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BRONCHIAL CARCINOMA: INCIDENCE AND AETIOLOGY*

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A little over a hundred years ago Dr. Gavin Milroy took an active part in the establishment of the Epidemiological Society. The object of the Society was to study "epidemic and endemic diseases, with special reference to the investigation of (*a*) the various external or physical agencies, and the different conditions of life, which favour their development or influence their character, and (*b*) the sanitary and hygienic measures best fitted to check, mitigate, or prevent them." In 1850, interest was focused on the great epidemic diseases, but the methods Milroy urged—the collection of statistical data on the natural history of disease over large areas and over periods of years followed by inductive reasoning from the observed facts—are as applicable to-day to the study of lung cancer as they were then to the study of plague, typhus, and cholera. And the rapid increase which has been recorded in the mortality from lung cancer suggests that it is urgent to determine the measures "best fitted to check, mitigate, or prevent" it.

Incidence

No figures are available for assessing the incidence of lung cancer in Britain, other than the mortality statistics of the Registrars-General. Because of its great fatality, the number of persons dying from it is nearly equal to the number affected, and, from this point of view, mortality statistics provide a reasonable estimate of the incidence. They are, however, subject to the inaccuracy inherent in the certification of causes of death.

The salient feature of the reported mortality is the extent to which it has increased in the last 50 years—and particularly in the last 25 years. In 1900 the crude annual death rate attributed to lung cancer in England and Wales was 8 per million persons; by 1925 it had risen to 20 and by 1950 to 278 per million.† In other words, the recorded rate increased two and a half times in the first 25 years, and 14 times in the next 25 years.

By 1950, 12,241 deaths were attributed to lung cancer in one year—10,254 in men and 1,987 in women. As a site of cancer, in both sexes taken together, the lung was second in importance to the stomach, but it was easily the most important site in men—giving rise to 28% more deaths than were attributed to cancer of the stomach and to more than double the number attributed to cancer of the colon. Of all cancers in men, 24% were classified as having arisen in the lung, but at ages 45–54, when lung cancer was relatively most frequent in proportion to other cancers, the proportion was 40%.

Compared with non-malignant diseases, lung cancer was recorded as a more common cause of death in men than hypertension or respiratory tubercle; but only a third as many deaths were attributed to it as were attributed to coronary artery disease. Of all male deaths in 1950, 4% were attributed to lung cancer; at ages 45–54 the proportion was 10%.

There is no reason to suppose that these figures have yet reached their maxima. On the contrary, the trend in mortality rates suggests that lung cancer will reach an even more prominent position. It is difficult to estimate the actual number of deaths which will occur. Trends do not always continue smoothly. For example, the trend in male mortality at ages 35–44 showed an almost steady increase from 1920 to 1946, when the rate reached the level of 166 deaths per million men. In 1950 the rate might have been expected to be about 190 per million, whereas in fact it remained the same as four years earlier. If future experience proves that the mortality in men aged 35–44 has, in fact, become stable, it is to be expected that the increase will also cease in the older age groups, but only after progressively longer periods of time have elapsed.

The maximum mortality from lung cancer, unlike that from every other major form of cancer in men, is not in the oldest age group. At present it lies in the age group 65–74, and in 1931–47 was a decade earlier (Fig. 1). Over the last 20 years the age distribution has become somewhat closer to that of the other major forms of cancer. If it can be assumed that the death rates under the age of 45 have now become stable, and that the trend in the age distribution continues until the distribution is similar to that of, say, cancer of the stomach, a rough estimate can be made of the number of deaths which will eventually be attributed to lung cancer. On such assumptions—admittedly highly speculative but, I think, not wholly unreasonable—the number of deaths, for a population of the same age and sex composition as at present, will eventually reach 20,000. In fact, the future population will almost certainly contain a higher proportion of old persons, so that the number recorded in 20 years' time may be as great as 25,000.

Increase in Incidence

The evidence that lung cancer has become more frequent derives from necropsy studies as well as from vital statistics and clinical series. Figures from Leeds General Infirmary

*The Milroy Lectures delivered at the Royal College of Physicians of London on February 10 and 12, 1953. (*Abridged.*)

†By 1952, the rate had reached the level of 321 per million.

published by Bonser (1934) and brought up to date by Watkinson (personal communication) show a rise in the proportion of necropsies at which a bronchial carcinoma was found from 1.4% in 1928–32 to 4.0% in 1949, and from 7.5% of all cancers found at necropsy to 16.9%. Figures from St. Mary's, St. Bartholomew's, and the Glasgow Western Infirmary also show increases over the last 15 years (Daff, Doll, and Kennaway, 1951). The only contrary experience recently recorded is that of Bryson and Spencer (1951); earlier reports are purposely not considered, as they would not seem to be relevant to a problem which has presented itself in an acute form only since they were written.

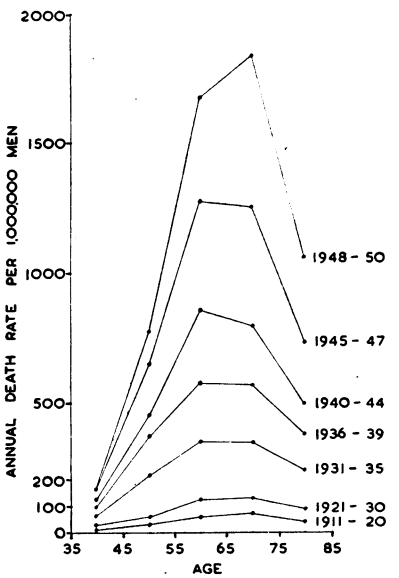

FIG. 1.—Mortality from lung cancer among men at different ages, 1911–50.

Bryson and Spencer's material was collected from the necropsy records of the Central Histological Laboratory of the London County Council over a period when the number of necropsies performed increased rapidly (from 684 to 1,723 a year), although the number of patients admitted to the 26 hospitals concerned fell by a quarter. It seems likely that, in fact, the type of subject coming to necropsy changed considerably, and this is borne out by finding that the proportion of cancers which arose in the large intestine increased from 5% to 13%. If, therefore, Bryson and Spencer's material suggests that bronchial carcinoma did not increase between 1936 and 1947, it also suggests that cancer of the large intestine did—which is contrary to the evidence of mortality statistics and to all clinical impression.

The increase recorded by vital statistics is partly due to the increasing proportion of the population who live to the cancer age. This, however, accounts for only a small part of the increase. If the sex and age distribution of the population in 1950 had been the same as it was in 1931, the general rate for the population would have been 236 per million instead of 278 per million; that is, there would still have been a five-fold increase in 19 years (Fig. 2).

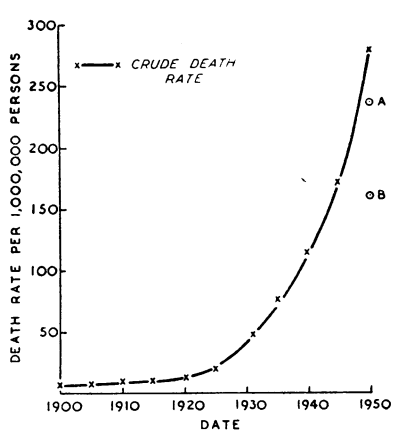

FIG. 2.—Death rate from lung cancer in England and Wales, 1900–50. A=Estimated death rate in 1950 with population of age and sex distribution as in 1931. B=Estimated death rate in 1950 with population of age and sex distribution as in 1901.

It has been held that the great increase in the recorded mortality in Britain may be due to the successive introduction of radiography, bronchoscopy, pneumonectomy, cytological examination of the sputum, and diagnostic thoracotomy. It would indeed be strange if the consequent increased facility in diagnosis had not been reflected in a more general recognition of a clinically obscure disease. It must also be recognized that improvements in therapy of the infectious diseases—particularly of pneumonia—must have reduced the number of deaths occurring from the early complications of lung cancer and so allowed a greater proportion of the cases to proceed to a readily diagnosable stage. In illustration of the close relationship presumed to hold between the lung cancer death rate and the standard of medical diagnosis and certification, Rigdon and Kirchoff (1952) have shown that the correlation coefficient between the death rate and the number of patients per physician in the 48 States of the U.S.A. is −0.66 : that is, the fewer the patients per physician the higher the lung cancer death rate.

In recent years Willis (1948) in Britain and Clemmesen and Busk (1947) in Denmark have, like Steiner (1944) in the U.S.A., expressed the view that the increase is spurious. It seems, however, as pointed out by Heady and Kennaway (1949), that Willis based his opinion on evidence collected before 1933—that is, before the greater part of the increase was recorded, while Clemmesen has revised his opinion (Clemmesen, Nielsen, and Jensen, 1953) and Steiner has been convinced that a real increase has taken place locally —for example, in Los Angeles (Steiner, Butt, and Edmondson, 1950).

Reasons for believing that there has been a real increase are :

(1) The increase in the recorded death rate still continues, despite the long period which has elapsed since attention was drawn to the importance of the disease.

(2) The disease is now so common that had the increase been entirely spurious it would be necessary to postulate that 50 years ago 95% of the fatal cases were wrongly certified.

(3) Necropsy examinations conducted under the supervision of single eminent pathologists, at teaching hospitals where over 90% of the subjects who died came to necropsy—for example, St. Mary's, London, and Leeds General Infirmary — have also shown considerable increases in the proportions of bronchial carcinomas to all cancers and to all necropsies.

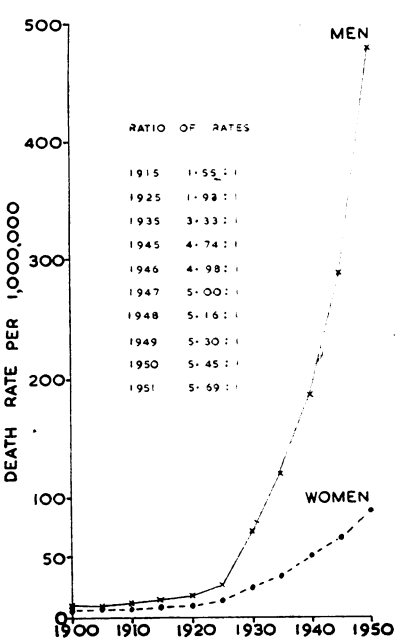

FIG. 3.—Death rates from lung cancer in England and Wales, 1900–50.

(4) The increase has been persistently greater in men. Passey and Holmes (1935) suggested that this might be due to the greater facilities for medical attention available to men under the National Health Insurance Act, but in the few years that have elapsed since the introduction of the National Health Service Act, in July, 1948, the disparity has become even greater (Fig. 3).

(5) The age distribution of lung cancer in men is different from that of all other major types of male cancer, and has been changing in form while its incidence has been increasing. Kortenweg (1951) notes that the trends in England and Wales are in conformity with the hypothesis that a real increase has occurred and that successive generations have been exposed to extraneous carcinogens to different extents. The same phenomenon has been observed in Denmark (Clemmesen, Nielsen, and Jensen, 1953).

(6) The death rates in town and country have, in England and Wales, retained the same relation to one another.

(7) The mortality among doctors, who may be presumed to be as carefully investigated as any section of the community, has been practically the same as that for the whole population (Kennaway and Kennaway, 1947; Dublin, Spiegelman, and Leland, 1947).

It cannot be said that all workers are agreed on the conclusions to be drawn; Rigdon and Kirchoff (1952), for example, continue to believe that the increase is wholly spurious. At the International Symposium on the Endemiology of Lung Cancer held last year at Louvain, however, it was agreed that "a significant part of this increase is absolute and represents a real increase in the number of people suffering from cancer of the lung" (Council for International Organizations of Medical Sciences, 1953), and the conclusion of the Symposium seems to me to be reasonable.

How much of the increase is real after standardizing for age and sex remains uncertain. The extent of the change in the last five years, when the importance of the disease has been recognized and facilities for diagnosis have been readily available, suggests that the real increase is likely to be large. I believe it may well be more than half. On the other hand, I would think it certain that some of the increase is nosological and some is due to the therapeutic advance which prevents death from pneumonia before the presence of the underlying growth is evident.

Possible Explanations of the Increase

The importance of the conclusion reached is that it holds out hope for prevention. An increase of the rapidity and extent of that presumed to have occurred cannot be accounted for on the basis of a changing inherent constitution. Some potent environmental factor must have become prevalent, and therefore, when the factor is identified, it may prove possible to reduce its influence.

Factors which have been considered are (1) atmospheric pollution with (*a*) the waste products of domestic chimney and factory smoke, (*b*) the exhaust fumes of vehicles, and (*c*) the dust from tarred roads; (2) the smoking of tobacco; and (3) the after-effects of certain respiratory infections—for example, influenza of the type associated with the 1918–19 pandemic and tuberculosis.

Animal Experiments

The effect of these and other factors has been studied extensively in animals. Unfortunately, although lung tumours have been described in many species, there is no laboratory animal which spontaneously develops tumours comparable to the ordinary squamous or anaplastic carcinoma of the bronchus of man. For example, the common pulmonary tumour of mice, which has been the subject of most experiments, is a papillary adenocarcinoma and, according to Grady and Stewart (1940), is of alveolar rather than of bronchial origin.

Many substances, when fed to mice, painted on the skin, or injected parenterally, increase the incidence of this tumour—the most effective method generally being intravenous injection. Not all strains of mice respond in the same way; strains with high and low incidences of spontaneously occurring pulmonary tumours have been separated and different strains react in different ways to the application of the same substance. Many—though not all—of the hydrocarbons known to be carcinogenic under other conditions have been shown, on testing by these methods, to produce pulmonary tumours. The most potent is urethane.

Tumours more like the human type have been produced in mice by Andervont (1937), by the insertion of a piece of cotton thread impregnated with 1,2,5,6-dibenzanthracene directly into the lungs; by Smith (1950), by the implantation of lung tissue from embryo mice along with solutions containing methylcholanthrene or dibenzanthracene into the thigh muscles of adult animals; and by Lisco and Finkel (1949), by the administration of radioactive cerium (Ce^{144}) in the form of an aerosol.

Substances derived from sources suspected of being implicated in causing human lung cancer have been tested by exposing mice to atmospheres containing the test substance in the form of dust or smoke, or by skin-painting. McDonald and Woodhouse (1942) found an increased incidence of pulmonary tumours in mice exposed to inhalation of soot collected from the air of an English city, and Leiter, Shimkin, and Shear (1942) produced sarcomas in mice at the site of inoculation with extracts of soot collected from the air of several American towns. Campbell (1934) found a greatly increased incidence of pulmonary tumours in mice exposed to an atmosphere heavily laden with the dust from tarred roads, and many animals also developed carcinoma of the skin, presumably from contact with the dust externally; road dust from which the tar had been extracted also increased the incidence of the tumours, but to a less marked extent (Campbell, 1937). Mice kept in an atmosphere of tobacco smoke by Campbell (1936) in Britain and by Lorenz, Stewart, Daniel, and Nelson (1943) in America showed no significant increase in the number of tumours.

In contrast, Essenberg (1952) has recorded an increased incidence in mice exposed to high concentrations of cigarette smoke. The mice came from a strain with a high spontaneous incidence, and tumours were obtained in 21 out of 23 (91%) in the experimental group against 19 out of 32 (60%) in the control group. It may be significant that the cigarette smoke was drawn directly into the animal box in Essenberg's experiment, whereas in the other experiments it was introduced through tubing. In no case have the conditions reproduced those to which men are exposed in smoking, nor can they do so unless animals are trained to smoke. Tar obtained from tobacco burnt at temperatures normally reached in pipe-smoking has resulted in the production of carcinomas when applied to the skin, both in mice (Flory, 1941; Graham, Wynder, and Croninger, 1952) and in rabbits (Sanders, Thomson, Cooper, and Lamb, 1932). The tumours have not been produced easily, but there is no doubt that tobacco tar can contain a carcinogenic agent. Experiments in which animals have been exposed to the exhaust fumes of cars have proved negative (Campbell, 1936; Twort, 1939).

The application of these results to the study of human lung cancer is problematical. In the first place, the pulmonary tumour of mice is histogenetically different from bronchial carcinoma, and tumours which more closely resemble the human type have been produced only by methods which do not appear likely to have any direct counterpart in naturally occurring carcinogenesis. The rarity of bronchial carcinoma in animals accords with the theory that the tumour in man commonly arises from some specifically human activity. In the second place, it is clear that most of the sources suggested as responsible for the production of bronchial carcinoma—atmospheric soot, dust from tarred roads, and tobacco tar—can be shown, by selected methods of application, to contain substances which are carcinogenic for some animals. Whether they are of importance in the production of the human disease can be determined only by observations on man.

Incidence in Different Parts of the World

It is always difficult to compare vital statistics from different countries, and particularly so when they relate to a disease like lung cancer, which is not easy to diagnose with certainty by clinical methods. Necropsy statistics have the advantage that the diagnoses can be relied on, but the populations from which the subjects are drawn are seldom known with accuracy, and much bias may be introduced into the figures, for this reason, without there being any evidence of its nature.

TABLE I.—*Death Rates from Lung, Respiratory, and Non-respiratory Cancers in Various Countries, 1949*

Death Rate per 1,000,000 Non-respiratory Cancer	Country	Death Rate per 1,000,000 Respiratory Cancer	Death Rate per 1,000,000 Lung Cancer	Lung Cancer as % of all Cancers Found at Necropsy
1,584	England and Wales	288	251	31·0, 21·4, 16·1
1,597	Scotland	256	228	20·4
1,086	Finland	171		
1,123	Uruguay	171*		
1,652	Switzerland	151	122	—
1,262	Holland	144	133	16·0
1,545	France	135		
1,256	U.S.A.	131	112	11·3, 10·4
1,474	W. Germany	131		
1,271	New Zealand	127		
1,041	S. Africa	110		
1,131	Canada	106		
1,462	Denmark	106	97	—
1,152	Australia	103		
1,292	Eire	99		
988	Italy	84		
1,407	Iceland	80†	58	3·1
666	Spain	67		
1,411	Norway	63	54	—
809	Chile	47†		

* 1947. † 1948.

Necropsy series.—England and Wales: St. Bartholomew's, 1945–8, St. Mary's, 1945–8, Leeds General Infirmary, 1945–9. Scotland: Western Infirmary, Glasgow, 1945–8. Holland: Amsterdam and Rotterdam, 1951 (Korteweg, personal communication). U.S.A.: Los Angeles, 1943–6 (Steiner, Butt, and Edmondson, 1950); Texas, 1945–9 (Rigdon and Kirchoff, 1951). Iceland: Reykjavik, 1940–50 (Dungal, 1950, and personal communication).

Not all countries which publish vital statistics separate lung cancer from other cancers of the respiratory system. Of those that do, the highest rates recorded in 1949 were in England and Wales (251 per million) and in Scotland (228 per million), the next highest in Holland, Switzerland, and the U.S.A. (all around 110–120), and the lowest in Iceland (58‡) and in Norway (54). Differences of this size (4½ to 1) cannot be accounted for by demographic differences. If, for example, the English rates had held for populations of the sex and age distributions of the U.S.A. and Norway, the death rates would have been 223 and 239 per million and still much higher than the rates actually recorded in those countries.

The forms of respiratory cancer other than cancer of the lung have, in all probability, different aetiologies; lung cancer, however, accounts for such a high proportion of all respiratory cancer that important differences in the mortality from respiratory cancer are likely to simulate underlying differences in the mortality from lung cancer. Figures for the death rate from respiratory cancer are shown in Table I for all those countries for which the statistics are published.

Table I also shows the death rates from all forms of cancer other than respiratory and, for some countries, the death rates from lung cancer alone and the proportion of bronchial carcinomas among all cancers found at necropsy in recent series—that is, in necropsies performed since 1940.

‡The rate for Iceland is for 1948.

The rates for all forms of cancer other than respiratory give an indication of the reliability of the national statistics. All forms of cancer may be relatively infrequent in some countries, but, in view of the great variety of factors responsible for the production of cancer in different sites, conditions favouring a generally low rate are unlikely to be common. A low rate for all non-respiratory cancers in conjunction with the low rate for respiratory cancer must arouse the suspicion that many cases are not diagnosed; a high rate for all non-respiratory cancers with a low respiratory cancer rate will, on the other hand, suggest (though it does not prove) that the respiratory rate is reasonably reliable. If necropsy studies in the same country also indicate a low proportion of lung carcinoma the impression will be strengthened.

With these considerations in mind, it would be unwise to attach importance to the low respiratory cancer rates reported from Italy, Spain, and Chile. On the other hand, in both Norway and Iceland there is no deficiency of diagnosis of cancer generally, and it seems reasonable to believe that the extremely low rates reported for lung cancer are real. In Iceland, moreover, Dungal (1950) found a very low proportion of lung cancers at necropsy at the University Clinic (where necropsy is routinely performed on all patients who die).

Very low incidences at necropsy have been reported from many parts of the world for which vital statistics are lacking (Table II). Gharpure (1948) found no case of lung cancer among 4,321 necropsies performed in Bombay during 1926–46, and Strachan (1934) found none among 1,901 necropsies on native South Africans. In this context, it is of interest that the death rate from lung cancer among the non-white population of the U.S.A. is of the same order as that among the white population, so that the apparent difference found between Europeans and native Africans is unlikely to be due to heredity. The average age at death in the Indian and South African native cases must have been much less than that in recent European series, and this, alone, will have considerably reduced the proportion found to be cancer of the lung. Nevertheless, an appreciable number of cancers were found in the sites which commonly give rise to cancer among Europeans, and it is unlikely that no case of bronchial carcinoma should have occurred in such large series if the condition was as common in India and South Africa as it is in Britain.

TABLE II.—*Incidence of Lung Cancer at Necropsy in Different Countries*

Author	Place	Period	Lung Cancer as % of All Necropsies			Lung Cancer as % of All Cancer Necropsies		
			M	F	M+F	M	F	M+F
—	England (average for St. Mary's, St. Bartholomew's, and Leeds G.I.)	1945–8	6·2	2·6	5·0	29·6	11·0	22·8
See Daff, Doll, and Kennaway (1951)	Turkey (Istanbul)	1945–9	2·8	0·8	2·1	20·3	7·8	17·0
	Yugoslavia (Ljubljana)	1945–9	1·5	0·6	1·1	11·8	3·1	7·1
Shik (1946)	U.S.S.R. (Moscow)	1936–43	—	—	1·8	—	—	15·6
Gharpure (1948)	India (Bombay)	1926–46	0·0	0·0	0·0	0·0	0·0	0·0
Nath and Grewal (1935)	India (Lahore, Lucknow, and Patna)	1914–34	—	—	0·1	—	—	1·5
Kouwenaar (1950)	Indonesia (Chinese)	—	—	—	0·9	—	—	9·2
	Indonesia (Javanese)	—	—	—	0·1	—	—	2·3
Davies (1948)	E. Africa	1931–47	—	—	—	—	—	1·4
Strachan (1934)	S. Africa (Bantus only)	1924–33	0·0	0·0	0·0	0·0	0·0	0·0

Attractive though it may be to conclude that a high death rate from lung cancer reflects principally a high standard of diagnosis, it is probable that real differences in incidence between different parts of the world do exist—particularly between Britain on the one hand and Norway, Iceland, and a number of Asiatic and African countries on the other—even though all of *some* of the recorded differences (and some of *all* of them) may be nosological.

One characteristic, however, is the same for all countries which have recorded vital statistics of lung or respiratory cancer for any length of time. In each one the death rate has increased substantially—even in Norway (Fig. 4).

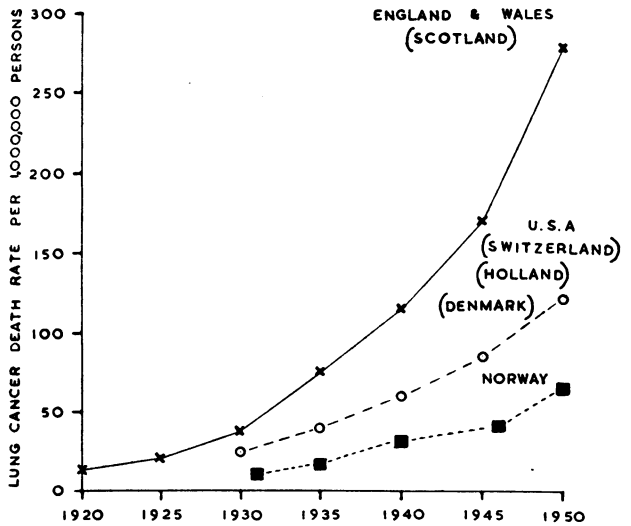

FIG. 4.—Lung cancer. Death rate in different countries, 1920–50. Rates for the countries shown in parentheses were close to the rates for the countries with which they are grouped.

Differences Between Town and Country

Important differences in incidence have also been noted between sections of the population within individual countries. Though mostly less dramatic than the differences between countries, they have hitherto been of greater value in elucidating the aetiology of the disease, since it has been possible to define more precisely the differences in environment to which the separate groups have been exposed. For example, differences in mortality have been noted between countrymen and townsmen and between the inhabitants of towns of different sizes. According to the Registrar-General, the death rate from lung cancer in 1950 was twice as high among the male inhabitants of Greater London as among men living in rural districts, and the difference was more pronounced in the older age group. The rates for other parts of the country fell between the Greater London and rural rates, in exact order of town size (Fig. 5). Female rates show the same trends, though the differences are less marked and the trends somewhat blurred, possibly owing to smaller numbers. Comparison of the relative differences at different periods shows that these differences have remained remarkably stable despite the great increase in the recorded mortalities.

Stocks (1952) has analysed the urban death rates for the period 1946–9 and has demonstrated a progressive increase with the increase in the number of inhabited houses. Within Greater London, he found that the boroughs with the highest mortalities were situated to the north and east of the town's centre. This, he suggests, may be related to the direction of the prevailing wind, which is from the south-west —and might therefore be expected to shift the area of maximum smoke density to just that part of the town in which the highest mortalities occur.

As always, when drawing conclusions from vital statistics, it must be asked whether the differences can be purely nosological; whether the "factor" is nothing more than a greater facility for diagnosis in the larger towns. This seems unlikely. In the first place, it would hardly be expected that diagnostic acumen should be so closely dependent upon the exact size of town; secondly, there is the stability of the urban : rural ratio; and, thirdly, there is direct evidence obtained by Doll and Hill (1952). They found, among 1,465 patients with carcinoma of the lung and the same number of matched control patients with other diseases, that the proportion who had ever lived for any long period in the country was lower among the carcinoma patients, irrespective of their present place of residence. That is to say, among patients residing in Greater London at the time of interview a lower proportion of those with lung carcinoma than of those with other diseases had ever lived for 10 or more years in a rural district—and similarly for each other place of present residence. The differences were small and not statistically significant, but they were all in the same direction, and provide some support for the belief that the risk of developing lung cancer is, in fact, lower in the countryside.

The observation of a town and country difference is not confined to Britain. Clemmesen, Nielsen, and Jensen (1953) have reported an even more pronounced difference between the capital and rural areas of Denmark. In their opinion, however, the difference is not constant, but may be explained by the spread of a new carcinogenic factor to the countryside, 10 years after it had begun spreading in the capital.

In Norway, the difference between urban and rural areas—as definite as in Britain, despite the low total incidence—is also increasing. Mortality statistics, for which I am grateful to Professor Kreyberg, provide the following comparisons:

Ratio of Death Rate in Town and in Country

	1931–5	1946–50
Men	1·8 : 1	2·5 : 1
Women	1·1 : 1	1·5 : 1

It seems, therefore, as if differences are constantly in the same direction, but that there may also be local differences which modify the trends in different countries.

Three substances known to be carcinogenic under suitable conditions have been identified in town air. According to Dawson (1952) radioactive material is present to the extent of $30–100 \times 10^{-12}$ curie per m.^{3} Activity in the open air of towns is not much greater than in rural areas, but within closed rooms the activity may be doubled, and in extreme cases, as in an underground shelter, it was found to be 100 times greater. Even this value is, however, only one-tenth of the tolerance concentration—unless it proves (as it may do) that the limit at present accepted is set too high.

The amount of arsenic varies, according to Goulden, Kennaway, and Urquhart (1952), from 0.04 μg. of As_2O_3 per m.^{3} in Bristol to 0.16 μg. per m.^{3} at Beckton, in London.

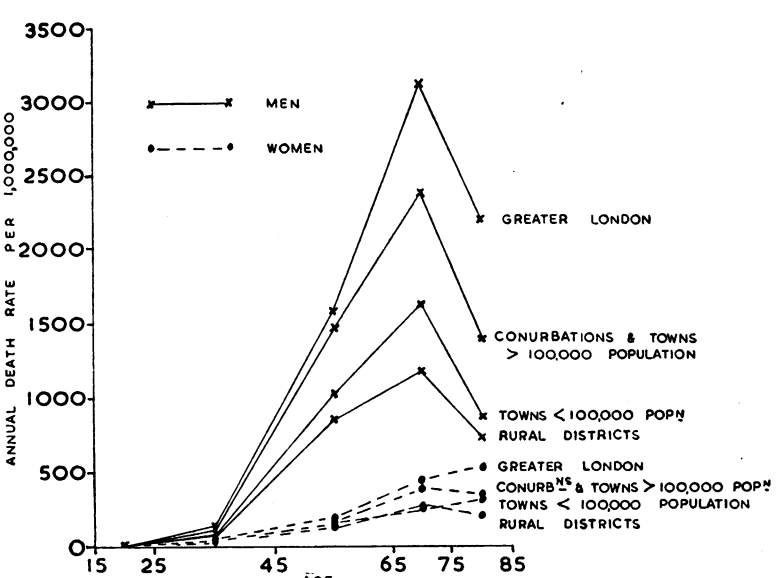

FIG. 5.—Death rate from lung cancer in different areas of England and Wales, 1950.

It is, however, difficult to ascribe any one value to a town, as there are considerable variations between stations within towns—for example, the concentration in the air at County Hall, London, was only a third of that found at Beckton and only slightly greater than that recorded in Bristol. The total amount inspired by a town dweller per year is estimated by Kennaway to be 0.5 mg., which is only one-tenth of the amount in the maximum official dose of Fowler's solution (0.5 ml.).

According to Waller (1952), benzpyrene is present in town air, in amounts varying from 0.013 μg. per m.^{3} in Bristol to 0.046 μg. per m.^{3} of air in the centre of London. Again, however, variations in the concentration make it necessary for many readings to be obtained before a fair estimate can be made of the content of the air of a town as a whole. Winter concentrations are three to four times greater than summer concentrations, and great increases are obtained during fogs. In Waller's opinion the variations in benzpyrene content suggest that most of it is derived from the smoke of domestic fires. Some has, however, been detected in motor exhausts, and, since the sizes of the particles in exhaust smoke are concentrated over a limited range of small sizes, this source could be of greater biological significance than appears from the proportion which it contributes to the total air pollution.

Occupational Risks

The classical method leading to the isolation of chemically pure carcinogens is the observation of specially high cancer risks in specific occupations. With lung cancer, exceptional risks have been recognized in several unrelated industries. These are: mining of various ores in Schneeberg (Germany) and in Jachymov (Czechoslovakia); chromate production; nickel-refining (in Clydach, S. Wales); asbestos manufacture; and the production of gas. To these should probably be added the handling of inorganic arsenic and, possibly, occupations providing excessive exposure to iron dust, with or without added exposure to silica.

The risks involved have been estimated only for chromate workers and gas-workers. Brinton, Frasier, and Koven (1952), extending the initial observations of Machle and Gregorius (1948), have compared the sickness and mortality experience of insured workers in the seven chromate-producing plants in the U.S.A. with the whole sickness data obtained by the U.S. Public Health Service and the death rates for the U.S. population. They found that the mortality from lung cancer among white males employed in the plants was 14 times the expected, and among coloured males it was 80 times the expected. According to Bidstrup (1951) the risk is unlikely to be as great in the British chromate industry.

Doll (1952) studied the causes of death among 2,071 male pensioners of a London gas company and found that the number of deaths from lung cancer was approximately double that expected by comparison with male inhabitants of London of the same age distribution—that is, 25 deaths against 13.8. Confidence that this small excess is real derives from the observation that for all other causes of death studied the numbers observed were not significantly different from those expected; it is also of the same order as that determined by Kennaway and Kennaway (1947), when they drew attention to the possibility of there being a risk in the gas industry.

Of the other occupational risks, that incurred in the Schneeberg and Jachymov mines is likely to have been the highest: as much as 50 to 75% of all deaths among the miners may have been due to lung cancer (Haerting and Hesse, 1879; Lange, 1935; Peller, 1939). The risk in the Clydach nickel refinery—at least till the reorganization of the plant in 1924—must also have been considerable (Chief Inspector of Factories, 1949). In the manufacture of asbestos and arsenical sheep dip the risk is more likely to have been of the same order as that involved in the production of gas. For example, Gloyne (1951) found that of 52 men dying with asbestosis, about 20% gave evidence of the presence of a primary lung cancer, whereas among men with other forms of pneumoconiosis the proportion was 7%. As is shown later, there are reasons for believing that the incidence among men with pneumoconiosis is generally close to the average.

The evidence of the existence of a risk of lung cancer in the handling of inorganic arsenic derives from an investigation by Hill and Faning (1948) into the causes of death among men employed in a factory making sheep-dip. They traced five deaths due to lung cancer among these men, whereas they estimated, by comparison with the causes of death in other workers in the area, that there should have been only one.

The existence of special cancer risks in most of these industries is not surprising, since the workers in them have been exposed in the past (and in some cases still are exposed) to unusual concentrations of known carcinogens. According to Evans (1950) the mean concentration of radon in the air of the Jachymov mines is about 3×10^{-6} curie per m.^{3}, while the tolerance concentration is at the most 10^{-7} curie per m.^{3}—that is, one-thirtieth of that found in the mines. Hueper (1952) has produced sarcomas in mice at the site of injection with suspensions of finely dispersed nickel powder, and nickel must be presumed to be deposited in the respiratory passages on the decomposition of nickel carbonyl, a gas produced in the refining process at Clydach. Gas-workers are exposed to coal tar—one of the most prolific sources of carcinogenic hydrocarbons and including benzpyrene. Finally, arsenic is known to produce cancer of the skin in man when ingested over long periods, and large quantities (up to 1,000 μg. per m.^{3}) were found in the atmosphere of the sheep-dip factory (Perry, Bowler, Buckell, Druett, and Schilling, 1948).

No direct evidence is available on the nature of the carcinogenic factor in the chromate and asbestos industries.

The position with regard to iron-workers is obscure. Turner and Grace (1938) found that foundry-workers, smiths, and metal-grinders had a mortality from lung cancer higher than that of any other occupational group in Sheffield; and Turner and Martin (1949) found that out of 32 cancer deaths among grinders with silicosis the lung was the primary site in 19. Metal-grinders also suffered a high mortality from lung cancer in Kennaway and Kennaway's (1947) material. These observations might be thought to imply that silicosis predisposed to lung cancer, but this has been convincingly shown not to be true (Miners' Phthisis Medical Bureau, 1936; Kennaway and Kennaway, 1947). If there is any excess among special groups of metal workers it must be presumed to be due to some other, and more specific, industrial hazard.

An attempt has been made to discover whether any other common occupation carries a special risk by interrogating patients with and without bronchial carcinoma about their past occupations. The questions were asked as part of a general investigation into the aetiology of bronchial carcinoma which has been described previously (Doll and Hill, 1950, 1952). Altogether 1,357 men with bronchial carcinoma and 1,357 men with other diseases were interviewed. Occupations in which the men had been employed for three or more years were recorded; no account was taken of time spent in the Services unless the patient had served as a regular, and no analysis was made of employments under the age of 20, when changes of occupation were frequent. Many men had worked in two or more occupations for the minimum of three years, so that the number of occupations recorded was greater than the number of men interviewed—2,281 for the men with lung carcinoma and 2,415 for the same number of men with other diseases. Of all the 76 groups into which the occupations were classified, there were only two in which the differences between the numbers of

bronchial carcinoma and of control patients who had been employed in them could be considered, by the usual statistical criteria, to be significant. The occupations recorded of the bronchial carcinoma patients included 80 in coal-mines and 16 in the police forces; of the control patients, there were 113 in coal-mines and 32 in the police forces. In view of its correspondence with the results of the analysis of the national mortality data made by Kennaway and Kennaway (1947), the deficiency of coal-miners among the bronchial carcinoma group may reasonably be taken to confirm that coal-miners are subject to a lower incidence of bronchial carcinoma than other industrial groups. The deficiency in the cancer group of men who had been employed as policemen may, in the absence of other evidence, be attributed to chance, since there is nothing surprising in finding one difference of this extent when so many groups have been studied.

The most important excess in the cancer group occurred in men who had been directly concerned with the production of gas; the cancer group contained 23 such men, the control group 14. Other evidence has shown that gas-workers are exposed to a special risk of lung cancer, and the present figures are corroborative—although, by themselves, not statistically significant.

The closeness of the numbers in the two disease groups who had been employed in many of the other occupations is striking. This is particularly so for occupations which might have been expected to be disproportionately represented in the lung-carcinoma group, if exposure to the dust of tarred roads or to motor exhaust fumes was responsible for many cases of the disease.

	Men with: Lung Carcinoma	Other Diseases
Motor mechanics, garage hands	19	25
Drivers of cars, lorries, or buses	105	101
Bus and tram conductors	10	21
Van drivers (horse)	33	25
Other road transport	17	25
Roadmen, council labourers, dustmen	39	39

The failure to find any difference in the relative proportions of men employed on the roads or in the service of cars is of interest. It accords with the conclusion of Kennaway and Kennaway (1947) that none of the open-air occupations, where there was special exposure to road dust, had a high incidence of cancer of the lung.

The results provide little or no support for the suggestion of Wynder and Graham (1951) that painters and what they describe as "hot" metal workers may suffer special risks.

	Men with: Lung Carcinoma	Other Diseases
Painters and decorators	70	59
Furnacemen, foundrymen, and smiths	26	23
Other metal workers	150	157

The evidence from a study of occupational factors is therefore that the development of bronchial carcinoma may result from prolonged exposure to a number of atmospheric carcinogens; some of these substances, like radon, benzpyrene, and arsenic, are present in town air—though in very much lower concentrations than occur in industry; others, like nickel, are peculiar to specialized industrial processes; others are as yet undetermined. So far as it goes, the evidence is against the hypothesis that motor fumes and road dust are responsible agents.

Although one occupation—the refining of nickel—is also responsible for a high incidence of cancer of the nasal sinuses, it is a remarkable fact that none of the occupations known to be associated with a high incidence of lung cancer appears to carry any increased risk of laryngeal cancer. It is probable, therefore, that the factors which are responsible for the production of carcinoma of the bronchus and for carcinoma of the larynx are independent.

Sex Ratio

According to all reports the incidence of lung cancer is much greater in men than in women. The extent of the difference is, however, uncertain. In this country the mortality statistics of the Registrar-General gave, in 1950, a ratio of 5.2 male deaths to every female death, and the proportion has been increasing steadily, though slowly, from year to year. During the first half of 1949 Mackay's (1951) study of in-patients discharged from a number of selected hospitals (mainly teaching hospitals) gave a ratio of 5.1 to 1 and the national cancer registration scheme (which is believed to cover about half the cases in the country) gave, in 1946, a ratio of 6.9 to 1 (Stocks, 1950). Much higher ratios have been recorded in recent clinical series—varying from 7.3 to 1 to 12.6 to 1 (Fulton, 1949; Mason, 1949; Brooks, Davidson, Thomas, Robson, and Smithers, 1951; Doll and Hill, 1952).

The inconsistency may be partly due to the inclusion of a proportion of inaccurately diagnosed cases in the national

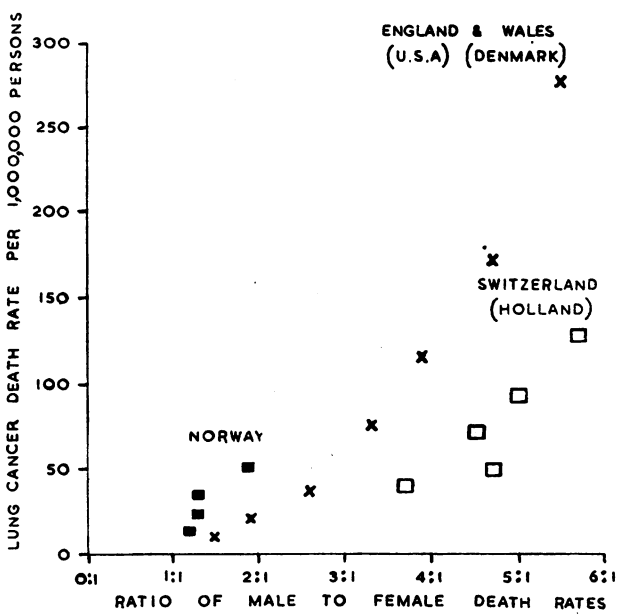

FIG. 6.—Lung cancer. Ratio of male : female death rates at different levels of incidence in different countries. Ratios for the countries shown in parentheses were at each level of incidence similar to the ratios for the countries with which they are grouped.

figures (though this should not apply to the cancer registration scheme), but it may also be due to the process of selection, which to some extent accompanies the collection of any clinical series—for example, through the exclusion of out-patients, the relative exclusion of the very old, or the availability of male and female beds.

Experience of the full and accurate registration scheme which is now operating in Denmark suggests that the true ratio is probably somewhat—though not much—higher than that indicated by death certificates, and it is reasonable to believe that the true ratio in the United Kingdom is, at the present time, of the order of 6 or 7 to 1.

At the beginning of the century the sex ratio, judged by mortality data, was as low as 1.3 to 1. In Norway the ratio is to this day not much greater. Generally it would appear that in all countries the higher the incidence of the disease the greater the male preponderance (see Fig. 6). It is notable that the relation between the sex ratio and the total incidence is not the same in all countries, but that in some a given degree of male preponderance is reached at a lower general level of incidence. It seems probable, therefore, that the factor mainly responsible for the increase is one to which men are particularly exposed and that the extent of the relative difference in exposure of men and women varies from country to country.

(Part II will appear next week with list of references).