compare the results with the death rates from lung cancer. The figures in Table IV relate to the autumn and winter, and will be lower in spring and summer; so to correct for this the annual averages may be taken provisionally as four-fifths of these concentrations.

Taking the amount of air inspired by the "standard" man during working, resting, and sleeping as 7,300 cubic metres a year, the mean average intake of benzpyrene from the air on the maximum assumption would be: in the rural area (represented by Llangefni) about 41 μg., in the mixed area (average of Tattenhall, Chester, and Wrexham) about 157 μg., and in Liverpool about 450 μg. Table V shows the result of adding (1) one-fourth, and (2) one-twelfth, of these amounts to the estimated quantities derived from

TABLE V.—*Estimates of Combined Intake of Benzpyrene in a Year from Air and Cigarettes on Certain Assumptions*

	Assumption (1)				Assumption (2)				S.D.R.
	Rural	Mixed	Urban	Rural % of Urban	Rural	Mixed	Urban	Rural % of Urban	Rural % of Urban
Non-smokers	10·3	39	113	*9*	3·5	13	38	*9*	*11*
Cigarette smokers:									
Light ..	36	65	139	*26*	29	39	64	*46*	*29*
Moderate	72	101	175	*41*	65	75	100	*65*	*64*
Heavy ..	140	169	243	*58*	133	143	168	*79*	*92*
All males 45–74	43	76	165	*26*	36	50	90	*40*	*41*
Ratio to urban%:									
Intake					*40*	*56*	*100*		
S.D.R.					*41*	*51*	*100*		

cigarette smoking by each group of men, and comparing the relative figures with the relative death rates from lung cancer.

The measure of agreement between the relative values of benzpyrene intake on assumption (2) and those for the standardized death rates (S.D.R.) in the various groups is such as to justify a working hypothesis that benzpyrene might be the agent responsible for the associations of lung cancer with both smoking and urban residence, and to encourage research into the amounts of this and other hydrocarbons in the air, both outside and inside buildings, in different localities.

Summary

By means of data from the first two years of the study of environmental histories of persons with and without cancer which is being carried out by the Cheshire and North Wales Branch of the British Empire Cancer Campaign, death rates from cancer of the lung and bronchus have been calculated amongst men of different smoking habits living in a rural area of Wales, in a mixed area around Chester and Wrexham, and in Liverpool county borough. The death rates have then been related to measurements of benzpyrene and other substances present in the air at various places within those areas.

The rural death rate increases proportionately to the number of cigarettes smoked per week, and pipe smokers as a group rank with cigarette smokers of about 25 a week. Liverpool rates exceed the rural rates in every smoking category, but the urban/rural ratio falls progressively from about 9 to 1 amongst non-smokers to a small value approaching unity amongst heavy cigarette smokers.

The absolute urban excess is much the same in each smoking group, suggesting that an "urban" factor is added to the effects of smoking. Differences in smoking habits of the populations can account for only a small fraction of the contrast in total rates, and it is estimated that about half the Liverpool deaths of men from lung cancer arise from cigarette smoking and about three-quarters of the remaining half are due to a factor which is only slightly present in the rural area.

The concentration of smoke and of 3 : 4-benzpyrene, other polycyclic hydrocarbons, and sulphur dioxide in the air rises with increasing urbanization, the benzpyrene figure in Liverpool being 8 to 11 times as great as in the rural localities examined, a ratio which corresponds with the estimated mortality ratio amongst non-smokers living in those areas. When the death rates are compared with the calculated total intake, by different categories of smokers in the areas, of benzpyrene derived from air according to certain assumptions, plus that derived from the number of cigarettes smoked, the degree of correspondence is such as to suggest that benzpyrene might be the one agent involved.

This interim communication is being made because a supposition that benzpyrene plays a dual part, through cigarettes and air pollution, now appears to be tenable, and such a working hypothesis may assist research work in this field whether or not it is finally substantiated.

In collecting the patients' histories on which this study is based many people have co-operated, and acknowledgment is made to the medical officers of health, doctors, and health visitors in the counties of Anglesey, Caernarvon, Denbigh, Flint, and Cheshire, and county boroughs of Liverpool and Chester; to the Management Committees of Bangor, Wrexham, Chester, and Broadgreen Hospitals; and to the patients and their relatives. For help with the installation and operation of the air filters our thanks are due to Dr. E. T. Wilkins and Mr. J. R. Goss, of the Fuel Research Station at East Greenwich, to the sanitary officers at the various stations, the N.H.S. Executive Council at Liverpool, and Dr. K. C. Kershaw at Tattenhall. Professor J. W. S. Blacklock and Sir Ernest Kennaway, of the Department of Pathology, St. Bartholomew's Hospital, the Medical Research Council, the Department of Scientific and Industrial Research, and the Clinical and Pathological Register for Cancer in Liverpool are also thanked for their help.

References

Blacklock, J. W. S., Kennaway, E. L., Lewis, G. M., and Urquhart, M. E. (1954). *Brit. J. Cancer*, **8**, 40.
Cooper, R. L. (1954). *Analyst*, **79**, 573.
—— Goldup, A., and Lindsey, A. J. (1955). *Chem. and Industry*, p. 198.
—— and Lindsey, A. J. (1955). *Brit. J. Cancer*, **9**, 304.
—— —— and Waller, R. E. (1954). *Chem. and Industry*, p. 1418.
Curwen, M. P., and Kennaway, E. L., and N. M. (1954). *Brit. J. Cancer*, **8**, 181.
Department of Scientific and Industrial Research (1945). Technical Paper No. 1. Atmospheric Pollution in Leicester. London.
Doll, R., and Hill, A. B. (1950). *British Medical Journal*, **2**, 739.
Goulden, F., and Tipler, M. M. (1949). *Brit. J. Cancer*, **3**, 157.
Kennaway, E. L. and N. M. (1947). Ibid., **1**, 260.
Kotin, P., Falk, H. L., and Thomas, M. (1955). *Arch. industr. Hlth*, **11**, 113.
Seelkopf, C. Z. (1955). *Z. Lebensmitt-Untersuch.*, **100**, 218.
Stocks, P. (1936). *A.R. Brit. Emp. Cancer Campgn*, **13**, 240.
—— (1939). Ibid., **16**, 308.
—— (1947). Regional and Local Differences in Cancer Death Rates. General Register Office, Studies on Medical and Population Subjects No. 1. H.M.S.O., London.
—— (1952). *Brit. J. Cancer*, **6**, 99.
—— (1954). *A.R. Brit. Emp. Cancer Campgn*, **32**, 485.
—— (1955). *J. Fac. Radiol. (Lond.)*, **6**, 166.
Waller, R. E. (1952). *Brit. J. Cancer*, **6**, 8.
Wedgwood, P., and Cooper, R. L. (1953). *Analyst*, **78**, 170.
Wynder, E. L., and Graham, E. A. (1950). *J. Amer. med. Ass.*, **143**, 329.
—— —— and Croninger, A. B. (1953). *Cancer Res.*, **13**, 855.

TUBERCULOSIS IN STUDENTS AND NURSES

BY

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Six years have elapsed since the findings of the Prophit Survey on Tuberculosis (1948) in young adults was published; in that report the incidence and pathogenesis of the disease in medical students and nurses in the London area were reviewed. In the present paper we record the incidence of tuberculosis in students of all faculties of four representative universities during a three-year period and discuss the results of a B.C.G. vaccination programme in medical students and nurses of ten university centres. A comparable analysis of the tuberculosis problem in American medical schools and the results of B.C.G. vaccination there has been published by Abruzzi and Hummerl (1953), who reported an incidence of 3.34 per 1,000 per annum in medical students, compared with the 2.5 per 1,000 per annum of British students of all faculties. In relation to B.C.G. vaccination, three cases of clinical tuberculosis have occurred in each of the series of 4,400 American and 2,630 British vaccinated students.

Mass Radiography Survey

The miniature radiograph is our most potent weapon in the detection not only of the infectious student but also of the early pulmonary lesion.

Table I is an analysis of 43,431 examinations of students in the Universities of Edinburgh, Glasgow, Cambridge, and Belfast during the period 1950–3.

In Edinburgh in 1950–1 only first-year students were required to undergo *x*-ray examination; to the others it was optional, and, although every student was obliged to walk through the mass radiography unit to reach the matriculation office, and although each was invited to submit to the