

## PROFILES IN TOXICOLOGY

### A Short History of Lung Cancer

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“Lung cancer continues to be the leading cause of death in both men and women in the US, with over 158,900 deaths in 1999. Worldwide, lung cancer kills over 1 million people a year. Extensive prospective epidemiologic data clearly establish cigarette smoking as the major cause of lung cancer. It is estimated that about 90% of male lung cancer deaths and 75–80% of lung cancer deaths in the US are caused by smoking each year” (Hecht, 1999). Clearly, lung cancer is an important and widespread disease that constitutes a major public health problem. This was not always so. Some 150 years ago, it was an extremely rare disease. In 1878, malignant lung tumors represented only 1% of all cancers seen at autopsy in the Institute of Pathology of the University of Dresden in Germany. By 1918, the percentage had risen to almost 10% and by 1927 to more than 14%. In the 1930 edition of the authoritative *Springer Handbook of Special Pathology* it was duly noted that malignant lung tumors had begun to increase at the turn of the century and perhaps even more so after World War I and that, possibly, they still were on the increase. It was also noted that while most lung tumors occurred in men, there seemed to be a steady increase in women. Duration of the disease, from being recognized until death, was usually from half a year to 2 years and in practically all cases there had been a long history of chronic bronchitis.

What caused such a dramatic increase in an obscure disease? The handbook discusses at some length possible etiologic factors: increased air pollution by gases and dusts, caused by industry; the asphaltting of roads; the increase in automobile traffic; exposure to gas in World War I; the influenza pandemic of 1918; and working with benzene or gasoline. However, lung cancer rose at the same rate in countries with fewer automobiles, less industry, fewer paved roads, and in workers not exposed to benzene or gasoline—and had not risen in the 19th century after earlier flu pandemics. In 1 or 2 sentences, smoking was briefly mentioned as another possibility, but it was pointed out that as many investigations failed to show an association between smoking and lung cancer as there were positive findings. In summary, there was some suspicion, but by no means certainty that lung cancer would be caused by

extraneous agents and no particular importance was given to the smoking of cigarettes. It is interesting to note, however, that in 1929 (presumably too late to be included in the handbook) the German physician, Fritz Lickint published a paper in which he showed that lung cancer patients were particularly likely to be smokers. He then went on a crusade against smoking, and antitobacco activism actually became widespread in Germany.

In a new edition of the handbook in 1969, the views on what causes lung cancer—which still was on the rise—had radically changed. The role of cigarette smoking was discussed in detail over a full 25 pages. Air pollution was mentioned as another possibility; the existence of a city-rural gradient in lung cancer incidence was strongly suggestive. It was now also recognized that chemicals encountered in certain occupations could cause lung cancer: arsenic containing compounds in wine growers, asbestos, and nickel and chromium in mine and smelter workers.

The link between the smoking of cigarettes and lung cancer began to be suspected by clinicians in the 1930s when they noted the increase of this “unusual” disease. Publications began to appear and about 2 decades later the role of smoking as causative agent had been firmly established. A case control study was published in 1940 in Germany and its author flatly stated that “the extraordinary rise in tobacco use was the single most important cause of the rising incidence of lung cancer” (Müller, 1940). At this time, lung cancer had become the second most frequent cause of cancer death, stomach cancer being the first. In 1943, the German Institute for Tobacco Hazards Research disclosed a study which found that among 109 lung cancer cases only 3 were nonsmokers, a proportion much lower than in the control group. In the 1950s Doll and Hill in England and Cuyler Hammond and Ernest Wynder in the U.S. provided further evidence for a causal association between smoking and lung cancer. Yet, it took a long time until the truth was fully accepted. Smokers, including many physicians, who enjoyed cigarettes could or would not want to imagine or refused to believe that the habit (addiction would be more appropriate) was detrimental to their health. In this context it is interesting to note that 2 personalities who helped like few others to make us aware that chemicals in the environment

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could cause cancer, strangely failed to grasp the impact of smoking. Wilhelm C. Hueper started out as a physician in industry. By repeatedly and doggedly pointing out possible links between exposure to chemicals in manufacturing processes and the increased incidence of cancer in workers he became unpopular with management, to the extent that on some occasions he was barred from presenting or discussing his findings and conclusions. And yet he maintained that smoking was not a factor in the etiology of lung cancer in humans. Rachel Carson, who in her *Silent Spring* warned of impending disaster of cancer caused by environmental chemicals never mentions tobacco smoke. Since then, tobacco smoke has become not only the most important carcinogen in our environment, but probably also the only one where we could accomplish—and in many places actually already have accomplished—zero exposure.

The smoking of cigarettes had become popular shortly before the turn of the century. Originally, cigarettes were hand rolled and this made them expensive. In 1876, the cigarette manufacturer Allen & Ginter offered a prize for the development of a machine that would speed up the process. When James Albert Bonsack developed a machine that could make 70,000 cigarettes in a 10 h day, Allen & Ginter did not want to use it—partially out of fear that the machine would produce more cigarettes than the market demand justified. James Buchanan Duke had no such qualms; he acquired 2 of the machines and went on to commercial success. In 1889, “Buck” Duke became president of the new American Tobacco Company.

World War I helped to popularize the smoking of cigarettes. Soldiers in the trenches smoked to relieve stress, and so did many civilians, including an increasing number of women at home. General John J. (“Black Jack”) Pershing reportedly stated: “You ask me what it is we need to win this war. I answer tobacco as much as bullets.” In the following decades, smoking continued to be “enjoyed” by hundreds of thousands until, after the first report of the Surgeon General in 1964, public awareness woke up and smoking became recognized as the hazard it is. The trend in lung cancer incidence slowly decreased and, at least in men, appeared to flatten out.

There was, however, one lung cancer where it had been obvious for a long time that it might be caused by an external agent. As early as 1500, attention was called to this particular condition. In two regions of Germany and Czechoslovakia, Schneeberg and Joachimsthal, there were productive mines, yielding first silver, later nickel, cobalt, bismuth, and arsenic. The word “dollar” actually stems from the word “Thaler;” coins minted from the pure silver of Joachimsthal were called “Joachimsthaler” (i.e., originating from Joachimsthal) or, abbreviated, “Thaler.” The miners working these mines developed almost invariably a deadly disease, called “Bergkrankheit” (mountain sickness). Between 1876 and 1938, 60 to 80% of all miners died from the disease which, on average, lasted 25 years. Certain regions of the mines were known as “death pits,” where all workers got sick. As a result, lung

cancer in miners was recognized as an occupational disease—and the miners therefore entitled for compensation—in 1926 in Germany and in 1932 in Czechoslovakia. While it was thought that chemical constituents of the ore that was produced, most notably arsenic, might be involved in the etiology of these lung cancers, it was early on suspected that “radium emanation” was the main culprit. Measurements published in 1924 in a German physics journal confirmed that the air in the mines contained high concentrations of radon gas, the highest more than 18,000 picocuries per liter.

The manufacture of the atomic bomb and the maintenance of a nuclear arsenal called for large amounts of uranium. In the U.S., uranium was mostly mined on the Colorado plateau. The European experience should have alerted the mining companies to the potential hazards their workers were going to face. However, responsibility for protection was not given to the Atomic Energy Commission, but rather left to the individual states who lacked expertise and equipment to deal with the problem. Although it should have been obvious by then that poorly ventilated uranium mines caused lung cancer, evidence pointing in this direction was suppressed; apathy, bureaucratic conservatism, and government censorship prevented the problem from being tackled. It was said by the mining industry that “ventilating the mines was unnessecary and too expensive.” It is estimated that 4000 to 5000 Americans have died or will die from lung cancer caused by working in inadequately ventilated uranium mines. And although the problem has now been recognized for the health disaster it was, compensations are slow to come.

During the last few decades, there has been a shift in forms of lung cancer. In the early studies, the predominant lung cancer form in smokers was squamous cell carcinoma, mostly originating from the epithelium lining the airways. First noticed in 1961, but confirmed mostly during the last two decades there occurred a shift to more peripherally located adenocarcinomas. This is most likely a consequence of changes made in cigarettes. Tar was considered to be the main carcinogenic agent in cigarette smoke, mostly because cigarette smoke condensates (“tar fraction”) were the first ingredients isolated from tobacco smoke that could be shown in skin painting studies to produce cancer in animals. It was hoped that production of low tar, low nicotine cigarettes and the addition of filters might decrease cancer risk. It did not, most likely because of changes in smoking pattern. To fulfill the craving for nicotine, smokers of filter cigarettes may inhale smoke more deeply into the lung and retain it longer. With the removal of polycyclic aromatic hydrocarbons in the filter, the preponderant carcinogens in smoke might be tobacco specific nitrosamines and volatile carcinogens in the gas phase. Animal experiments lend plausibility to this; polycyclic aromatic hydrocarbons do cause squamous cell carcinomas in the lungs of animals, whereas nitrosamines are more likely to produce adenocarcinomas.

All evidence linking lung cancer and smoking comes from human experience. Similarly, radon was recognized as a hu-

man carcinogen long before some animal data suggested that it was a carcinogen. It is likely that neither agent responsible for lung cancer, the smoking of cigarettes or radon, would have been recognized as a cancer causing agent had it not been for the fact that a previously very rare disease increased in parallel with increased consumption of a widely distributed and highly addictive agent or was associated with a specific occupation. It is an interesting thought that experimental toxicology has little contributed to our understanding of the disease. There are very few—some might say none at all—studies in which it has been unequivocally demonstrated that tobacco smoke can cause lung cancer in experimental animals.

#### SUGGESTED READING

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