A Reprint from

THE PREVENTION OF CANCER

EDITORS

Clinical Aspects

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Published by

BUTTERWORTHS

CHAPTER 26

BRONCHI AND LUNGS—TOBACCO

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The evidence implicating smoking as being causally related to cancer of the lung is very strong.*

There is a definite and undeniable positive association between tobacco smoking, especially of cigarettes, and lung cancer. Opposition to the view that this association is one of cause and effect now comes almost solely from those who maintain that the explanation is rather that the 'type' of person who smokes is the type of person who gets lung cancer (Fisher, 1959; Eysenck, 1965). However, the epidemiological and experimental evidence —both of which are discussed below—on the effects of smoking, make this genotype hypothesis unlikely. Moreover, whether or not the genotype hypothesis finally proves to be scientifically correct, from the point of view of present day public health, there can be no doubt that people should be encouraged not to smoke.

To avoid any misunderstanding a little elaboration of the cause and effect theory is needed: the theory is not that smoking is the cause or the only cause of lung cancer, it is that—although other factors may be involved—in the absence of the smoking habit, in particular of the cigarette smoking habit, the lung cancer death rate in the community would be a small fraction of its present level.

EPIDEMIOLOGICAL STUDIES

There is a variety of epidemiological evidence indicting smoking, especially of cigarettes, as a cause of lung cancer.

(1) The most important, the individual smoker's death rate from lung cancer is almost exactly directly proportional to his daily consumption of tobacco (Doll and Hill, 1964; Pike and Doll, 1965).

(2) The lung cancer rate in British doctors has decreased in the last 10 years concurrently with their known decrease in cigarette consumption, while the rate in the general population of the United Kingdom has continued to rise (Doll and Hill, 1964).

(3) Lung cancer rates in communities where smoking is forbidden are very much lower than in neighbouring communities where it is permitted (Wynder, Lemon and Bross, 1959; Rele, 1960).

* The Report of the Royal College of Physicians of England (1962) and the Report by the Advisory Committee to the Surgeon General of the United States Public Health Service (1964) provide most authoritative and comprehensive discussions of the whole issue of smoking and health. Full references to, and further discussion of, most of the points we raise here are given in these reports, and the authors have therefore kept references in this chapter to a minimum.

(4) The very large increase in the standardized death rates from lung cancer in many countries over the last 50 years has occurred in close association with large increases in *per capita* cigarette consumption.

(5) The standardized lung cancer rates of countries considered as a whole are significantly correlated with their *per capita* cigarette consumption, particularly the *per capita* consumption 20 years before the period to which the lung cancer figures relate.

The first kind of epidemiological evidence relates an individual's lung cancer risk to his actual amount and manner of tobacco consumption, and is derived from retrospective and prospective surveys. The retrospective surveys obtained the smoking histories of groups of lung cancer patients and compared them with the smoking histories of control groups without the disease. Twenty-nine of these surveys have been reported from a number of countries—14 for males only, 15 for males and females—and even though the nature of the control groups and other points of methodology have varied widely, these surveys have shown beyond doubt that for each sex there is a higher proportion of heavy cigarette smokers and a lower proportion of non-smokers among the lung cancer cases than among the controls.

The inaccuracies involved in requiring patients to remember habits of many years past could be expected to make this type of survey rather unreliable; nevertheless, in those surveys in which the amount smoked was taken into account, the degree of association between lung cancer and smoking increased with the amount smoked. Also, the association between smoking and lung cancer was weaker for former smokers than for continuing smokers.

While it is possible to find fault with certain aspects of any individual survey, the extraordinary consistency of the results as a whole provides convincing evidence for the association between smoking and lung cancer. These retrospective studies also showed that the association between smoking and lung cancer was stronger for cigarette smokers than for pipe and/or cigar smokers.

The evidence from the retrospective studies would appear overwhelming. However, the retrospective method has definite drawbacks, in particular, as mentioned above, the need for patients to recall past habits. These drawbacks have been overcome in 7 prospective studies, which also allow us further to quantitate the relationship. In these studies large numbers of people were first questioned about their age and smoking habits and then followed up in subsequent years. From these data it is possible to calculate the death rate from lung cancer in relation to smoking habits.

For example, the United Kingdom survey (Doll and Hill, 1964) showed that among male British doctors, non-smokers had a standardized death rate from lung cancer of 7 per 100,000 per year, which was increased 45 times to 315 per 100,000 per year for smokers of 35 or more cigarettes per day.

The improbability of the genotype hypothesis is, perhaps, best underlined by recent trends in national (England and Wales) death rates. During the period 1952–1961, there has been a marked fall in the percentage of doctors who smoke cigarettes (Doll and Hill, 1964). During the same period, there has been a 7 per cent fall in the lung cancer death rate for male doctors. Conversely, among the general male population, the change in smoking

habits has been trivial and the death rate from lung cancer has risen by 22 per cent. The third kind of evidence, that non-smoking communities have very low lung cancer rates, is also not readily compatible with this view.

A conclusion to be drawn from each of the 7 surveys is that an individual cigarette smoker's lung cancer death rate is directly proportional to the number of cigarettes he smokes per day. To make this observation compatible with the genotype hypothesis, one has to suppose that the part of the genotype that determines smoking habits is linearly related to the person's risk of lung cancer.

These prospective surveys also show that pipe and cigar smokers have much lower rates of lung cancer—at the same tobacco consumption—as cigarette smokers, but higher than non-smokers. They bear out the observation made from the retrospective studies that former smokers have lower rates than continuing smokers and show that the lung cancer rate of former smokers falls, within the first few years after they stop, below that of continuing smokers (at the same tobacco consumption). The difference between the rates increases with time since stopping. To bring this observation into line with the genotype hypothesis we would have to suppose not only that the genotype determines whether, and when, a person stops smoking, but also that the same moiety of the genotype 'protects' him from lung cancer; slightly to begin with and then increasingly with the passage of time.

The two forms of evidence on the relationship of total cigarette consumption and national lung cancer rates could never be conclusive evidence in themselves. In particular, time relationships in the case of a disease that can take several decades to appear are unlikely to be overwhelmingly clear, and differences in inhaling habits, length of cigarette butt and other factors known to be related to lung cancer, will influence the relative risks between countries as a whole. Nevertheless, to explain the increase in lung cancer during the last half-century, and the relationship of countries' rates with their cigarette consumption, the 'type' hypothesis has to propose that some other factor has arisen during this time in every country in which the incidence of lung cancer has increased, and that this has happened in just the manner necessary to produce these spurious associations with overall cigarette consumption. No factor has been suggested which adequately fills this bill. Air pollution is the factor most seriously put forward, but general air pollution has certainly not increased over the last 50 years, nor is the urban/rural lung cancer ratio anywhere near large enough to implicate it as the major cause (*see* Chapter 27).

The large male/female lung cancer ratio has also to be explained: the facts on male/female cigarette consumption fit this sex ratio naturally enough into the causal theory.

EXPERIMENTAL STUDIES

That smoking causes lung cancer in man cannot be proved by animal experiments. However, the fact that it has not proved difficult to show that condensed tobacco smoke induces cancer in animals provides support for the causal hypothesis. Positive results have been obtained by applying the condensate, suitably diluted with an organic solvent, repeatedly to the skin

of mice or rabbits, or by injecting the undiluted condensate under the skin, or into the lung, of rats, and 3 cases of carcinoma *in situ* and pre-invasive carcinoma have been induced in dogs by the direct application of condensate to the bronchial mucosa (Roe and Walters, 1965).

Attempts to induce lung tumours in mice by inhalation of smoke have not been uniformly successful, and two criticisms have been levelled at those studies in which a positive result is claimed. Firstly, the lung tumours which arose in mice exposed to tobacco smoke were all adenomas or adenocarcinomas, while the vast majority of human lung cancers are of the squamous or oat-cell types, and, according to some authorities, the adenomatous type of human cancer is not associated with smoking. Secondly all the strains of mice in which lung tumours have been induced by tobacco smoke have had a high 'spontaneous' incidence of adenomatous lung tumours, so that exposure to tobacco smoke did no more than increase the incidence of a 'spontaneous' disease.

The present position is that no-one has succeeded in inducing either an epidermoid or an oat-cell carcinoma in any species of laboratory animal by exposing it to tobacco smoke by inhalation. On the other hand, the number of attempts to do so with sufficient numbers of animals exposed to a dose of tobacco smoke equivalent to moderate or heavy human exposure for a sufficiently long time have been few. According to Roe (1965) the lungs of small rodents are anatomically the equivalent of small segments of peripheral lung in man, and it is possible that squamous-cell and oat-cell carcinomas can only arise from parts of the human lung which are not represented in the small rodent.

It is interesting to note that small amounts of 3,4-benzpyrene have been detected in extracts of unburnt tobacco and that these extracts are capable of inducing or promoting the development of cancer in mouse skin (Campbell and Lindsey, 1956; Wynder and Wright, 1957; Ranadive, Gothoskar and Khanolkar, 1963; Bock, Moore and Crouch, 1964). These findings are particularly relevant to the induction of cancer of the oral cavity in tobacco-chewers (*see* Chapter 10) and to the induction of cancer of the naso-pharynx in snuff takers (*see* Chapter 24).

Butt Length

Obviously, the further down a person smokes a cigarette the more he is exposed to carcinogenic materials in the smoke. An important fact that is not widely appreciated, however, is that the amount of particulate matter derived from equal sized puffs increases rapidly (exponentially) as the cigarette becomes shorter during smoking (Lindsey, 1959; Graham and colleagues, 1963). There are 3 reasons for this, as follows.

(1) The tobacco in the cigarette acts as a filter and the degree of filtration so achieved decreases exponentially as the cigarette shortens.

(2) For equal sized puffs the amount of tobacco burnt increases as the cigarette is smoked due to a decrease in the proportion of air drawn radially through the paper.

(3) There is a slight contribution to the condensible smoke products of later puffs from repyrolysis of material removed from earlier puffs by the unburnt tobacco.

The possibilities of chemically selective filtration of tobacco smoke are not limited to vapour phase constituents as was once thought. Nevertheless, the technical problems involved in the development of a filter which will significantly alter the chemical composition in a desirable direction are likely to prove considerable. The combination of these factors is illustrated by one test in which the last 20 mm of a cigarette yielded more than 3 times as much 3,4-benzpyrene as the first 35 mm.

The fact that the incidence of lung cancer in the United Kingdom is very high compared with that in other countries where the level of cigarette consumption is similar may partly be explained by the relative shortness of the average butt length here. The average butt length is 18·7 mm in Great Britain, but it is 30·9 mm in the United States of America (Doll and colleagues, 1959; Hammond, 1958).

Inhaling

The present epidemiological evidence on the relation between inhaling and lung cancer shows that, for light smokers, there is a positive association between inhaling and death rate from lung cancer. However, the strength of the association decreases with increasing amount smoked and no association is detectable in the case of heavy smokers (Doll and Hill, 1964). The explanation of this phenomenon is not known. One possibility is that the mode and extent of inhaling varies with the number of cigarettes smoked per day. It is also possible that replies to questions about inhaling habits are not only inaccurate but also biased—from personal observation the authors find it difficult to believe that any heavy smokers do not inhale.

The suggestion stated most emphatically by Fisher (1959) that inhaling and lung cancer are negatively associated is so widely quoted that it is worth while to discuss the basis of this fallacious notion. The only study showing a negative association between inhaling and lung cancer was the retrospective survey of Doll and Hill reported in 1952. However, the difference recorded by them was neither statistically significant nor without explanation. In particular, the control group of Doll and Hill consisted of hospital patients and included persons suffering from diseases that we now know are also associated with smoking and inhaling (for example, bronchitis), so that comparisons of habits associated with both diseases were obscured.

Pipe and Cigar Smoking

As pointed out above, the epidemiological surveys have shown that the lung cancer risk—at the same level of tobacco consumption (1 cigar = 5 cigarettes, 1 oz. tobacco = 28 cigarettes)—of pipe and/or cigar smokers is less than that of cigarette smokers, but more than that of non-smokers. This information has received widespread publicity, with the result that some cigarette smokers have changed to a pipe or cigars.

The epidemiological data relating to cigar and pipe smokers are, however, very few compared with those for cigarette smokers, and it may be that such differences between the different types of smoker in their chances of developing lung cancer relate to the mode and extent of inhalation and not to the type of tobacco. In the laboratory, condensates prepared from cigar and pipe smoke are at least as carcinogenic for mouse skin as those prepared

from cigarette smoke (Croninger, Graham and Wynder, 1958). Also, the epidemiological evidence points to the conclusion that pipe and cigar smoking increases the risk of cancer of the mouth and upper respiratory tracts to about the same extent as cigarette smoking (Doll and Hill, 1964).

It is therefore possible that the relatively lower risk of developing lung cancer, particularly in cigar smokers, is due to the fact that cigar smoke, and to a lesser extent pipe smoke is more irritant and therefore inhaled to a lesser extent. If the person changing from cigarette to pipe or cigar does not also change his mode of smoking, he might be no better off, unless, of course, he also inhales less or reduces his total tobacco consumption.

A 'SAFE' CIGARETTE

The development of 'safe' or safer cigarettes by the design of selective filters has received much attention. Cigarette smoke consists of an aerosol of oily droplets (particulate phase) suspended in a mixture of atmospheric and non-atmospheric gases (vapour phase). The mechanism of filtration of this aerosol, whether by shredded tobacco or by other means is far from simple and is not understood in detail. For instance, as the 2 phases of the aerosol are in dynamic equilibrium, their chemical constituents are in no sense sharply distinct or likely to remain constantly distinct as the relative concentrations of the 2 phases change during passage through a filter.

Non-selective filters which are now incorporated in 'filter' cigarettes, cut down the amount of particulate matter drawn into the mouth. Any consideration of such filters begins with the realization that tobacco packed into a cigarette is itself a good filter and that it is quite feasible to replace the mouth end of the cigarette with a filter tip which is less efficient as a filter than the tobacco it replaces. In the past, because smokers preferred them, brands of cigarettes with low retention efficiency filters were marketed. Such 'filters' were first introduced as an economy measure in order to save tobacco that was otherwise thrown away with the butt. Now, however, all filter tips on the United Kingdom market are more efficient than the tobacco they replace; in general they remove between 25 and 55 per cent of particulate matter compared with 15 per cent by a 15 mm length of tobacco. Brands with the highest retention efficiency are not in great demand.

Finnegan, Larson and Haag (1945) distinguished between 2 types of smokers: 'With many individuals, nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit.' Obviously, many smokers fall between these 2 categories, but one would have thought that smokers to whom nicotine is not important could well take advantage of high retention efficiency filters. For the nicotine addict, on the other hand, cigarettes with a high concentration of the alkaloid relative to the total amount of particulate matter are likely to be safest.

The fact that smoke condensate (particulate phase only) has been repeatedly shown to induce skin cancer in laboratory animals, implies that any selective filter acting only on the vapour phase is unlikely to contribute much to the reduction of carcinogenicity of cigarette smoke. Nevertheless, two such filters have been developed in the United States of America, one

for phenols (Hoffman and Wynder, 1963) and one for ciliostatic gases (Kensler and Battista, 1963). It is not clear whether the presence of these agents affects the carcinogenicity of the smoke, but the removal of the ciliostatic gases might be of some value in diminishing the bronchitis risk as the same agents that paralyse cilia also stimulate the secretion of mucosa in the bronchial tree.

The possibilities of chemically selective filtration of tobacco smoke are not limited to vapour phase constituents as was once thought. Nevertheless, the technical problems involved in the development of a filter which will significantly alter the chemical composition in a desirable direction are likely to prove considerable. At present, moreover, the desirable direction is hardly known.

Basic research on the chemistry of tobacco smoke has not led to a completely satisfactory explanation of its carcinogenicity. The concentrations of known carcinogenic polycyclic hydrocarbons are much too low to explain the carcinogenicity of the smoke condensate for mouse or rabbit skin: cigarette smoke condensate has been found more carcinogenic for mouse skin than a solution of 3,4-benzpyrene in acetone, despite the fact that the concentration of the carcinogen was 50 times higher in the latter than in the former (Roe, 1962). In other words, the concentration of one of the most potent carcinogens so far isolated from cigarette smoke is less than one fiftieth of that needed to explain its carcinogenicity. So far, attempts to find other, more potent carcinogens such as nitrosamine derivatives in tobacco smoke have met with little success (Boyland and colleagues, 1964a; Boyland, Roe and Gorrod, 1964b).

There is both experimental and epidemiological support for the theory that the carcinogenic action of tobacco smoke is due to the combined effects of small amounts of carcinogens such as 3,4-benzpyrene and co-carcinogens (Gellhorn, 1958; Roe, 1962; Doll and Hill, 1964). Its main activity may lie in its co-carcinogenic constituents, and these may enhance the activity not only of carcinogens in tobacco smoke, but also that of carcinogens acquired from other environmental sources such as polluted air or occupation sources.

We conclude that, at the moment, the use of high retention efficiency filters offers some advantage. Until more is known about the mechanism of carcinogenesis by tobacco smoke, there is no logical basis for modifying raw tobacco with a view to reducing the lung cancer risk. Moreover, because known carcinogens are produced from such a wide variety of organic materials during the process of pyrolysis, it is most unlikely that a completely safe form of tobacco smoking can be evolved.

EARLY DETECTION OF HIGH RISK GROUP

Passey (1962) suggested that chronic bronchitis predisposes to lung cancer, but provided no satisfactory evidence that this is the case (Roe and Walters, 1965). Dean (1966), in a retrospective study of cases of lung cancer and matched controls, asked relatives of probands and controls whether at a time at least 3 years before death, the deceased suffered from a morning cough. A cough was more common in lung cancer subjects of both sexes than in controls, and the percentages in both groups having cough increased

with the number of cigarettes smoked per day. If Dean's conclusion 'that a smoker with persistent morning cough is in a group with a considerably higher risk for both lung cancer and bronchitis than a person with the same smoking habits and no cough' is proved correct, there may clearly be considerable preventive value in being able to advise particular individuals that they are at specially high risk of developing lung cancer if they continue to smoke; but in view of the studies of Rigler, O'Loughlin and Tucker (1953) we must question whether the interval of 3 years allowed by Dean was sufficient to exclude the possibility that the complaint of cough at that time was, in reality, a symptom of an early cancer.

In a study by Wynder and Fairchild (quoted by Dean, 1966) no association was found between persistent cough and the development of lung cancer among smokers of 30 or more cigarettes a day. A recent report by Boucot and her colleagues (1966) on a 9 to 10-year prospective study of men aged 45 years and over, examined by chest radiography at 6-month intervals and by questionnaire, throws further doubt on the predictive value of cough in relation to risk of developing lung cancer. The report is concerned with data from 84 new cases of proven lung cancer among the 6,071 men included in the survey. The incidence of cancer was twice as high among smokers with chronic cough as among smokers without this symptom. However, the risk of cancer among cigarette smokers who had smoked heavily for 40 years or more was similar whether they were chronic coughers or non-coughers (5·3 per cent against 6·7 per cent). Boucot and her colleagues (1966) concluded that cigarette smokers in whom cough was not a symptom were nevertheless at significant risk of developing lung cancer. It is interesting that among the 58 cases in whom the first radiological evidence of the disease was within 9 months of a radiograph showing no abnormality 45 per cent were non-coughers. Doll (personal communication) questions whether cough in the relatively light smoking groups of both Wynder's and Boucot's studies is anything more than an indication that the individual has been a heavier smoker than a man without a cough (for example, he may have inhaled more, taken more puffs per cigarette or smoked the cigarette to a shorter butt). Another possibility is that where cough and cancer co-exist, the former is a manifestation of the latter rather than evidence of a state of irritation which predisposes to the latter.

The question of the relationship between cough and risk of cancer remains open. At present it would be palpably unwise for any smoker to believe that smoking is not increasing the risk of his developing lung cancer on the grounds that he has no cough. (The relationship between chronic bronchitis and lung cancer is discussed in Chapter 28.)

CONCLUSIONS

If the immediate complete discontinuation of smoking were feasible for all smokers, then the recommendation that this be done need have been our only conclusion, since it is clear that every form of smoking increases the risk of lung cancer. To stop smoking, however, does not appear to be a practical proposition for a high proportion of smokers. Even smokers who are fully exposed to the knowledge of the harmful consequences of the tobacco habit—and lung cancer is only one of several such consequences—

find themselves unable to give it up. Smoking serves many purposes in a sophisticated society by satisfying a wide variety of social, psychological and possibly physical needs. A better understanding of these needs and of alternative ways of satisfying them is essential before there can be any real hope of persuading a majority of smokers to stop smoking.

In the meantime, every effort should be made to encourage smokers to reduce the level of their exposure to tobacco smoke. In this connection it may help to make the following suggestions.

(1) Reduce the amount smoked, perhaps by confining smoking to certain periods of the day.

(2) Inhale as little as possible.

(3) Throw away a long butt if they smoke cigarettes. This may be one of the most important pieces of advice. A man who smokes 2 cigarettes halfway down takes in much less particulate matter than a man who smokes 1 cigarette down to a short butt-length.

The epidemiological evidence indicating a lower lung cancer death rate in pipe or cigar smokers than in cigarette smokers, has prompted some cigarette smokers to change to pipes or cigars. Indeed, a number of experts have advised this change, and encouragement has been given by the selective ban on television advertising of cigarettes but not of pipes or cigars. In the authors' view, however, there is insufficient evidence for actually recommending a cigarette smoker to simply change to pipe or cigars. Only if the change resulted in a reduction of both inhaling, and/or total tobacco consumption, could benefit be expected. Such a reduction is likely to be easier in the case of changing to pipe or large cigars, both of which are physically very different from cigarettes from the point of view of holding in the hand or mouth. However, the popularization of small, cigarette-size cigars may carry the danger that smokers will smoke them in the same way, and in the same amount, as cigarettes.

The government, local authorities, transport organizations, and those responsible for public places of entertainment such as theatres and cinemas, could help in the prevention of lung cancer by placing restrictions on smoking. Some shops and store owners have done this on the grounds of hygiene and to prevent damage to goods caused by tobacco smoke and cigarette ash and butts. The problem here is to what extent it is justifiable and commercially feasible to curtail the rights of the individual, particularly in respect of a habit which satisfies certain personal and social needs. Compromise is indicated, but without a doubt more restrictions than apply at present are necessary and would be well tolerated by the general public (Cartwright, Martin and Thomson, 1960).

Epidemiological findings indicate clearly that to stop smoking is eminently worthwhile. Reduction, even though it falls short of complete elimination of the smoking habit would therefore be of value. Smokers, irrespective of the extent to which they feel able to reduce their own exposure to the lung cancer risk, have a special obligation to set an example to young people. If parents hope that their children will not smoke they must make every effort to arrange the home environment so that smoking is not an integral part of it. By asking themselves why they find it personally necessary to smoke, they may be able to organize a home life in which smoking is not a

necessity. Doctors and teachers are both looked to for guidance in matters such as this, and their example, more than anything they say, will be what is noted.

In the past, and still to some extent today, despite section 2 (d) of the United Kingdom Advertising Code for Cigarettes and Hand-rolling Tobacco, advertising seems to do precisely the opposite from that which we suggest parents, doctors and teachers should be doing: it suggests that smoking is not only socially desirable but that it is an important factor in living a full life. Indeed, the advertisers would have us believe that the smoking of a particular brand of tobacco is the hallmark of integrity. Ultimately, it is hardly to anybody's advantage to ignore the true facts of the relationship between smoking and health, and the government should be pressed to take action at least against this type of advertising.

One thing that could be done immediately is to introduce legislation with regard to the information provided on cigarette packets. For instance, the efficiency of cigarette filters or, preferably the amount of condensable material and nicotine currently obtainable from cigarettes of the particular brand smoked under standard conditions, should be stated in a meaningful way. Whether such information should be accompanied by health warnings is debatable.

At present, among the greatest bars to government action is the enormous revenue obtained from duty on tobacco and the fact that the tobacco industry, with its extensive labour force, is extremely vulnerable to changes in smoking habits by the public. There are some who despair of ever persuading others to smoke less. Perhaps they are in too much of a hurry. It has taken many decades for cigarette consumption to reach its present level, and it may take as many for it to subside again. The first signs of subsidence are already apparent in that more students, young scientists and doctors are non-smokers than ever before. It is hoped that their example will gradually spread.

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