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Bronchogenic Carcinoma: Some Aspects of its Aetiology and Prevention

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Abstract

Fifty years ago, bronchogenic carcinoma was a rare disease; to-day it is the most frequently encountered intra-thoracic neoplasm and it is one of the commonest of all the killing tumours. It still bears a grave prognosis despite the advances in surgical and diagnostic technique which allow the treatment to be begun much earlier than was possible in former days. The general public, let alone the medical profession, is becoming increasingly alarmed by this condition, not only on account of its lethal character, but because of the correlation between it and the almost universal habit of cigarette smoking. Questions of ethics and sociology, of politics and economics, of industry and international relations are some of the problems closely interwoven in the suspected aetiology and in the hoped-for prevention of bronchogenic carcinoma.

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Bronchogenic Carcinoma: Some Aspects of its Aetiology and Prevention

By JAMES A. GRAY

BASED ON A DISSERTATION READ BEFORE THE ROYAL MEDICAL SOCIETY
ON FRIDAY, 18TH OCTOBER 1957.

*For thy sake Tobacco, I,
Would do anything but die.*

LAMB: *Farewell to Tobacco.*

FIFTY YEARS AGO, bronchogenic carcinoma was a rare disease; to-day it is the most frequently encountered intra-thoracic neoplasm and it is one of the commonest of all the killing tumours. It still bears a grave prognosis despite the advances in surgical and diagnostic technique which allow the treatment to be begun much earlier than was possible in former days. The general public, let alone the medical profession, is becoming increasingly alarmed by this condition, not only on account of its lethal character, but because of the correlation between it and the almost universal habit of cigarette smoking. Questions of ethics and sociology, of politics and economics, of industry and international relations are some of the problems closely interwoven in the suspected aetiology and in the hoped-for prevention of bronchogenic carcinoma.

Most authorities agree that the rising mortality from lung cancer represents a real and not merely an apparent increase. A possible explanation for this is the increasing presence of a carcinogen which was formerly not so much in evidence. Moreover, the preponderance of male to female deaths suggests that men, by reason of their occupation or habits, may be more exposed to such an influence than women. Women are beginning to smoke as much as men and the female incidence may possibly rise because of this; on the other hand, it has been postulated that the male bronchial mucosa may be more susceptible to malignant changes. In 1950, however, Doll and Hill (14) presented figures consistent with the view that amongst non-smokers living in the same area (Greater London) the risks of developing lung cancer were approximately the same in men and women, a fact which tends to minimise the possibility of an inherent sex predisposition irrespective of external influences.

It has been known for many years that certain occupations bear a lung cancer hazard. The well-known miners' cancer of the cobalt and pitch-blende workings in Schneeberg and Joachimstal was first described in 1879. Pitch-blende has a uranium content of 70% but also contains manganese, iron, cobalt, silica and nickel. Radioactivity has often been quoted as the factor responsible but this is not known for certain (25). More recently, other industries have been shown to have a significant lung cancer hazard. Haematite miners are exposed to such a risk, not thought to be due to any specific carcinogen, but rather to the irritation by silica, ferric oxide and chronic infection. Siderosis, therefore, predisposes to carcinoma of the bronchus (19), whilst pneumokoniosis in Welsh coal miners shows rather the opposite effect (21). The nickel refiners at Clydach in North Wales and asbestos textile workers (12) have an increased lung cancer

hazard. An investigation into the bichromates industry in three factories in Great Britain (1) showed that the workers were exposed to a risk which was quite independent of their social, residential, smoking or other habits. Coal gas workers have an increased ratio of registered to expected deaths from bronchogenic carcinoma which is $2\frac{1}{2}$ times that for the general population. (11) At one time it was thought that the incidence of bronchogenic carcinoma might be greater amongst those exposed to tar from roads or to exhaust fumes from motor engines and that this might help to explain the rising mortality figures over the last fifty years. However, no such correlation has been found despite investigations amongst road-menders, asphalters and garage-hands (13 and 20).

The legacy of chronic infection was at one time suspect in the aetiology of bronchogenic carcinoma. Active tuberculosis and lung cancer may be found concurrently and even when an unequivocal diagnosis of tuberculosis is made, the possibility of an associated neoplasm should be borne in mind. Cancer of the lung has been reported in the neighbourhood of healed tuberculous foci and it is rather doubtfully argued that the drop in mortality due to tuberculosis might so have increased the number of healed tuberculous lesions, that there followed a rise in incidence of bronchogenic carcinoma. (13) A lower respiratory tract infection which does not subside should always be regarded with suspicion and it must be remembered that such an infection is more likely to be the result than the cause of a lung cancer. Doll (10) concluded from his study of the mortality from bronchogenic carcinoma among non-smokers, that neither occupational hazards nor the previous occurrence of certain respiratory diseases is likely to be of frequent aetiological importance.

The mechanism causing one small group of pulmonary carcinomas, the scar cancers, is obvious from the name. Reparative hyperplasia following trauma frequently simulates neoplastic change and there is often an indistinct borderline between the two processes. It is sometimes found therefore that scars in lung tissue form precancerous foci. Obstruction of lymph drainage allows anthracotic material to accumulate with the possible liberation of carcinogens. Tuberculous lesions, infarction and inhaled foreign bodies, as well as scars can form the nidus of irritation in which such cancers develop. Each of the three classical histological types of bronchogenic carcinoma has been observed in scar cancers. Usually these tumours are peripheral but may be perihilar because of the centripetal lymph drainage. A central lesion may simulate the primary and yet be in fact a metastasis from some small unrecognised subpleural focus (29).

The two most controversial and important factors in the aetiology of lung cancer remain to be discussed: atmospheric pollution and tobacco smoking. Both could well explain the increased lung cancer mortality and smoking in particular the marked preponderance of male to female deaths. Doll (9 and 10) showed that in 1950 the annual lung cancer mortality per 1000 of the population for both sexes and for all age groups between 25 and 74 was least in rural districts, was greater in urban areas and was maximal within the confines of Greater London. In 1952 a group of workers in Liverpool (27) showed that of 100 lung cancer patients, 47% had been exposed to dust, fumes and smoke whilst of 200 carefully matched controls, only 43% had been similarly exposed. Likewise there was a small, though statistically insignificant, increase in the number of cancer patients who lived within an industrial area as compared with the number of controls whose residence was similarly situated. For a series of cases between 1946 and 1947, the incidence of cancer of the male and female lungs and

of the male larynx was positively correlated with the density of the population whilst, for some obscure reason, the reverse was true for cancer of the female larynx (7).

In 1955, Stocks and Campbell (30) investigated this remarkable tendency for increased mortality from bronchogenic carcinoma in urban as opposed to country areas. They chose three districts for their study: rural Wales, a mixed area round Chester and Wrexham and a Liverpool county borough and found that the death rate from bronchogenic carcinoma rose in proportion to the number of cigarettes smoked per week, pipe smokers being arbitrarily classed with those smoking 25 cigarettes weekly. The Liverpool mortality exceeded the rural death rates in each smoking category, but the urban/rural ratio fell progressively from about 9:1 amongst non-smokers to a value approaching unity amongst heavy cigarette smokers. The absolute urban excess was found to be similar in each smoking category and suggested that an "urban" factor was added to the effects of smoking. By comparing the amounts of 3:4 benzpyrene in the air of the Liverpool district and the rural area in question, they concluded that this carcinogen might be the agent responsible for the association of lung cancer with both smoking and urban residence.

Attempts to correlate smoking and lung cancer have been directed along four separate channels, three of them statistical and one experimental. The first method was to demonstrate the rising incidence from bronchogenic carcinoma in relation with the increased tobacco consumption of the population. In this respect Ochsner (28) graphically demonstrated the correlation of the death rate from pulmonary neoplasm in the U.S.A. between 1920 and 1933 with the rising production of tobacco and automobiles. A similar trend has been reported by workers in this country and elsewhere (8). Moreover, lung cancer is rare in Iceland, where it holds ninth place amongst the cancers found at post-mortem examinations, and Dungal (17) suggested that this might be due to the comparatively low tobacco consumption in that country. Kennaway (22) pertinently remarks, however, that a simultaneous increase in tobacco consumption and lung cancer cannot prove that there is any aetiological relation between the two. Other changes have occurred at the same time, for example the increased issue of wireless licences, which show a remarkable parallelism when matched against the lung cancer mortality graph. On these grounds it is therefore doubtful what significance can be placed on this method of approach to the problem.

The second and more successful attempt to investigate the suggested correlation between smoking and lung cancer has been to inquire into the smoking habits of a group of patients with the disease and to make a simultaneous inquiry into a group of carefully matched controls not suffering from the disease. Many workers have demonstrated that there are significantly more smokers than non-smokers who develop bronchogenic carcinoma, and that there is a greater number of heavy cigarette smokers amongst the cancer patients than amongst the groups of control patients without cancer. The classical study of this problem by Doll and Hill (14) in 1950 is worthy of note, not only because it proves its point, but because it emphasises what caution must be exercised by the statistician when he criticises his data if he is not to create a false impression by the mass of figures he displays. Even Disraeli who described three types of falsehood: "Lies, damn lies and statistics," would have been hard pressed to pick faults in the findings which Doll and Hill presented. They were meticulous in ensuring that their conclusions were unbiased.

The cancer and control patients were selected to be of the same age and sex throughout and the only differences were in their place of residence and their social status. Misdiagnosis was considered unlikely. The interviewers used a standard questionnaire and the memory and veracity of the patients in regard to their smoking habits was checked upon. The bias of the interviewers to scale up the smoking habits of the cancer patients was negligible nor did they select controls who had unusually light smoking histories. The cancer patients who were aware that they at least had some chest condition, did not therefore exaggerate their smoking habits any more than did other patients with non-malignant respiratory diseases. The investigation took into account whether the patient had at any period smoked, the ages of stopping and starting the amount smoked before the onset of the illness which brought him into hospital, the main changes in his smoking history and the maximum ever smoked, the varying proportions of pipes or cigarettes and whether or not the patient inhaled. These precautions taken, Doll and Hill suggested that their findings indicated that, above the age of 45, the risk of developing the disease increased in simple proportion to the amount smoked, and that it might be approximately 50 times as great amongst those who smoked 25 or more cigarettes a day as amongst non-smokers.

The third and final statistical approach to the problem of smoking and bronchogenic carcinoma was undertaken by the same workers (15 and 16). This time Doll and Hill took, instead of a "backward" series as before, a "forward" series or in other words, instead of comparing the smoking habits of patients who had already developed the disease with a group of controls, they first assessed the smoking habits of a group of people, the Medical Profession of this country, and are now waiting to see how many die from the disease. Doll and Hill received over 40,000 replies to the questionnaire they sent out and although the investigation only began in 1951, there have been sufficient deaths already to indicate a marked and steady increase in the mortality from lung cancer as the amount smoked increases; the trend is a feature of each age group over 35 and the mortality is greater amongst cigarette smokers than pipe smokers; the death rates fall as the length of time increases over which smoking has been given up; the mortality for smokers of 25 or more cigarettes a day is 40 times that for non-smokers.

The fourth and most direct method of showing the link between smoking and lung cancer is the demonstration of carcinogenic agents in tobacco. Arsenic was at one time considered important and certain American cigarettes were shown to have a high arsenic content. However, the high death rate from bronchogenic carcinoma in Istanbul where arsenic free cigarettes are commonly smoked, suggests that arsenic is not a factor. Moreover, when it is applied to the skin of laboratory animals, it fails to produce cancer in the way in which tobacco tar does (13).

The temperature of combustion of a cigarette often exceeds 650° C whilst pipe smoking is a cooler process with temperatures around 500° C (18). At the higher ranges polycyclic hydrocarbons are formed and some of these substances can produce squamous carcinomas in strains of mice which are free from any predisposition to spontaneous cancer. As much as 4.0 μ g of 3:4 benzpyrene has been gathered from the smoke of 500 cigarettes and the cigarette paper too liberates carcinogens when burnt, although these are insignificant amounts (5 and 6). Cigarette paper had previously been suspected as a cause of the higher mortality of cigarette—as opposed to pipe—smokers, but it appears more likely that the temperature differences, the condensation of quantities of tar in the pipe stem and

the amount inhaled are more likely to be the factors involved (4 and 32). Petrol lighters have been suspected but it was found that they were not used any more often by patients with bronchogenic carcinoma than by non-cancer patients (13).

The tar collected from "smoking machines" is carcinogenic and in 1954 Graham (20) found that an acetone solution of cigarette tar produced epidermoid carcinoma in mice after 71 weeks which is a little more than half their average life span of two years. This period, he pointed out, was equivalent to the 30 to 50 years required in man to produce lung cancer by smoking. Campbell (3) showed that 70% of the mice surviving after repeated exposure to dust from the sweepings of tarred roads developed cancer of the skin but the concentration of tar present was far higher than that to which human beings are ever subjected. Unfortunately similar experiments cannot be employed with cigarette smoke because mice rapidly succumb to nicotine poisoning if allowed to inhale significant quantities (20). Lung tumours, however, have been

OPERA OCCULTA

With a mixture of pride and humility I began to turn the pages of the great leather-backed volumes which enclose the early Dissertations of the Royal Medical Society. It was something to be done with care, for the pages are brittle and cachetic. The regular, flowing, almost copper-plate writing is only slightly faded and is eminently legible. We, who can achieve immaculate script only through the medium of machinery, might pause and consider the scholarship of our predecessors who wrote Greek, Latin or English with artists' hands.

The fascination of these works, however, does not end in the contemplation of their beauty. Into these pages has been poured all the erudition and earnest speculation of more than two hundred years ago. Not only do they carry a mass of information of the state of medical knowledge in the eighteenth century, but they also breathe an aura of the life, manners and social conditions of the time. So much is there that is interesting, so much to amaze or amuse, that it seems scarcely possible to pick out isolated passages of adequate brevity for the confines of this production. However, with the hope that the authors would have excused the mutilation of their opera, I have selected at random a few passages. They will be found in this and subsequent issues.

Diagnosis?

From a letter to the President of the Society in 1777.

"At eleven o'clock that night a messenger came to me, saying that Watson was going mad. I found him perfectly sensible, complaining of a lightness across his stomach, with a peculiar sensation (to quote his words) 'his entrails moving up and down as if they were alive,' and he said he could not drink. I had a looking glass brought privately to me, and held it up before him: the sight of which threw him into violent agitation. I then persuaded him to try to drink; but on the fluid approaching near his lips he was in a similar agitation to that which the glass produced. It next occurred to me that the accession of cold air to the body, according to some author, had the same effect; I therefore fanned him with my hat . . ."

demonstrated in rats treated with 3:4 benzpyrene, methylcholanthrene and the condensate from cigarette smoke (2).

It may be argued that tobacco will evoke different responses in human beings and in animals. Yet in 1956, Lasnitzki (24) working on human foetal lung explants showed how quantities of benzpyrene similar to those obtained by smoking 500 or more cigarettes, could induce bronchiolar epithelial hyperplasia. The change consisted of an increased proliferation of the lining epithelium from the normal one row of cells to rows with cells 6 or 12 deep. They frequently spread to cause partial or complete obstruction of the lumen and showed an irregular increase in size as well as abnormal mitoses. Short of experiments on living human subjects, these findings must surely be conclusive. Moreover, Auerbach's examination of post-mortem material (23) showed that there was a remarkable parallelism between the smoking habits of the deceased and the occurrence of basal cell hyperplasia, stratification, squamous metaplasia and even carcinoma-in-situ. This was present in many cases and was often wide spread on the bronchial mucosa and rather unexpectedly on the trachea itself.

That the aetiology of bronchogenic carcinoma, with the possible exception of the adenocarcinoma, is linked with cigarette smoking is now apparent and may be summed up in the words of the Medical Research Council's statement in June of this year (26):

- (1) A very great increase has occurred during the past 25 years in the death rate from lung cancer in Great Britain and other countries.
- (2) A relatively small number of the total cases can be attributed to specific industrial hazards.
- (3) A proportion of cases, the exact number of which cannot yet be defined, may be due to atmospheric pollution.
- (4) Evidence from 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 is that the relationship is one of direct cause and effect.
- (5) The identification of several carcinogenic substances in tobacco smoke provides a rational basis for such a causal relationship.

* * * *

PREVENTION

IT WAS only through improvements in sanitation and hygiene that the inhabitants of this country were spared from further major outbreaks of cholera during the seventeen years which preceded Koch's demonstration of the *Vibrio cholerae*. To-day we are in a similar position with regard to lung cancer. Cigarette smoking is a known aetiological agent in bronchogenic carcinoma and although the exact mechanism of the disease is not fully understood, it is surely common sense to dissuade the public from a habit which predisposes them to a fatal condition.

Moderation in the smoking habit seems to be the only way of lowering the intake of carcinogens. No filter is yet available which will exclude all harmful substances whilst still providing a sufficient pressure drop and retaining the flavour of the tobacco. Modification of pyrolysis or the removal of some precursors of known carcinogens before the cigarettes are manufactured may eventually provide one solution to the problem (31).

The tobacco consumption of this country continues to rise and the age at which smoking becomes a regular habit appears to be falling. It is unfortunate that so few members of the Medical Profession, apart from influencing the public against the cigarette habit, have failed to, or have not wished to, grasp the fact that smoking predisposes to bronchogenic carcinoma. Besides it is very difficult to bring home forcibly enough to the layman the view that the disease may take from twenty to thirty years to make itself manifest. Despite appeals from bodies like The British Medical Association, the Government dallied long before making any declaration to the public. It seems as if in this age of enlightenment, the chance of disappointing the electorate and of losing an annual revenue of over £700 million from tobacco excise can stand in the way of the nation's health.

To use the time honoured adage, "Prevention is better than cure," and when true cure is available to so few lung cancer patients, prevention must be the line adopted. There is a wealth of wisdom contained in the following words written by William Lambe in 1815:

We are constantly deluded by language. We say a person dies of a cancer. . . . The truth must be that a person dies of the causes of cancer; and the cancer is not the cause but the mode of dying.

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