THE INCIDENCE AND AETIOLOGY OF PRIMARY CARCINOMA OF THE LUNG

By C. E. Drew, M.V.O., F.R.C.S.

Westminster Hospital, London

The lung now rivals the stomach as the most common site of primary malignant disease. While the cause of the malady remains unknown, statistical studies have shown the way to a better understanding of some of its characteristics.

Sex Incidence

There is no doubt that it is much more common in the male, but reports vary from 3.74 to 1—Ochsner and DeBakey (1941) to 18.5 to 1—Wynder and Graham (1950). Lindskog and Bloomer (1948) found the ratio in 100 consecutive cases from 1938-1943 to be 4.5 to 1, but in 1947-1948 analysis of a similar number of patients showed the incidence in men to have increased to 24 to 1: Mason (1949) in a review of 1,000 cases found the ratio between male and female to be 9 to 1.

Increase in Incidence

Figures published by the Registrar General suggest that there has been a marked increase in the disease since the beginning of the century. In 1922 the deaths recorded were 612, while in 1947 the number had risen to 9,287 for that year, an increase which is roughly fifteen fold—Doll and Hill (1950). It is impossible to say how far these figures should be corrected for factors which inevitably would have produced an apparent increased incidence of the disease.

In this country it was not until 1926 that Barnard demonstrated that many tumours which had been called oat cell sarcoma of the lung and lymphosarcoma of the mediastinum were in fact pleomorphic carcinoma of the lung, which leads one to suspect the accuracy of earlier autopsy diagnoses.

It is also reasonable to assume that many deaths supposedly due to inflammatory lung conditions and certified as such, were in truth caused primarily by cancer. The increase in our knowledge of chest disease, most marked in the past twenty-five years, with the development of radiographic diagnosis particularly in the realm of mass radiography, the more frequent use of the bronchoscope and examination of bronchial secretions, must have brought to light many cases which otherwise would have been misdiagnosed.

The first successful pneumonectomy by Graham for carcinoma of the lung in 1933, which showed that such a lesion was amenable to treatment, was a tremendous stimulus to its recognition. It is not unusual for a major therapeutic advance to increase awareness of the condition which is being treated and by so doing to make it seem more common.

Rigdon and Kirchoff (1952) suggest that the progressively greater number of persons between the age of forty-five to sixty-five years of age relative to the rest of the population would account for much of the apparent increase in incidence, as this age group is particularly susceptible.

According to the Bureau of Census in 1920, 16 per cent. of the total population of the United States belonged to this age group, while in 1950 there was an increase to 21 per cent.

Despite these considerations Doll and Hill (1950) and Graham and Wynder (1950) are convinced that there has been a considerable real increase in its frequency.

Aetiology

Lung Cancer as an Industrial Hazard

The possibility that inhaled carcinogens may be responsible for pulmonary carcinoma has been noted for many years and in certain industries has been recognized as a serious occupational hazard.

Peller (1939) showed that about one half of the miners in the Joachimstal area of Czechoslovakia died with this disease and Lange (1935) gave similar figures for Schneeberg—quoted by Perry (1952). The main ores which are mined are the sulphides and arsenides of nickel and cobalt and include some radio active substances, but opinions
differ as to which chemical in the inhaled dust is to blame.

Machle and Gregorius (1948) found that in workers over 50 years of age at chromate plants in the United States, deaths from lung cancer were about forty times as common as those in other comparable industrial groups.

Hill and Faning (1948) called attention to the carcinogenic properties of arsenic by showing that those engaged in the manufacture of sheep dip suffered a mortality from cancer of the skin and bronchi double that of the neighbouring population.

In the light of these observations it is reasonable to search for other more widely distributed substances which when inhaled might produce a like effect.

Lung Cancer and Tobacco

Much has been written about the relationship between smoking and this disease. Adler (1912) in a monograph reporting 374 cases which he collected from the world’s literature, suggested that tobacco smoking may be a causative factor. Tylecote (1927) in a letter to The Lancet suggested the same possibility, while Mueller (1939) published a small series of cases suggesting the existence of such a relationship. Only 3 of 86 male patients with lung cancer were non-smokers and 56 were heavy smokers, whereas in a control series of patients who did not have the disease 14 were non-smokers and 31 were heavy smokers.

Patient and penetrating independent statistical studies by Graham and Wynder in the United States and by Doll and Hill in England and Wales, published in 1950, throw much light on this problem.

The American investigators stressed the sex difference and attempted to correlate smoking habit with the type of tumour, although it was pointed out that histological classification is sometimes difficult because more than one cellular pattern may be found in the same specimen, and interpretation by different pathologists is often inconstant. In 684 proved cases, 605 were men who had a squamous cell tumour, or its variant the anaplastic round cell or oat cell type. Of these, 51.2 per cent. had smoked over thirty cigarettes or their equivalent daily for over twenty years. Only 2 per cent. were non-smokers and over 96 per cent. of men with lung cancer and a history of smoking had smoked for twenty years or more. In a control series of 780 patients who did not suffer from the disease, only 19.1 per cent. smoked to a similar extent. Of the 25 women patients with cancer of similar histology 10 or 40 per cent. were non-smokers.

The criticism that women now smoke as much as men and should presumably develop the disease in like proportion if cigarette smoking is indeed an important aetiological factor, is answered by the statement that among 522 women patients without lung cancer between the ages of 30 and 79, 79.6 per cent. were non-smokers. Despite the recent trend towards sex equality in regard to cigarette smoking, few women have smoked to excess for twenty years or more and long exposure to the habit appears to be necessary for the development of the disease. Of 52 patients with adenocarcinoma there were 59 men of whom four were non-smokers, and of 13 women with similar histological type of disease 9 did not smoke and two were only light smokers. The remaining two patients in the series were women who were suffering from the rare 'alveolar cell' tumour. On this evidence Graham (1951) boldly referred to the squamous cell carcinoma and its anaplastic variants as 'cigarette cancer' while he regarded the adenocarcinoma as possibly having no such close relationship to smoking.

The work of Doll and Hill was carried out on similar lines, using a standard questionnaire on large groups of patients with and without the disease.

Of 709 patients in the former group living in Greater London, 60 were women. Only 0.3 per cent. of the men, and 31.7 per cent. of the women were non-smokers, while in the non-smoker control group the figures were 4.2 per cent. and 53.3 per cent respectively. Among the smokers, 26 per cent. of the male and 14.6 per cent. of the female patients smoked 25 cigarettes a day or more, while of the controls only 13.5 per cent. of the males and none of the females smoked to this extent. The writers agree with Graham and Wynder that on a statistical basis the preponderance of the disease in men can be entirely explained by the fact that the proportion of smokers to non-smokers is greater in the male sex. Using the smoking histories of the control series a rough estimate was obtained of the smoking habits in the population of Greater London and hence the relative risks among different grades of smoker as shown from the group known to have lung cancer.

While admitting that the figures are speculative, the frightening conclusion is drawn, that after the age of 45, the risk of developing the disease may be about 50 times as great in those who have smoked 25 cigarettes or more daily for 20 years, as for abstainers.

A second report published in 1952, of a larger series of cases taken from different parts of England, confirmed their previous findings. The use of petrol lighters was not considered to
be significant but pipe smokers appeared to be subject to a lowered risk while a similar but less definite trend was noted in those who used cigarette holders or filter tips. Despite the stress laid on the association of cigarette smoking and lung cancer it was not suggested that this was the only factor as some patients with the disease had never used tobacco.

**Experimental Evidence**

Despite many theories and much experimental work the responsible agent in tobacco smoke has not been isolated. It is known that tobacco and cigarette paper contain arsenic which is known to be a carcinogen.

Leitch and Kennaway (1922) showed that painting the skin of a mouse with potassium arsenite produced a squamous cell carcinoma and metastasizes at the end of five months. Thomas and Collier (1945) found that the arsenic content in the puffed smoke of cigarettes was about twice as high as that of pipes and four times as high as that of cigars.

The difficulties of analysis are considerable because much of the arsenic may be derived from insecticide so that the concentration varies from brand to brand and even in single cigarettes from the same batch.

Daff and Kennaway (1950) estimated the arsenic content of 15 different brands and found that it was almost non-existent in Turkish tobacco. As there is a high incidence of lung cancer in Istanbul, where Turkish tobacco is smoked exclusively, Daff, Doll and Kennaway (1951) conclude that arsenic does not seem to provide the link between smoking and this disease.

Benzpyrene might be invoked as the factor involved, but Waller (1952) could find no evidence of this substance in tobacco smoke.

Flory (1941) produced squamous cell carcinomas in mice by painting the skin with tobacco tars but was not successful in rabbits. Graham (personal communication) with Wynder and Croninger, using a strain of mouse which is known not to develop spontaneous skin tumors, was able to obtain skin cancers in 32 mice or 40 per cent. of a series subjected to painting with cigarette tars. Using a smoking machine which smoked 60 cigarettes at a time, the smoke was driven into flasks cooled with dry ice and the tars were dissolved in acetone. The solution was used to paint the skin while acetone alone was applied to a control series. The average time required to develop a skin cancer was one year, about one half the life span of the mouse, which matches observations in man that many patients with lung cancer admit to excessive cigarette smoking for more than 25 years. The carcinogenic agent in the tar is unknown.

**Lung Cancer and Other Respiratory Disease**

There is no evidence that chronic lung disease renders the sufferer more prone to carcinoma. It is no more common in the bronchiecstatic or the phthisical than it is in those with healthy lungs. The statement that influenza is a predisposing cause is refuted by Dungal (1950) who showed that lung cancer is rare in Iceland where the pandemic of influenza in 1918 'raged with a force hardly paralleled in any other country.'

**Atmospheric Pollution**

Dust from tarred roads, exhaust fumes from motor vehicles and smoke from chimneys, all containing substances which are experimentally carcinogenic, have been invoked as possible factors in the production of lung cancer. Stocks (1947) found 'an inverse correlation between the annual amounts of sunshine in 20 large towns and their lung cancer mortalities.' He concluded that either smokiness of atmosphere is an important factor in producing cancer of the lung or that sunshine is an important factor preventing its incidence. Doll and Hill (1952) calculated that after allowing for difference in smoking habits there is a higher death rate in the towns than in the country from this disease, and thought it likely that some other factor than tobacco (domestic chimney smoke or exhaust fumes) might be responsible. Stocks (1952) in a study on the endemiology of cancer of the lung showed that there was a tendency for mortality to increase with the density of the population and the number of chimneys. He suggests that in large towns the effects of tobacco and atmospheric pollution may be additive.

At the present time our knowledge of the incidence and aetiology of lung cancer is drawn almost entirely from mathematical tables, some contradictory, but many leading to identical conclusions.

Stocks writes as follows:

'Although, as one is continually reminded, statistics in themselves cannot establish causation and in common with other types of cancer research they often lead up blind alleys, they can start what biochemists and pathologists will finish and they may even succeed in making sense out of a chaos of isolated findings by other research workers. It seems possible that this may happen sooner for lung carcinoma than for any other form of cancer.'
Carcinoma of the Bronchus: Medical Aspects

By John Anderson, M.D., F.R.C.P.
St. Thomas’s Hospital, London

Here we shall consider the recognized modes of presentation of the disease and discuss the means at present at our disposal to confirm the clinical diagnosis.

Clinical Patterns

It is convenient for purposes of discussion and description to divide the clinical manifestations of carcinoma of the bronchus into more or less well defined clinical entities while it remains clear that such division is largely arbitrary and considerable over-lapping in fact exists.

Cough

Cough is the predominant symptom in only about a quarter of the cases (Brooks et al., 1951), and it is so common a complaint that, in any event, it is unprofitable to discuss it further beyond saying that persistent cough or sudden change in cough habit calls for complete investigation.

Haemoptysis

Haemoptysis is often admitted to by chronic bronchitic subjects and is, in fact, on further investigation and follow-up, found to have no important cause in the great majority who suffer it.

Of proved bronchial carcinomas, on the other hand, it is the presenting symptom in 14 per cent. (Brooks et al., 1951) and 60 per cent. suffer from it during the course of the illness (Price Thomas, 1948).

In these circumstances a single small haemoptysis which amounts to staining or streaking of the sputum when there are no abnormal physical signs and the chest films (PA and laterals where necessary) are normal can safely be dealt with by taking a further film in six weeks and another film three months later.

Whether all patients who have blood spitting should be bronchoscoped is an unresolved problem. Medical experience dictates that such a degree of thoroughness is in fact both unnecessary and impracticable. Surgical experience, digesting the discoveries by bronchoscopy in what is admitted to be a selected series of cases, largely referred by physicians, finds four cases of bronchial carcinoma out of 71 patients who had haemoptysis and normal chest radiographs (MacHale, 1953). This figure is one to think on and an antidote to complacency. However, when the haemoptysis is repeated, it will be necessary to go further into the problem by bronchoscopy and, if this is negative, by bronchography and examination of the sputum for malignant cells. It is essential to stress that repeated haemoptysis, no matter how individually small or how widely spaced in time, calls for a complete investigation because bronchial carcinoma may cause repeated haemoptyses for...
The Incidence and Aetiology of Primary Carcinoma of the Lung
C. E. Drew

Postgrad Med J 1953 29: 592-595
doi: 10.1136/pgmj.29.338.592

Updated information and services can be found at:
http://pmj.bmj.com/content/29/338/592.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/