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The Problem of Cancer of the Lung in the Industrial Area of Liège during Recent Years

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(With the assistance of the late Professor Batta, and of Mme Castermans, M. Desoignies, M. Van Lancker, Mlle Thomas)

THE information that we acquired from the study of air pollution in Liège is our reason for giving this paper.

At the end of December 1930 a dense, poisonous fog occurred in the Meuse valley. There were about 9,000 people living in an area, half rural, half industrial, who suddenly collapsed on the third or fourth day of this severe fog—80 of whom died a few hours later. The fog had spread all over the east of Belgium. It was not specially dense in Liège, but was very noxious in the industrial valley for a distance of 10 to 15 kilometres directly upstream from Liège. In that area most of the patients, and especially those who died, showed on the third or fourth day slow, gasping breathing, cardiovascular failure, hypotension and alkalosis (Fig. 1). Death occurred after only a few hours.

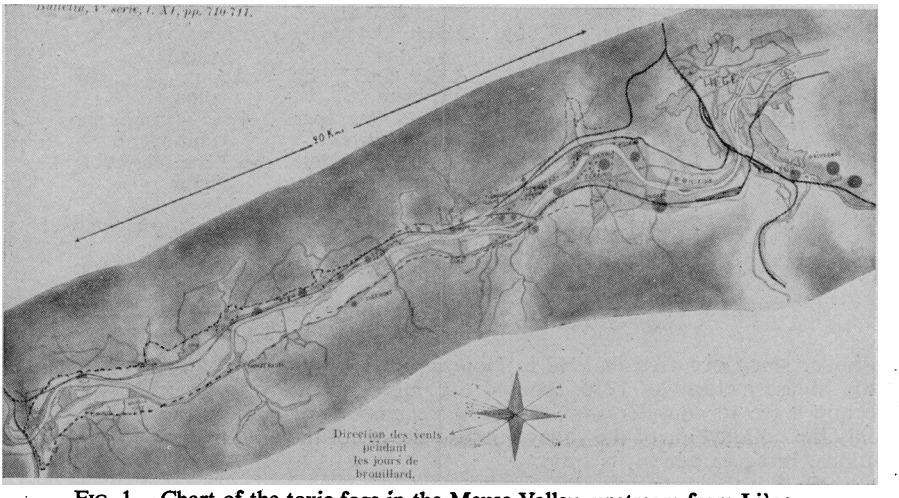

FIG. 1.—Chart of the toxic fogs in the Meuse Valley, upstream from Liège.

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While carrying out our research we found the results of some chemical analyses in the University archives which had been made quite fortuitously during the year 1899. In these the quantity of sulphur on the soil had been measured immediately after snow had fallen and washed the atmosphere while falling. In the same places, thirty years later, our chemists found ten times as much sulphate in equivalent amounts of freshly fallen snow.

During the year 1931 we asked our British colleagues, in particular Dr. J. B. Haldane, how toxic incidents, similar to those we had experienced upstream from Liège, had never been observed in London during dense fogs which lasted longer than ours. Haldane replied that heat emanation from such a large concentration of people living in London, prevented the meteorological ceiling from descending so near to the ground and that therefore the fog polluted by industrial smoke could spread freely and laterally towards the neighbouring hills around the city. In fact, we know that particles of soot, acidified or not by SO_2, dissolved in water from the fog, did not fall quickly to a level where human beings could inhale them. The risk of London fogs reaching a threshold of toxicity was not therefore, at that time, so great and severe respiratory complications were less likely to occur. If we use Stokes' formula, we find that, during cold, foggy weather with no wind, a particle of soot 1 μ in diameter and issuing from a chimney 80 metres high takes six days to reach the ground. Similarly, in the same meteorological conditions, a particle 2 μ in diameter would take about three days, and a particle measuring 4 μ, one and a half days.

The steady increase of air pollution in industrial communities during the last half-century is well demonstrated by the three following dates: Professor Prost's results of 1899, the experts' analyses in Liège in 1931 and the London experience of 1952.

But how may these dense, smothering fogs be related to the increased incidence of pulmonary cancer observed at the present day?

The meteorological conditions which caused the heavy mortality in 1930 are quite unusual in Liège. They were caused by the following series of events: a considerable cooling of thick dusty air, a fog filled with fumes (especially sulphurous ones), an east wind of only 1 km. per hour and a meteorological ceiling hanging at an average of 75 metres above the ground. The ceiling was thus lower than the tops of the hills bordering the valley, which are mostly about 80 metres high. The wind was blowing *upstream* very nearly in the direction of the valley. It carried along with it all the dust from the town and although fog covered the town no symptoms of poisoning were reported among its inhabitants.

Similar conditions over a period of over four days have been seen only five times from 1901 to 1930. Twice they caused comparable accidents; once they did less harm, by occurring in a branch rather than in the main valley of the Meuse; and on two occasions they happened during a period when industrial activity was much below normal.

Table I shows the substances which were measured more especially, namely those which caused acute symptoms on the third and fourth days of fog.

TABLE I.—MEASUREMENTS ON 20 KM. OF THE VALLEY UPSTREAM FROM LIÈGE AND TOWARDS HUY

Nature of products	Toxic content after several hours of exposure	Maximum content reached after 1 day	Maximum content reached after 4 days
CO_2	More than 2% by volume	About 0·4% by volume	About 1½% by volume
CO	More than ½%	About 0·03% by volume	About 1½% by volume
NO_2	12 to 16 cg. per cubic metre of air	1 to 2 mg. per cubic metre	4 to 8 mg. per cubic metre
HF	In the region of 4 mg. per cubic metre of air	0·08 mg. per cubic metre	0·3 mg. per cubic metre
SO_2	20 to 30 mg. per cubic metre of air	25 mg. per cubic metre	100 mg. per cubic metre
H_2SO_4	4 mg. per cubic metre of air	38 mg. per cubic metre	152 mg. per cubic metre
		(On supposition of the complete oxidation of SO_2.)	

A similar smog occurred in 1948 in Donora, an industrial valley in Pennsylvania, and, like the Meuse incident of 1930, aroused the interest of the whole world.

We now have to consider whether the same amount of gaseous substances, including not only the polluted air of the valley but also the air of the city, might not, in some other conditions, bring cancer in its train.

We know that the meteorological conditions which provoked such toxic effects upstream from the Meuse were quite unusual as far as the direction of the wind is concerned. Indeed, the prevailing wind is from west-south-west. It is generally not very strong, with an average speed of 5 to 10 km. per hour. In a general way, Liège and its outskirts which include 500,000 inhabitants live in a foggy or a smoky atmosphere, extending over a wider stretch of ground. Hills border the city on the north side and are about as high as those limiting the valley upstream. Those special conditions should be taken into account when we examine the particular geographical factors of the region, even if they do influence conditions for only a very short time.

When we try to explain the increase in frequency of primary cancer of the lung which has been observed these last forty years in Liège, as well as in Western Europe and in America, we cannot find a single determining factor in any given region. Undoubtedly, primary lung cancer has always existed. When I was in my twenties, it was uncommon, just as primary cancer of the liver still is in Europe, though frequent in the tropics. And when it first became obvious, say between 1920 and 1930, we believed the increase in frequency to be only apparent and resulting from better methods of radiological, cytological or clinical detection. It gradually became clear, however, that the increase was real.

For the last fifty-four months we have diagnosed, in the whole Province of Liège, 820 cases of primary pulmonary cancer, of whom 788 were men and 32 women. All these cases were confirmed either by biopsy or through exfoliative cytology or by both. Among the 900,500 citizens in the province a number of pulmonary cancers must have escaped our microscopic investigation. If this disease were spreading throughout Belgium among the population at the same rate, it might be said the total number of patients suffering from pulmonary cancer in the whole country was about 6,000. These figures almost agree with the Dutch cancerologist Korteweg's opinion, when he says that primary lung cancer is

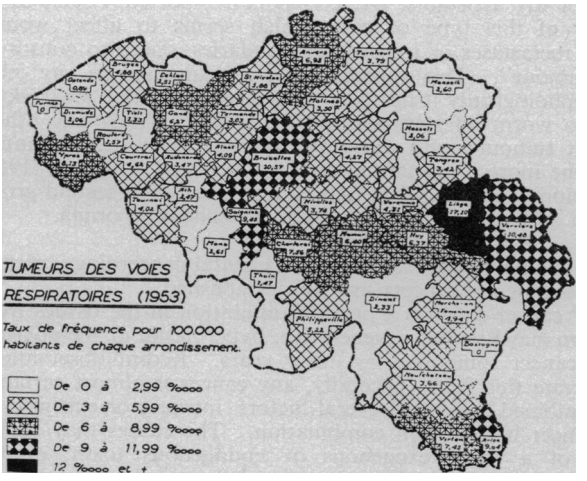

FIG. 2.—Map of Belgium giving the primary lung cancer in the different districts.
Reproduced from Tuyns (1954) by kind permission.

fast approaching 40% of the total mortality due to cancer in Western Europe. Those figures should draw the attention of the Belgian medical authorities to the fact that unless 250 or 300 new cases of pulmonary cancer per year are discovered out of every one million of Belgians (a number below the populations of each of the provinces of Antwerp, Brabant, and Flanders and Hainaut) our methods of examination have not been sufficiently thorough (Fig. 2).

In our province of Liège we appear to have the highest incidence in the whole of Belgium. But, until we can be sure of the efficiency of our detection system throughout the country we do not feel justified in concluding that the incidence varies in the different regions. No doubt our province has been somewhat favoured because all pathological and microscopic examinations are centralized in our Department of Pathology. This department is run as a public service and during the last five years has undertaken more exfoliative cytology than any other centre in Belgium.

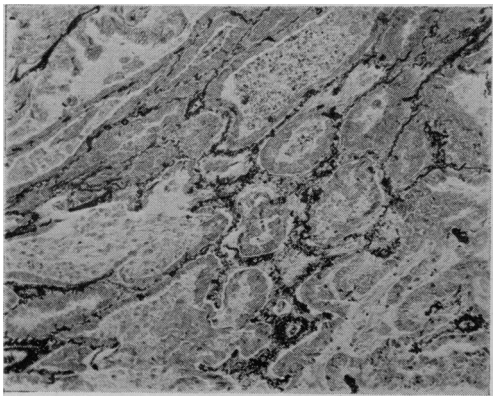

FIG. 3.—Adenomatosis with mucus in the epithelial cells and elastic fibres of the stroma stained.

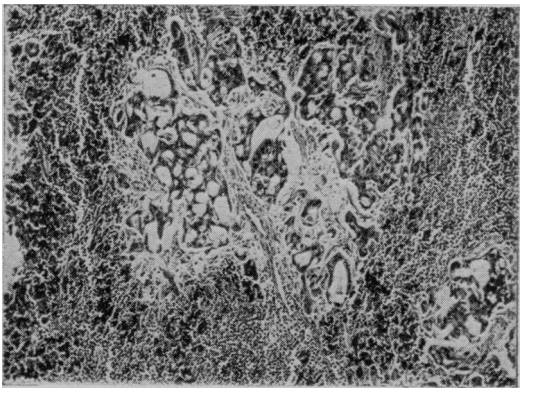

FIG. 4.—Metastasis of the same cancer in a hilar gland.

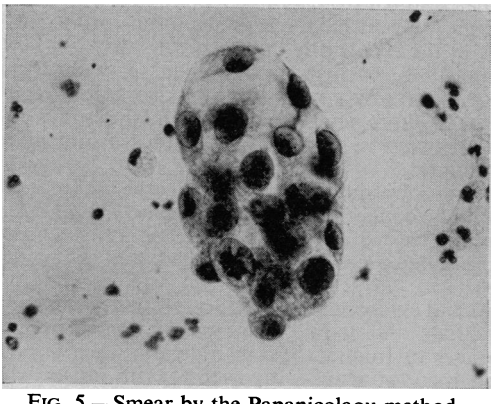

FIG. 5.—Smear by the Papanicolaou method of an adenomatosis.

Why primary cancer of the lung has been increasing is one of the most important problems of pathology which our generation has to face. Some types of lung cancer seem to be particularly responsible for the general increase. Next in frequency were two other types of adenocarcinoma: pulmonary adenomatosis and cancer arising from bronchial glands (Figs. 3, 4, 5).

In 1942, Neubuerger and Geever identified 25 cases definitely similar to these last, and 15 doubtful ones. In 1954 one of my assistants, Dr. Desoignies, reported 4 such cases. The comparatively small number of this type of case, which seems to affect women as well as men and often leads to metastases or to several secondaries, seems to constitute a particular type, "the alveolar tumour". This appears to be as malignant as any other type of pulmonary tumour. Morphologically it has been compared with the "jaakziekte" of sheep which is certainly due to worm infestation (Dungal, 1946). With many others we tend not to classify these last tumours with those we referred to at the beginning. But the question has become all the more important since Campbell and Kreyberg (1956) appear not to agree with this opinion. The fact that tumours of Kreyberg's second group occur in an equal number of men and women seems to point to endocrine origin.

Both by clinical observation of human cancers and by experimental cancerology, certain aspects of the pathogenesis of spontaneous cancers are well established.

Firstly, it seems clear that every cancer requires a previous alteration in the tissues from which it originates. This alteration may be either regenerative, hyperplastic or metaplastic, and precedes the appearance of cancer sometimes by many years. Recent observations of cancers "in situ" help to illustrate this fact. Secondly, any cancer is almost certainly the result of the cumulative or combined action of several factors, intrinsic or extrinsic, of which each particular form of cancer has its own combination. The causes may be the presence of a virus, deficiency of a food, exogenous or endogenous toxin, or the lack or excess of a genetic or endocrine factor. I am convinced that in the present case, carcinogenic hydrocarbons play a part and 3:4 benzpyrene a predominant one. Stocks and Campbell (1955) show figures from England and Wales which indicate that certain quantities of benzpyrene, expected to have been inhaled with air or cigarette smoke play a most important part. This was the basis for further work devoted to pulmonary incidence of various degrees of air pollution, in other countries where conditions are quite different. Thirdly, any spreading cancerization is the result of carcinogenic factors that must exert their action for a very long time. Pulmonary cancers observed in the miners of Schneeberg, which certainly may be ascribed to radioactive dust from nickel, arsenical cobalt, silver, &c., did not appear until at least eighteen years had been spent at work in the dusty galleries. Often they only appeared several years after the men had ceased from this noxious work.

But apart from these general ideas, we are much less well informed as to the part in carcinogenesis played by chronic infectious processes in the bronchi, chronic bronchopneumonia, bronchiectasis, the effects of poison gas, or by psittacosis. We cannot believe that the pandemic influenza towards the end of the First World War bears a particularly heavy responsibility, in spite of the bronchial metaplasia it caused. Moreover, in 1923, Staehelin (1919) in Basel pointed out that his post-mortem department had recorded an increase in the frequency of primary pulmonary cancers which had started in 1912—some five years before the 1917 epidemic of influenza. A similar observation had been made by Mönckeberg in Strasbourg before 1914.

The direct experimental approach to the problem in man seems very promising when we consider that several chemicals may lead to primary tumours in lower animals following their inhalation and especially in view of Blacklock's (1957) evidence that the intrapulmonary inoculation of hydrocarbons such as 3:4 benzpyrene or methylcholanthrene can induce both sarcoma and carcinoma of the lung in rats. Yet, it is certain that though several tumours have been produced, none has resulted from a direct action of a carcinogenic hydrocarbon on the respiratory epithelium. They have certainly been produced in sarcomas in the body of the tissue but not in the recovering epithelium. That is why the experimental techniques used by Andervont (1939) by means of threads set with crystals of dibenzanthracene were able to transform recovering epithelium into one type of cell or another. Thus one is struck by the numerous factors which lead to a similar result. Over 200 organic substances, or even plain metals, proved to be carcinogenic towards one animal species or another, by means of such a technique.

On the other hand, virus, food deficiencies, hormonal alterations, and radio-activity can have a similar effect. And we must only conclude that carcinogenic agents are so many and so diverse that it is virtually impossible for any tissue to escape all exposure to irritating factors which, as the years go by, become more and more varied, and are made in ever larger quantities.

On studying the literature on occupational and environmental factors, we find that uranium and its substitutes, chromates, nickel, beryllium, and some carcinogenic hydrocarbons are chiefly incriminated. These are all substances of frequent use in industry. We also find a good deal of pulmonary cancer among men working with asbestos in mines where pneumoconiosis occurs. Yet we must acknowledge that the causal relation is seldom fully established.

Hammond and Machle (1956) have accepted, as we all do, a connexion between cigarette smoking and lung cancer, yet we must admit that the first approach to this problem was only conjectural. Hammond and Horn (1958) made an enquiry in 1954 bearing on 187,783 men, of whom 4,854 died within approximately twenty months from the time they were questioned. According to the death certificates, 844 were due to cancer, of which 167 were attributed to primary cancer of the lung. Then, Doll and Hill (1950) made a preliminary report on a similar study of 24,389 British physicians, aged 35 and over, and followed for twenty-nine months (Table II, from Mayer and Maier, 1956).

TABLE II.—SUMMARY OF FINDINGS REPORTED BY 14 RETROSPECTIVE CLINICAL STUDIES ON THE ASSOCIATION OF SMOKING AND LUNG CANCER

		No. of cases		% who were non-smokers among those		% who were heavy smokers among those		Relative risk of lung cancer	
Country	Date	with lung cancer	without lung cancer	with lung cancer	without lung cancer	with lung cancer	without lung cancer	All smokers	Heavy smokers
Ger.	1939	86	86	3·5	16·3	50	10·5	5·4	22·2
Ger.	1943	93	270	3·2	15·9	31·2	9·3	5·7	16·7
Neth.	1948	136	100	5	19	55	19	4·5	11
U.S.	1950	82	522	14·6	23·9	18·3	9·2	1·8	3·3
U.S.	1950	444	430	7·2	30·4	—	—	5·6	—
U.S.	1950	605	780	1·3	14·6	51·2	19·1	13	30·1
Eng.	1952	93	186	5·4	6·5	38·5	23·8	1·2	1·9
Eng.	1952	1357	1357	0·5	4·5	25	13·4	9·4	16·8
U.S.	1953	63	133	4·1	20·6	67·6	29·3	6·1	11·6
U.S.	1953	477	615	3·8	13·2	46·8	30·7	3·8	5·3
Fin.	1953	728	300	0·6	18	65·8	20	36·4	79
U.S.	1954	518	518	3·7	10·8	75·6	44·2	3·2	5
U.S.	1954	490	2365	8	26·9	52·7	22·7	4·2	7·8
U.S.	1954	265	287	1·9	9·7	73	57	5·5	6·5

We see that an association between cigarette smoking and cancer has been difficult to bring out clearly, even though no one to-day would deny its existence and importance. We are of the opinion that cigarette smoking is one of the causal factors in the development of lung cancer, but that its relationship may not be a simple one.

GENERAL ATMOSPHERIC POLLUTION

Only a small proportion of our population is employed in factories or industrial firms where there is a considerable risk of contracting lung cancer. But the whole population inhales the air which is polluted in various degree by many organic substances. Most of the pollution is from soot, smoke from coal and fuel oil and fumes from motor cars or tarred roads. In general, whenever an organic material is heated, carcinogenic elements are liable to be introduced into the atmosphere, either by distillation, or following cracking or burning. In combustion, hydrocarbons yield a great variety of substances which tend to concentrate on cooling and Campbell and Kreyberg (1956) have used the benzpyrene content as an indicator of hydrocarbon pollution.

The same point could, of course, be made about radio-active substances. These were comparatively rare some fifteen years ago, before the present vast production of radio-isotopes for military and scientific purposes got into its stride. Factories dealing with thousands of tons of uranium must, surely, be sources of activity, whatever the proportion of air-scatter from them may be. Nevertheless, systematic analyses show that the cancer rate of the general population is comparatively little increased from this particular source.

We thought it might be interesting to show a record of five years in the life-history of 500 pulmonary cancer cases living in a city in which the distribution of airborne dust is fairly well known. In Fig. 6 we have plotted the place of residence of known cancer patients on the map of the Liège area, and the valley joining it from the south-east. Generally it would appear (Fig. 6) that the houses of cancer patients are largely concentrated in the centre of the city, stopped by the hill bordering the city in the north, extend eastward, north-east, and some south-east. But if we look in detail at that distribution of dwellings, we see some interesting facts. Many workers are busy in the huge metallurgic establishments just upstream of the City (Cockerill and Ongare). These workers live in dwellings which were built for them about ten to fifteen years ago. Because of the prevailing wind, the area which they all occupy is one of the least polluted by chemical dust. Yet the number of pulmonary cancers is fairly large. In contrast, in the centre of the area which is surrounded by a horseshoe of the Meuse, immediately north-east of the first

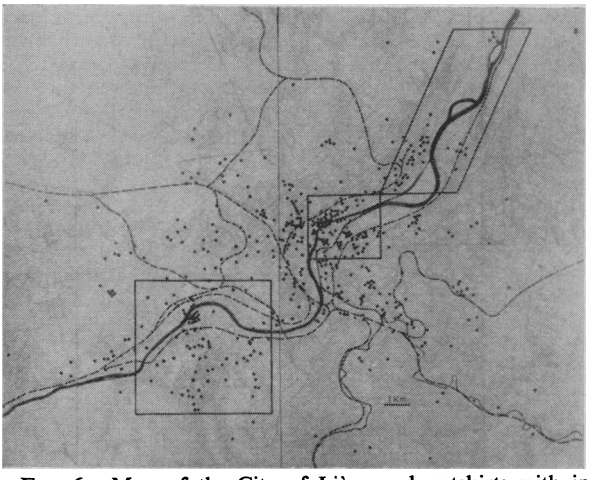

FIG. 6.—Map of the City of Liège and outskirts with in black points all the residence of the patients affected with lung cancer during the last five years (1952–1957).

area, there are few cancer patients, even though this is a sort of tableland on which dust is rather abundant. But there is no industry on the plateau and it has been a pleasant residential area for about forty-five years with many trees and occupied by the well-to-do middle class. The high dust pollution of this area was, of course, not known at the time it was built.

We have been struck by the large number of persons with cancer living in the centre of the city and especially in streets beside railways or canals carrying coal-burning boats. Our attention is drawn to these by their names, "Rue de la Gare, Rue de la Station, Rue du Chemin de fer, Rue du Vincinal". Railway engines are an obvious source of air pollution and steamboats also clearly pollute the air around docks. These sources have been emphasized recently in Canada. During 1955 the incidence of lung cancer was found to be five times higher among engine drivers than among the whole population in the same neighbourhood. Engine drivers of course inhale carcinogenic hydrocarbons either from the sooty exhaust of diesel engines or the smoke of coal-burning locomotives.

In Belgium, too, we can see a striking correspondence between smoke and lung cancer. In the vicinity of factories in Herstal, including the famous Belgian Fabrique Nationale, one can find many men out of work because of cancer. But as the valley runs north the incidence suddenly drops and, at the same time, the smoke disappears and the sky assumes the lovely milky hue it shows in Holland and which has been rendered famous by the Dutch painters of the eighteenth century. Towards the east the smoke continues and with it the cancer.

From our five years of research we must conclude that lung cancer has a complex ætiology. Of several causes cigarette smoking is a very important, but not always an essential, one. Indeed, it seems to us that polluted air, and particularly the hydrocarbons contained in soot, remains the most important cause.

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