

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY DECEMBER 13 1952

SMOKING AND LUNG CANCER

Six years ago the Medical Research Council called a conference to consider whether the remarkable increase in death rates from lung cancer, as indicated by the Registrar-General's statistics, justified a search for the causes of this phenomenon. At that time many were sceptical about the reality of the apparent rise, attributing it to the increasing use of radiography in the diagnosis of thoracic disease; but fortunately the conference was not deterred by such doubts from advising researches both of a statistical and an experimental nature. Among the conclusions arrived at by a Symposium on the Endemiology of Cancer of the Lung held by the Council for the International Organizations of Medical Sciences at Louvain in July, 1952, was a statement of belief that a significant part of the apparent increase is absolute. In England and Wales the graph of death rates shows no sign as yet of levelling out, some 13,000 deaths having been registered in 1951.¹ It may be true that a large proportion of the cases now being certified would not have been diagnosed if they had occurred 10 years ago, but the fact remains that, out of any random sample of 400 men now aged about 55, at least 10 must be expected to die of lung cancer within the next 20 years, in comparison with 200 from all other causes, even though death rates remain at their present level. This merits serious attention, and it is well that the studies initiated by the General Register Office and Medical Research Council are yielding results of great importance, unpopular though they must be.

Dr. Richard Doll and Professor A. Bradford Hill published in this *Journal* two years ago² a first report of an inquiry, most carefully conducted among 2,475 patients in 20 London hospitals, leading to the conclusion that "smoking is a factor, and an important factor, in the production of carcinoma of the lung." Their results were confirmed in almost all respects by a similar study of 684 cases of bronchogenic carcinoma by Wynder and Graham in the U.S.A.³ In the

opening pages of this issue Doll and Bradford Hill report the results of an extension of their inquiry during 1950 and 1951 to patients in Bristol, Cambridge, Leeds, and Newcastle-upon-Tyne hospitals and a continuation of it in eight of the London hospitals. The method of investigation, described in the first paper, was to obtain notifications of patients admitted to hospital with cancer of the lung, stomach, and large intestine, who were then questioned about tobacco-smoking, and to match each lung-cancer case with a patient of the same sex and age group suffering from a disease other than cancer. In the extended inquiry the almoners visited the provincial hospitals at intervals and interviewed patients with suspected cancer of lung who happened to be in-patients together with matched control patients having other diseases. The final classification was usually based upon the diagnosis at the time of discharge from hospital. In addition to obtaining the history of tobacco-smoking, the almoners asked questions about the proximity of gasworks, methods of heating, places of residence, and previous history of respiratory diseases.

This second report is based upon the whole series from the start of the investigation. It now comprises 1,488 patients with carcinoma of lung, of whom 1,465 were paired with control patients having diseases other than cancer, and another control group of 1,278 which included patients suffering from cancer of the stomach and the intestine. Comparison of the 1,465 patients suffering from lung cancer with their matched controls showed no significant social class differences; but there were fewer resident in Greater London (791, compared with 900 among the controls), more resident in other urban areas (500, against 394), and fewer resident in rural districts (155, against 164). Since tobacco consumption is rather greater in London this inequality would tend to reduce any excess in usage of tobacco by the lung-cancer group rather than exaggerate it. In the interviews with some pairs of patients questions about brands of tobacco, filter-tipped cigarettes, petrol lighters, and cigarette-holders were added to those described in the first report about frequency, quantity, and duration of smoking. Non-smokers were defined, as before, as persons who had never consistently smoked as much as one cigarette a day for as long as one year. Among the various quantitative measures of smoking employed were the most recent amount smoked, the maximum amount ever smoked regularly, the estimated total amount ever smoked, and the average amount smoked daily over the 10 years preceding illness, and of these the first and last were judged to be the best.

¹ See *Journal*, p. 1316.

² *British Medical Journal*, 1950, 2, 739.

³ *J. Amer. med. Ass.*, 1950, 143, 329.

⁴ *Brit. J. Cancer*, 1952, 6, 99.

⁵ *British Medical Journal*, 1952, 2, 710.

⁶ *Ibid.*, 1952, 2, 982.

Among 1,357 men with lung cancer only 7 (0.5%) were non-smokers, compared with 61 (4.5%) among the same number of control patients with other diseases; and at the other extreme 25% had smoked 25 or more cigarettes a day (or the equivalent in pipe tobacco), compared with 13% of the controls. Among 108 women with lung cancer 37% were non-smokers, against 55% of the controls; and 11% had smoked 25 or more cigarettes a day, against only 1% of the controls. The figures for patients in Greater London interviewed during 1950-1 agreed closely with those for 1948-9 which were analysed in the first report. In men the contrasts between smokers and non-smokers were similar in the provincial centres to those in London. From the 28 women seen in the provincial towns no conclusion could be drawn. Estimated death rates for Greater London in groups of men who had smoked different quantities of tobacco—calculated from the patients not suffering from cancer as a basis for smoking habits in the population as a whole—indicated that mortality from lung cancer may increase in approximately simple proportion with the amount smoked.

No appreciable differences were found between patients with lung cancer and other patients in the regular use of petrol lighters (43 and 41%) or of hand-rolled cigarettes (21 and 19%). Rather fewer patients with lung cancer had ever used a cigarette-holder regularly (5%, against 12%), and only three out of 504 had smoked filter-tipped cigarettes, compared with 15 out of 467 controls. Though inconclusive by themselves, these differences point in the same direction as does the finding that among men with lung cancer a lower proportion of smokers had smoked only pipes (4%, against 7% among the male controls who smoked), suggesting partial removal of an active agent before it reaches the respiratory tract. Analyses of the answers to questions about proximity of gasworks to the home and use of coal or gas in living-rooms showed no appreciable differences.

Rather fewer of the patients with lung cancer lived in the country; but the difference does not appear to be large enough to account for the observation by Stocks⁴ that county-borough death rates of males were more than twice those in rural districts for the country as a whole during 1940-6, and that London rates were two and a half times those of rural districts during 1947-9. Doll and Bradford Hill conclude in this connexion that "it would seem likely that some agent other than tobacco (present perhaps in domestic chimney smoke or in the exhaust fumes of cars) is at least partly responsible for the excess mortality in towns." The percentages of non-smokers deduced from the control patients resident in Greater

London, county boroughs, other urban districts, and rural districts were, after correction for the differing age distributions, 5.1, 6.8, 8.4, and 10.4 respectively, and the percentages of smokers of 25 or more cigarettes daily were 14.6, 9.9, 8.9, and 7.7, but the proportions smoking 5-24 cigarettes daily showed no consistent difference according to urbanization. Those who smoked only pipes contributed 10% to the smokers in rural districts, however, compared with 5% in Greater London.

Where do we go from here? Statistics, it is said, cannot prove causation, but neither could Koch's postulates, although the lives of millions are affected and controlled on the assumption that they have established beyond question the causative agents of certain infective diseases. All that these things can do is to show that the probability of a causative connexion between an agent and a disease is so great that we are bound to take what preventive action we can, accepting the theory as though the proof were absolute until further research leads to some modification. It would seem that such a position has now been reached with lung carcinoma, in that tobacco has been incriminated as the vehicle conveying an agent responsible for a large proportion of the cases. The nature of the carcinogenic agent is not yet known: benzpyrene has not been found in tobacco, and though the arsenic known to be present in most brands of cigarettes has been suspected there is as yet no evidence to incriminate this. Intensive research on the chemical constituents of tobacco and of tobacco-smoke is now needed, and it is surely incumbent upon the tobacco manufacturers to do this. It is a reasonable expectation that if the carcinogenic agent can be isolated it can also be removed, so that smoking will become a less dangerous occupation than it appears to be now. In the meantime the younger generation will have to decide, each for himself or herself, whether the additional risk of contracting lung carcinoma is worth taking. For a middle-aged man lung cancer diminishes his expectation of living 20 years by about one-twentieth. The apportionment of responsibility for that to smoking and other factors such as atmospheric pollution can be roughly estimated, since the statistical pieces of the puzzle now seem to fall into place fairly well and make sense. If the annual total of deaths of men from lung cancer is taken as 11,000, of whom seven out of each 1,357 would be non-smokers, the total male non-smokers dying annually would be 56; and if the proportion of non-smokers in the population at the relevant ages is taken to be 5%, the remaining 95% would also be exposed to the same risks from causes other than tobacco—which gives a total of about

1,100 deaths of men due to those causes, compared with 10,000 attributable to tobacco. By similar reasoning, with an annual total of about 2,000 deaths among women, of whom 37 out of each 108 would be non-smokers, the total female non-smokers dying would be 685, and, taking 60% of the female population at the relevant ages to be non-smokers, we can estimate that the total lung-cancer deaths of women due to causes other than tobacco would be about 1,100, as for men, the other 900 being due to tobacco. This seems to dispose of the idea that there is a sex difference in susceptibility to lung cancer, the large excess of male mortality being explicable by greater use of tobacco among men.

These are tentative estimates which may have to be modified when the British Empire Cancer Campaign has completed its field study of cancer of the stomach and other organs in North Wales, the Liverpool hospital region, and the Isle of Man.⁵ The large apparent urban excess of lung-cancer mortality, and its correlation with size of town,^{4,6} is not fully explained by the apportionment suggested above, and it may be that continual exposure to atmospheric pollution by a carcinogenic substance such as benzpyrene lowers the threshold of resistance to tobacco smoking. In that case the total contribution of atmospheric pollution to the deaths would be greater than appears from these estimates. But whether that is so or not, there is now enough evidence to justify much more energetic research into the harmful constituents of the air of towns. For more than a century the General Register Office has called attention so often to the high death rates from respiratory diseases in our northern towns that we tend to accept this as a natural phenomenon. Is it not time that abatement of atmospheric pollution was added to the regular responsibilities of public health departments instead of being left to a few enthusiasts regarded rather as troublesome cranks by the Ministry of Health?

ABUSE OF ANTIBIOTICS

The letter from Mr. Norman C. Lake in this issue (p. 1307), protesting against the "unthinking universal employment" of chemotherapeutic agents, calls attention again to a trend in present-day therapy which merits serious consideration. He cites two cases, in one of which the prophylactic use and in the other the therapeutic use of antibiotics obscured the development of serious complications. The example of therapeutic use and its consequences poses a distinct problem, and one which does not appear to have been generally recognized or adequately studied. It is understandable that partially effective chemotherapy should abate fever and improve the

patient's general condition without actually arresting the progress of infection. But it is not clear why, if peritonitis still exists, it should fail to show any of the usual signs. There are no reasons for supposing that antibiotics have any action except on bacteria, and in very mixed infections of this kind they often eliminate the sensitive majority, leaving a minority of resistant types which are not necessarily highly pathogenic. Whenever streptomycin is used there is always the possibility of acquired resistance, and the turn for the worse taken by the patient described by Mr. Lake may well have followed escape of bacteria from the influence of this drug, with consequent renewed multiplication. As a possible explanation of the absence of signs it may be assumed that restrained or low-grade infection fails to excite the reflexes on which these signs depend. Whatever the explanation, this warning is one which should be heeded, and further published experience of the silent progress of infection during antibiotic therapy would be helpful.

Prophylactic use of antibiotics is another matter, because it is arguable whether in given circumstances it is indicated at all. It is a common practice to give penicillin before and after a clean operation for the dual purpose of protecting the operation site against accidental contamination and of preventing chest complications. It sometimes fails in the latter purpose, and when it does so the infection developing is penicillin-resistant and consequently much more difficult to treat. It is evidently impossible to lay down hard-and-fast rules about this practice, although there are certain types of patient in whom it is clearly indicated. Penicillin cover is certainly necessary for dental extraction or tonsillectomy in a rheumatic subject. It is equally clearly indicated in operations in a septic field, where any interference may otherwise cause an acute exacerbation. This applies particularly to the surgery of infected bone, and the use not only of penicillin but of other antibiotics has greatly facilitated major operations on the lung. Operations on the alimentary tract are in a different class, since here only the normal flora is usually to be feared. The use of sulphonamides or antibiotics as intestinal antiseptics preparatory to operations on the colon is sound and established practice, but it relies rather on the local than on any general effect. There is no similar procedure for operations on the stomach or oesophagus, nor is there the same need for it, the flora of this area being much scantier and the factor of distension by gas inoperative. Whether systemic antibiotic prophylaxis is indicated in such operations may presumably depend on the features of the individual case, but in a straightforward gastrectomy the necessity for it is at least doubtful, and if there is