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ENVIRONMENTAL FACTORS IN THE AETIOLOGY OF LUNG CANCER AND BRONCHITIS

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In an earlier communication (Ashley, 1967) I examined data on the mortality experience for the county boroughs and administrative counties of England and Wales and showed that the frequency of lung cancer was lower than would be expected in areas where the dusty coal and textile industries were prominent, and that in those areas the death rate from bronchitis was higher than might have been expected. Preliminary analyses in that paper suggested that population density, social class, and air pollution were not responsible for this difference and that the low frequency of lung cancer was due to some other independent cause.

The present investigation comprises a more detailed analysis by the technique of multiple regression (Seal, 1964) of the data available for 53 county boroughs of England and Wales. The standardized mortality ratios for lung cancer in men and women and for bronchitis in men were determined as in the previous paper (Ashley, 1967) for the years 1958 to 1963 using the death rate data and population distribution given by the Registrar General in his reports (1960a, 1960b, 1962, 1963, 1964, 1965; General Register Office, 1964), making a separate calculation according to whether the county borough formed part of a conurbation or was greater or smaller in size than 100,000 people. The population density was given as persons per acre by the General Register Office (1964). The social class index was that used previously in an examination of the distribution of perinatal mortality rates (Ashley, 1968a) and comprised the proportion of the male economically active population over the age of 15 who were in the Registrar General's classes 10 (semi-skilled manual workers), 11 (unskilled manual workers), and 15 (agricultural workers) (General Register Office, 1965).

The concentrations of smoke and of sulphur dioxide in the atmosphere were extracted from the report of the air pollution laboratory and refer to residential areas within each of the towns (Department of Scientific and Industrial Research, 1963). The dusty coal and textile towns were defined as those in which more than 4% of the male population were employed in these industries (General Register Office, 1956). These data were published in the previous paper (Ashley, 1967).

Initially, simple correlation coefficients were calculated to show the relationships between the various pairs of factors analysed (Table I).

There is a strong correlation between the amount of smoke in the atmosphere and the amount of sulphur dioxide, and between the concentrations of these two pollutants and the social class index, but not with the density of population. Population density is, however, weakly associated with the social class index.

Mortality from lung cancer in men is strongly correlated with lung cancer mortality in women and

TABLE I

CORRELATION COEFFICIENTS BETWEEN THE FACTORS ANALYSED

	SMR Lung Cancer Male	SMR Lung Cancer Female	SMR Bronchitis Male	Population per Acre	Social Class Index	Smoke Conc.
SMR lung cancer male						
SMR lung cancer female	0·45**					
SMR bronchitis male	0·38**					
Population per acre	0·51**	0·52**	0·42**			
Social class index	0·07	0·26	0·58**	0·33*		
Smoke concentration	−0·22	0·08	0·52**	0·15	0·38**	
SO_2 Concentration	−0·23	0·26	0·46**	0·23	0·41**	0·78**

**Highly significant P < 0·01
*Significant P < 0·05

with mortality from bronchitis in males. All three mortality indexes were strongly correlated with population density, and bronchitis mortality was strongly positively correlated with the other three parameters, social class index and the two air pollution factors. Lung cancer in males showed a negative but non-significant correlation with the two air pollution parameters while lung cancer mortality in women showed a positive but non-significant correlation with these two factors.

In the separation into towns with and without the two dusty industries, the correlation coefficient cannot usefully be employed. Instead, the mean SMRs and the mean values for the other four parameters have been calculated (Table II). The mean SMR for lung cancer both in males and in females is lower in the coal and textile towns than in the remainder, whereas the mean SMR for bronchitis is higher. The environmental parameters show some differences. The population density is rather lower in the coal and textile towns while the degree of air pollution, especially of smoke, is higher and a higher proportion of the population belong to the lower socio-economic grades.

TABLE II

MEAN VALUES FOR SMRs AND ENVIRONMENTALPARAMETERS IN COAL AND TEXTILE TOWNS COMPARED WITH OTHERS

	All Towns	Coal/Textile	Other
SMR lung cancer male	106·9	92·8	112·6
SMR lung cancer female	104·9	97·9	107·6
SMR bronchitis male	112·8	117·2	110·6
Population per acre	15·9	14·2	16·6
Social class index	269	289	259
Smoke	119	162	100
SO_2	130	151	120

The multiple regression analysis, which in effect determines the correlations for each of the factors holding the remainder constant, helps an understanding of this analysis. Table III shows the several regression coefficients.

Analysis of the significance of the parameters was undertaken using the F test (Seal, 1964). The two social parameters, population density and social class index, were combined. The separation between the coal and textile towns and the others was considered separately, and the air pollution parameters were considered at first together and then separately (Table IV).

TABLE IV

SIGNIFICANCE OF REGRESSION COEFFICIENTS (F)

	Lung Cancer Male	Lung Cancer Female	Bronchitis Male
Population density } Social class }	12·81**	6·57**	8·76**
Coal/Textile	8·86**	2·37	1·31
Smoke/SO_2	4·58*	1·08	4·93*
Smoke	1·84	0·74	5·96*
SO_2	7·88**	2·05	0·27

**Highly significant $P < 0{\cdot}01$
* Significant $P < 0{\cdot}05$

The regression coefficients are positive between each of the SMRs and population density and are also positive but numerically smaller between the SMRs and the social class index. When these two social factors are combined, their effect is shown to be highly significant in each of the mortality rates.

The regression coefficient for the factor dust, the coal and textile towns contrasted with the others, was negative in each instance. This coefficient was highly significant in lung cancer in men but was not significant for the other two SMRs.

Air pollution was a significant factor in lung cancer in men and bronchitis in men but not in lung cancer in women. When the two components of air pollution were separated it was shown that the negative regression of lung cancer in males on the sulphur dioxide concentration in the atmosphere was highly significant and that the positive association between the smoke concentration in the atmosphere and bronchitis mortality in males was significant.

DISCUSSION

These analyses confirm the reduction in lung cancer in the coal and textile areas compared to the towns in which those industries are not important employers of labour. This negative association is also present but is not statistically significant in lung cancer in women and in bronchitis in men. Reasons for the lower frequency of lung cancer in mining and textile areas have been put forward elsewhere (Ashley, 1967, 1968b) and are mentioned

TABLE III

MULTIPLE REGRESSION COEFFICIENTS

SMR	Population Density	Social Class Index	Coal/ Textile	Smoke	Sulphur Dioxide
Lung cancer male	1·41	0·08	−9·52	0·08	−0·15
Lung cancer female	1·61	0·05	−3·24	−0·07	0·10
Bronchitis male	0·93	0·21	−4·33	0·20	−0·04

in connexion with the relationship between air pollution and lung cancer. The lower level of lung cancer in the men of these towns is significant even when allowace is made for the somewhat lower population density and the higher degree of air pollution.

The SMR for lung cancer in women shows a non-significant negative regression coefficient with the separation of towns into those with and without the dusty industries. This sex difference can readily be related to a difference in occupational environment. More men than women are employed in the dusty atmosphere, and any specific effect of dust in the lungs may be expected to be greater in men than in women.

The SMRs for bronchitis in the coal and textile towns are rather higher than in the other towns although the multiple regression coefficient is negative. This anomaly may be related to the high atmospheric pollution by smoke in these towns and to the concomitant association with the specific respiratory disease, pneumoconiosis. The contribution to the estimated SMR from this factor is small and, in default of any other evidence, can probably be disregarded.

The association with general social factors has also been confirmed. Buck and Brown (1964) showed a strong association between population density and lung cancer incidence and between the social index and bronchitis. The data analysed here show clearly that these two factors taken together are of significance in determining the frequency both of bronchitis and of lung cancer and that these differences are independent of the specific effects of air pollution and of the coal and textile industries.

It is an easy step to associate the higher mortality from lung cancer and from bronchitis in the towns compared to the rural areas to the heavier load of pollutants in the air which the townsman breathes by comparison with that enjoyed by the countryman. This view is supported by the marked acute association between episodes of severe atmospheric pollution, fog, and 'smog' and deaths from respiratory disease (Fairbairn and Reid, 1958; Martin, 1961) but the relationship between the long-term level of air pollution and the chronic respiratory diseases is less clear. A positive association between the death rate from bronchitis and the amount of smoke in the atmosphere has been shown by several workers (Fairbairn and Reid, 1958; Stocks, 1960; Buck and Brown, 1964), and a similar association with the concentration of SO_2 in the atmosphere has also been observed (Pemberton and Goldberg, 1954; Buck and Brown, 1964). The concentrations of smoke and of SO_2 in the atmosphere are highly correlated (*vide supra*) and it might therefore be expected that an association with the one would presuppose an association with the other.

The association between air pollution and lung cancer is less clear. McConnell, Gordon, and Jones (1952) failed to find an excess of men working in polluted atmospheres or living close to industrial establishments which released large amounts of fumes among their series of men suffering from lung cancer. Wicken and Buck (1964), however, showed a higher frequency of lung cancer in the men of the Urban District of Eston where many men work in conditions of high atmospheric pollution than in the neighbouring districts. Stocks (1959, 1960) found a positive association between the atmospheric concentration of smoke and the death rate from lung cancer and showed that this relationship held true when the factor of population density was held constant. Other workers, however, failed to find significant associations between either of the components of air pollution and lung cancer (Fairbairn and Reid, 1958; Buck and Brown, 1964).

The data from this analysis confirm the association between mortality from bronchitis and the concentration of smoke in the atmosphere but suggest that the observed association with the concentration of sulphur dioxide is due to the strong correlation between the levels of these two substances and is not related to a specific effect of sulphur dioxide. This association remains even when the effects of the other environmental parameters are removed by the multiple regression technique.

In lung cancer in the male, but not in the female, there is a surprising, highly significant, negative association between the standardized mortality ratio and the concentration of sulphur dioxide in the air. In the course of the analysis regression coefficients were calculated omitting the variables in turn. The coefficient related to sulphur dioxide was negative, whichever of the other factors was omitted, and, when sulphur dioxide itself was omitted, the coefficient for the smoke concentration became negative.

The small positive coefficient for the relationship between lung cancer deaths in men and the concentration of smoke was not significant. This finding, which has not previously been reported, suggests that sulphur dioxide in the atmosphere may, to some extent, protect the lungs against carcinogenic agents. Two alternative mechanisms for this effect may be suggested. In the lower frequency of lung cancer in the coal and textile areas generally and in miners as an occupational group, I postulated that the load of dust borne by the lungs of miners and those living in mining and textile areas might lead to a state of immunological enhancement in the lungs which would lead to the rejection of cells which had undergone some of the changes of neoplastic transformation (Ashley, 1967, 1968b). Some mechanism of this type could be invoked in this instance.

An alternative suggestion is based on observations that thiols, and in particular the sulphur-containing amino acid cysteine, offered some protection against the action of carcinogenic and mutagenic substances (Fenner and Braven, 1968; Braven, Bonker, Fenner, and Tonge, 1967) and the suggestion that the carcinogenic action of tobacco smoke is due to the removal of amino thiols and their conversion to thiazolidines by the mildly oxidizing action of acetaldehyde in tobacco smoke. It may be suggested that sulphur dioxide in the atmosphere could counteract this effect either because of its slight reducing action or because it might react directly with the acetaldehyde in the smoke.

Data on the consumption of tobacco in the several areas studied were not available. This, however, does not invalidate the analyses. Buck and Brown (1964) found that differences in cigarette consumption in the areas they studied did not account for the differences attributed by them to population density, and Todd (1966) found little difference in cigarette smoking in the different social grades and occupations and in the urban and rural areas of Great Britain. There is undoubtedly a strong association between cigarette smoking and lung cancer (Doll, 1953; Wynder and Hammond, 1962; Kreyberg, 1962) but this is not the entire story. Not all cigarette smokers develop lung cancer and some individuals in whom this tumour develops have never smoked. Lung cancer, like most other forms of malignant disease, is the end result of a process of change in cells which probably involves a number of discrete events whose cumulative effect is to cause a 'malignant' change in the phenotype of one or more cells. These changes may be caused by any of many environmental carcinogenic agents, among them cigarette smoking. The data presented here suggest that there is some factor associated with relatively crowded living conditions but not directly with air pollution, as measured by the currently available techniques. Carcinogenesis is a complex process and the total load of neoplastic disease can be reduced by attention to all the various aetiological factors. Smoking and living in crowded conditions are 'causes' of lung cancer but there is no single 'necessary cause'. To eliminate the disease all causes must be removed as far as possible.

Summary

A multiple regression analysis of the relationship between mortality from lung cancer and bronchitis and a series of environmental factors has been carried out.

There was a significant positive association with increasing population density and lower social class in lung cancer in men and women and in bronchitis in men.

There was a negative association between the concentrations of the coal and textile industries and mortality in all three groups. This association was significant in lung cancer in men.

There was a significant positive association between air pollution, in particular the smoke concentration in the atmosphere, and the death rate from bronchitis in males.

There was a significant negative association between the concentration of sulphur dioxide in the atmosphere and the mortality of men from lung cancer.

It is suggested that the effect of the coal and textile industries in reducing lung cancer mortality may be related to an enhanced state of immunological preparedness in the lungs of people constantly exposed to dust. A similar mechanism may operate with sulphur dioxide, or, alternatively, there may be a more specific effect on the reaction between sulphur-containing amino acids in the bronchial mucosa and carcinogenic agents in the inspired air.

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