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NEOPLASTIC DISEASE AT VARIOUS SITES

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VOLUME I

CARCINOMA OF THE LUNG

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ASBESTOS

The first case of lung cancer to be described in association with asbestosis was reported by Lynch and Smith (1935) in the U.S.A. Since then over 60 cases have been reported from Britain, Canada, Germany and the U.S.A.—the majority from Britain. That the association was not just coincidental was indicated by comparison of the incidence of lung cancer at autopsy in cases of asbestosis and cases of silicosis. Merewether (1949) found that lung cancer was reported in 13·2 per cent of subjects with asbestosis (31 out of 235) and in 1·3 per cent of subjects with silicosis (91 out of 6,884) and Gloyne (1951), on personal examination, found corresponding incidences of 14·1 and 6·9 per cent (17 out of 121 and 55 out of 796). It should, moreover, be noted that women formed an appreciable proportion of the subjects with asbestosis and that the incidence among men with the disease was even higher—17·2 per cent in Merewether's series and 19·6 per cent in Gloyne's. Since all—or almost all—silicotics are likely to have been men, the contrast between subjects of the same sex is likely to have been somewhat greater than that actually reported for both sexes together. These results are most readily explained if asbestosis predisposes to the development of lung cancer and this explanation was subsequently borne out by Doll's (1955) study of the mortality recorded among asbestos workers. He studied 113 men who had worked for 20 or more years in places where they were liable to be exposed to asbestos dust and found that between 1922 and 1953 39 died, whereas on the basis of the mortality rates suffered by men of the same ages in the whole population only 15·4 deaths would have been expected. Of the 39 deaths 11 were due to lung cancer, whereas less than 1 (0·8) would have been expected. All the cases of lung cancer were confirmed histologically and all were associated with asbestosis. Precautions to prevent the dissemination of dust greatly reduced the amount to which the men were exposed from 1933 onwards and the incidence of the disease has become progressively less as the number of years during which the men were exposed to the pre-1933 conditions has diminished. It is evident, therefore, that lung cancer is a specific industrial hazard of asbestos workers, but that with scrupulous attention to the control of dust the risk may be greatly reduced and may, perhaps, be eliminated.

The fibrils of asbestos consist of giant molecules of polymerised silico-oxygen tetrahedra arranged in chains or bands. In the case of Canadian asbestos, the silica is present as hydrated magnesium silicate containing 6 per cent of iron oxide; in other, industrially less important, types the silicates may be calcium and magnesium or sodium and iron. Animal experiments have, in general, failed to show any significant carcinogenic activity from asbestos fibres and the mode of production of the disease is uncertain. In Hueper's view (1957a) the activity may result from the occurrence of the material in the form of a linear polymer and the mechanism by which cancer is produced may be similar to that with various polymerised carbon compounds, which have been shown to be carcinogenic experimentally.

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CHAPTER VI

THE SMOKING OF TOBACCO

RICHARD DOLL

THE evidence linking tobacco with the production of lung cancer is derived from two principal sources. The great mass of evidence has been obtained from the retrospective study of patients with lung cancer and the comparison of their past smoking habits with the past habits of patients with other diseases, or with the habits of healthy persons. More recently, evidence of another type has been obtained by comparing, over a period of years, the mortality in groups of persons whose smoking habits had previously been defined.

RETROSPECTIVE STUDIES

The first serious study of the subject was reported by Müller in Germany in 1939. He obtained the smoking histories of 86 men with bronchial carcinoma from hospital notes, by personal interview or from a questionnaire sent to the relatives of those who had died and he compared the histories with those given by 86 healthy men of the same ages. The results showed gross differences between the groups in the proportion of non-smokers and of heavy smokers. By 1957, 20 studies of this general type had been reported from 8 countries. The principal results are summarised in Table X. All agree in showing that there are more heavy smokers and fewer non-smokers among patients with lung cancer than among patients with other diseases, and, with one exception (the difference between the proportions of non-smokers found by McConnell, Gordon and Jones 1952), the differences are large enough to merit serious attention. More detailed results of two of the investigations are shown in Tables XI and XII. From these it is seen (1) that there is a steady increase in the relative proportions of lung cancer to control patients as the amount smoked daily increases, and (2) that the difference in smoking habits holds for both sexes, but is more marked for men than for women.

The method of smoking was not studied separately in all the investigations. When it was the results agreed in showing that the difference between the lung cancer and the control groups was principally due to a difference in the proportion of cigarette smokers. The results with regard to pipe smoking and cigar smoking were inconstant. In some investigations it appeared that the disease was equally associated with all types of smoking (McConnell, Gordon and Jones 1952; Randig 1954); in the majority the disease was most closely associated with the smoking of cigarettes. Few of the investigators made specific inquiries about inhaling. In one study it was found that the proportion of patients who said they inhaled was similar among the lung cancer patients

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TABLE X

Principal Characteristics of the Smoking Histories of Men with and without Lung Cancer, Reported by Various Authors

Author	*Date*	*Country*	*Number of men*		*Percentage of 'non-smokers' among men*		*Percentage of 'heavy smokers' among men*	
			with lung cancer	*without lung cancer*	*with lung cancer*	*without lung cancer*	*with lung cancer*	*without lung cancer*
Müller	1939	Germany	86	86	3·5	16·3	65	36
Schairer and Schöniger	1943	Germany	93	270	3·2	15·9	52	27
Wassink	1948	Holland	134	100	4·5	19·0	55	19
Shrek *et al.*	1950	U.S.A.	82	522	14·6	23·9	18	9
Mills and Porter	1950	U.S.A.	444	430	7·0	31·0	—	—
Levin *et al.*	1950	U.S.A.	236	481	15·3	21·7	—	—
Wynder and Graham	1950	U.S.A.	605	780	1·3	14·6	51	19
Doll and Hill	1950	Britain	649	649	0·3	4·2	26	13
McConnell *et al.*	1952	Britain	93	186	5·4	6·5	35	22
Doll and Hill*	1952	Britain	708	708	0·7	4·8	24	14
Sadowsky *et al.*	1953	U.S.A.	477	615	3·8	13·2	—	—
Wynder and Cornfield	1953	U.S.A.	63	133	4·1	20·6	68	29
Koulumies	1953	Finland	812	300	0·6	18·0	66	31
Lickint	1953	Germany	224	1,000	1·8	16·0	74	29
Breslow *et al.*	1954	U.S.A.	518	518	3·7	10·8	74	42
Watson and Conte	1954	U.S.A.	265	277	1·9	9·7	73	57
Randig	1954	Germany	415	381	1·2	5·8	34	18
Gsell	1956	Switzerland	150	150	1·3	19·3	67	15
Kreyberg	1956	Norway	213	4,158	1·4	13·2	18	7
Schwartz and Denoix	1957	France	602	1,204	3·1	15·8	13	7

Note—It has not been possible to make all the figures completely comparable. Some series, for example, include a few women. The individual papers should be referred to before any detailed use of the figures is made.

* Doll and Hill's 1952 paper gave results for 1,357 men with lung cancer: the results shown here relate only to those which were not included in the 1950 paper.

(1956), who cultured human foetal lung *in vitro*, with and without the addition of benzpyrene. The addition of the benzpyrene was found to result in hyperplasia of the bronchiolar epithelium with 3 or 4 layers replacing the normal one and irregular enlargement and abnormal mitosis in the hyperplastic cells, similar to that described for the initial stages of carcinogenesis in mouse skin after painting with benzpyrene.

The possibility must also be considered that cigarette smoke does not itself initiate carcinogenesis, but that it acts as a co-carcinogen or activator to substances already present in the air from other sources. For example, pyridine, pyrrole and other solvents are found in the smoke and these might be supposed to elute the benzpyrene adsorbed on to carbon particles in town air and so render the town air more active. Such an effect might contribute to the difference in lung cancer mortality between urban and rural areas, but it is unlikely to account for the whole effect of cigarette smoking since there is a well marked relationship between smoking and the disease in areas of minimal atmospheric pollution (pp. 86 and 87).

Evidence that cigarette tar might act as a co-carcinogen or as a promoting agent in conjunction with other environmental carcinogens has been obtained by Gellhorn, Klausner and Hibbert (1956). It is conceivable also that it might act in conjunction with weak initiating agents produced in pulmonary scars.

Conclusion

It was concluded earlier in this Chapter that cigarette smoking should be regarded as one of the causes of lung cancer, so long as this conclusion did not conflict with any of the established facts which were relevant to it. In the author's view, the relevant facts are not inconsistent and the hypothesis should, therefore, be accepted. The credibility of the conclusion is strengthened by (1) the observation that histological changes which commonly precede the development of cancer are also related to smoking, (2) the discovery of several carcinogenic substances in tobacco smoke—including one which is believed to be widely effective in man and (3) the demonstration that extracts of tobacco tar can, under suitable conditions, cause cancer of the skin in animals.

The failure to reproduce the disease in the bronchi of animals cannot justify the rejection of the conclusion, nor would it do so, even if it were possible to reproduce the conditions of human smoking. Species differences in susceptibility are a commonplace in cancer research and positive results in one animal can never be overthrown by negative results in others. Moreover, as Kennaway (1957) says: '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'. Positive results, however, would undoubtedly reinforce the conclusion and would be invaluable in helping to isolate the responsible agent.

In the author's view the conclusion that cigarette smoking is a cause—and an important cause—of the disease is inescapable, but the picture is not yet complete. It is not known whether the polycyclic hydrocarbons in tobacco smoke

are sufficient to account for the production of the disease, or whether some other carcinogenic agent has yet to be detected. It is not clear whether the explanation that has been offered is adequate to account for the whole of the difference in mortality between Britain and other countries (particularly the U.S.A.) nor to what extent the temporal changes in mortality can be attributed to changes in tobacco consumption. These questions cannot be answered until more is known about the mechanism of carcinogenesis and the part played in the production of the disease by atmospheric pollution. The few data on the effect of inhaling are conflicting and there is also some conflict in the evidence regarding the relative risks of smoking tobacco in pipes and in the form of cigars and cigarettes. The reason for these differences in risk is also unknown. The fields of uncertainty are, however, small in relation to the extent of established knowledge and do not justify throwing doubt on the main conclusion.

This conclusion is not accepted by all who have studied the subject. Kotin (1956) and Hueper (1957*b*) believe that cigarette smoking is a relatively unimportant cause of the disease and Rigdon (1957) and Fisher (1957*a*) doubt if it is of any causal significance at all. These views, however, do not represent the generality of scientific opinion; for example, they are not supported by any of the independent commissions which have been appointed to review the evidence.

In Holland a commission was set up at the request of the Director of Public Health, and it concluded that there was a connection between cigarette smoking and lung cancer. In the commission's view it was not possible to be sure that the connection was causal, but the other possible factors, which were also studied, 'all proved to be less probable in this respect than smoking' (Netherlands Ministry of Social Affairs and Public Health, 1957).

In the U.S.A. a study group was organised by the American Cancer Society, the American Heart Association, the National Cancer Institute and the National Heart Institute. Their report was published *in extenso* in the national press and provides a valuable survey of the principal data. They concluded that, 'The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung'. (Study Group on Smoking and Health, 1957.)

In Britain the Ministry of Health constituted a panel under the chairmanship of the Government Actuary to advise on the statistical aspects of the subject and, as a result of their report, the Standing Advisory Committee on Cancer and Radiotherapy of the National Health Service advised the Minister of Health that '(1) It must be regarded as established that there is a relationship between smoking and cancer of the lung. (2) Though there is a strong presumption that the relationship is causal, there is evidence that the relationship is not a simple one . . .' (Minister of Health, 1954.) Three years later, more evidence was available and the Medical Research Council (1957) advised the Minister that: 'In scientific work, as in the practical affairs of everyday life, conclusions have often to be founded on the most reasonable and probable explanation of the observed facts and, so far, no adequate explanation for the large increase

in the incidence of lung cancer has been advanced save that cigarette smoking is indeed the principal factor in the causation of the disease. The epidemiological evidence is now extensive and very detailed, and it follows the classical pattern upon which many advances in preventive medicine have been made in the past. It is clearly impossible to add to the evidence by means of an experiment in man. . . . Evidence from many investigations in different countries indicates that a major part of the increase is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect.'

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