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OCCUPATIONAL CANCERS OF THE RESPIRATORY TRACT

Lung cancer today accounts for greater than 125,000 deaths yearly; less than 50 years ago it was considered a rare disease. Taken together with other cancers of the respiratory tract, such as nasal sinus cancers, laryngeal cancers, and mesotheliomas, more than 5% of all deaths in the United States are attributed to these diseases. Of some note is that in 1985 lung cancer replaced breast cancer as the leading cause of cancer deaths in females. While cigarette smoking clearly plays a large role in the etiology of lung cancer, among particular occupational groups there are exposures of importance in the development of lung cancer, and the interaction with cigarette smoking is a biological phenomenon of some note.

Occupational lung diseases have long occupied the interest of individuals concerned with workers' health. In 1556, Agricola's treatise on mining, *De Re Metallica*, was published and reviewed the health hazards to the lung in miners and smelters of ores.[3] He particularly wrote of a condition called "miner's phthisis," a wasting disease affecting the lungs which was thought by many to be due to exposure to dust or other agents. Paracelsus wrote similarly in 1567.[70] The true etiology of this disease in many individuals was solved by Harting and Hesse, who in 1879 wrote of the deaths of the miners of Schneeberg.[34] It was at the mines of Schneeberg, which had been opened in the early 15th century, that miners had been developing this wasting disease for many years. In 1879 it was determined that many of these miners were dying of lung cancer. The full explanation became clearer some years later, when the pitchblend taken from these mines yielded a new agent, radium, as described by Marie Curie. With the understanding of radioactivity, the true etiologic reason for the lung cancers in the miners of Schneeberg became known.

At the beginning of the 20th century, lung cancer was still remarkably uncommon. With the advent of the automatic cigarette-making machine and the generosity of the American Red Cross in sending cigarettes to soldiers in Europe, the widespread habit of cigarette smoking began in the second decade of the century. At the present time approximately 87,000 males die each year of lung cancer, as well as 39,000 females.[5] The rate of increase has been greater in females over the past three decades then among men, and most of the increase in total cancer mortality in the United States is accounted for by the increase in lung cancer. On a worldwide basis, the incidence of lung cancer varies greatly but in many countries it is the leading cause of cancer deaths.

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Fowler's solution. Multiple cancers of one or many organs have been noted among many individuals who develop arsenical cancers,[82] and there has been a report that lung cancers related to arsenic exposure are more commonly found in the upper lobes.[46]

ASBESTOS

The occupational carcinogen that has been most widely publicized has been asbestos. Asbestos is a term that is used to designate several varieties of fibrous hydrated silicate minerals. These minerals share common properties, in that the fibers can be easily woven or fabricated, are chemically resistant, and are useful as insulators against heat, cold, and electricity. Asbestos minerals can be divided into two classes, the amphiboles and the serpentine form of asbestos. Among the amphiboles are amosite, crocidolite, anthophyllite, and tremolite, while the single member of the serpentine class is chrysotile. More than 90% of all asbestos used in the United States has been chrysotile, and the potential health problems related to asbestos were known early in this century. In the second decade of the 20th Century, a major life insurance company refused to write policies on some asbestos-exposed workers.

Lung cancer associated with asbestos exposure was first reported by Lynch and Smith, who in their paper of 1935 suggested that exposure to asbestos may have a role in the development of lung cancer.[57] In his treatise, *Occupational Tumors and Allied Diseases*, Hueper wrote in 1942 that he considered asbestos an occupational lung carcinogen.[37] Doll in 1955 published the first major epidemiological study demonstrating the relationship between occupational exposure to asbestos and the development of lung cancer.[21] In a series of 105 consecutive autopsies from an asbestos textile works, approximately 17% of the workers had died of lung cancer, whereas only 4% were expected to die. Reports in occupational settings going back more than 50 years have not been as well appreciated as they might have been, leading to the current widespread concern in both occupational and non-occupational settings with regard to asbestos-related cancers.

In addition to asbestosis affecting the parenchyma and pleura of the lung, there is a wide range of cancers that are now known to be related to asbestos exposure. These includes lung cancer, mesothelioma, laryngeal cancer, and a variety of gastrointestinal tract cancers, including cancer of the esophagus, stomach, colon, and rectum.[93] Among heavily exposed asbestos insulators, approximately 20% of all deaths are from lung cancer, compared to about 5% in the general population, and between 5–10% of such workers can be expected to die of mesothelioma. Overall, approximately 45–50% of asbestos insulators can be expected to die of some form of cancer, a rate about twice that of the general population.

Cell-type distribution in relation to cases of lung cancer had been well studied by Churg and Kannerstein[16, 41] some years ago and more recently by Suzuki.[96] All such studies have noted that the cell-type distribution is similar to that for all

BERYLLIUM

Although there continues to be scientific debate as to the carcinogenicity of beryllium, the available evidence suggests that beryllium should be considered a substance capable of producing lung cancer.[17, 32, 61, 87] In addition to producing acute and chronic beryllium disease, lung cancer excess appears to be a risk for the more than 30,000 workers who are exposed at the workplace. Complicating the study of beryllium-related cancers is the fact that with the development of acute beryllium disease many workers will die and therefore not enter the cohort of beryllium-exposed individuals who have a risk for developing lung cancer many years later.

CHLOROMETHYL ETHERS

Following the work of Van Duuren, who published on the carcinogenicity of the chloromethyl ethers in animals,[97] reports of workers exposed to these substances who developed lung cancer found their way into the literature.[26, 84] Two of the ethers are of particular importance, chloromethyl methyl ether (CMME) and bis(chloromethyl)ether (BCME). Both are highly volatile colorless liquids, and CMME is produced by the reaction of methanol, formaldehyde, and anhydrous hydrogen chloride, while BCME is produced by saturating a solution of paraformaldehyde in cold sulfuric acid with hydrogen chloride. Small amounts of BCME will contaminate CMME.[49] BCME is a more potent carcinogen than CMME, and as little as 0.1 ppm of BCME has been shown to produce large numbers of bronchogenic carcinoma in mice. In one series of cases the mean age at diagnosis was 45, with a range from 35 to 55 years of age. Also in this group, the majority of lung cancers were of the oat cell type.[36] As a general rule, when an unusual distribution of cell-type pattern is seen among a group of individuals, it should give rise to some thought about a specific occupational origin for such malignancies.

CHROMIUM

Hunter cited the first reported case of malignancy associated with chromium exposure, that of Newman, who in 1890 reported on the development of an adenocarcinoma in the nose of a middle-aged man with a history of 20 years exposure to chromates.[39] In this century, Pfeil made note of two cases of lung cancer occurring in the same German chromium manufacturing facility, one in 1911 and one in 1912, but he did not report them in the scientific literature until 1935.[73] Additional work by others in the United States,[58, 62] Europe,[28] and Japan[1] have confirmed the risk of lung cancer associated with chromate exposure. Chromates and chromium, which are derived primarily from chromite ore, are used in the production of various pigments, alloys, and in refractories. Over 100 job categories

bladder cancer, and leukemia, there appears to be an elevated risk for developing lung cancer in certain job classifications, especially in the curing area of rubber plants.[27, 66] Printers also have been shown to have an excess risk for developing bronchogenic carcinomas, and they are exposed to carbon black and a variety of solvents.[10, 30] In addition to an excess of scrotum cancers seen in workers exposed to cutting oils, a recent study has demonstrated the risk of excess secondary primary tumors among such workers, notably with lung cancers.[102] The Japanese have reported on a possible excess risk of lung cancer among workers in a benzoyl chloride plant.[85] Hueper has reported on the excess risk of lung cancer in the small isopropyl alcohol industry.[38] It appears as if there may be as much as a 20-fold increased risk of developing lung cancer following exposure to isopropyl oil, which is made into the alcohol.

Among miners it has been demonstrated that hematite, that is, iron ore, miners have an increased risk of lung cancer. Heuper has reviewed this in some detail.[38] Other studies from Europe have also noted an excess of lung cancer in iron ore miners, and in addition investigators claim that these lesions most often occur in the upper lobe in peripheral areas and may be related to areas of pneumoconiosis. With regard to other mining activities, there is the continuing question of the relationship of coal mining to the development of lung cancer. At present most evidence points to cigarette smoking among coal miners as the major determinant of the development of lung cancer, and recent American[6] and British[79] studies have not found any relationship between coal mining and the development of lung cancer.

MUSTARD GAS

Bis(beta-chloroethyl)sulfide, also known as mustard gas, was one of the poison gasses widely used in World War I. In addition to the acute toxic effects of this material, exposure lead to many cases of chronic respiratory disease. Case and Lea had suggested that there was an association between mustard gas exposure and the development of lung cancer among British soldiers gassed during World War I that were subsequently followed by them.[14] Yamada reported in 1959 about the excess risk of lung cancer among Japanese industrial workers who had manufacturered mustard gas during World War II, although it was never used during the conflict.[105] He had reviewed the medical records of the small group of workers who had produced mustard gas on one of the smaller Japanese islands and found that the lung cancer rate among exposed manufacturing workers was 16%, compared with less than 1% expected in an appropriate control group. Subsequently, Wada published further on the mortality experience of this group and noted that the latent period was generally greater than 20 years and that in about one half of all cases the cell type was that of squamous cell carcinoma.[98] Laboratory models for the study of mustard gas and related compounds exist, and there continues to be a small ongoing study of former British soldiers who had been exposed. Of

mining in the United States.[101] Also, there has been a similar experience at a fluorospar mine in Newfoundland, where the mine was contaminated with radon daughters.[19]

Oat cell carcinomas of the lung predominate in cases of radiation-induced lung cancers.[7] Similar to the experience with asbestos, cigarette smoking is synergistic in the production of lung cancer,[9] but it has also been well documented that non-smoking miners, namely Navajo indians who have worked on the Colorado plateau, have an elevated risk of lung cancer even in the absence of smoking.[8, 86] Saccamanno and his colleagues have done much work on this group of individuals, and much of what is now known about cytologic investigations for lung cancer has come from the work of these investigators.[83] Such cytologic testing has been applied to other groups with known occupational lung cancer hazards, such as among asbestos workers[31] and nickel processing workers.[65]

MISCELLANEOUS COMPOUNDS

In addition to the agents noted above, a variety of other agents are suspected of being occupational lung carcinogens in man. Among these is vinyl chloride, which has been definitively shown to cause the development of angiosarcomas in both animals[59] and man.[18] Surveys among vinyl chloride-exposed workers have shown that a large number have abnormal x-rays,[51] and recent scientific information from Maltoni's laboratory in Italy has demonstrated an increase in cellular abnormalities and dysplasias in the respiratory tract.[60] Although not yet clearly proven, it has been suggested that humans have a higher risk of developing lung cancer following exposure to vinyl chloride, in addition to the risk for developing angiosarcomas.[103]

In addition to asbestos, other fibrous materials have a documented carcinogenic potential. Noted earlier, fibrous zeolites have been implicated in the development of mesothelioma, and animal studies have demonstrated that various preparations of fibrous glass can produce mesotheliomas in animals.[94] A study among fibrous glass workers done at a relatively early stage in this industry, without sufficient time for malignancies to be well documented, has shown an increased risk for deaths from chronic respiratory diseases, but the question of excess lung cancers remains unsettled.[12] This issue is important, however, since asbestos is increasingly being eliminated from society and substitutes are being used. One must be cautious that the substitute does not replace a known carcinogenic risk for one that is not yet well appreciated.

Synthetic rubber is made from the monomer chloroprene. A study among Russian workers has identified this material as a lung carcinogen,[44] and there has been some work among American workers exposed to this substance.[53]

Although it is well recognized that an important class of pulmonary diseases can be caused by vegetable dusts such as bagasse, cotton, flax, tea, and various fungi, these hypersensitivity diseases of the lung are not directly related to cancer. However, there have been reports of lung cancers among brewery workers,[67] grain

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