

The Production of Malignant Tumors of the Lung and Pleura in Dogs from Intratracheal Asbestos Instillation and Cigarette Smoking

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Nine dogs were given yearly intratracheal instillations of crocidolite asbestos for periods up to three years. The maximum dose totalled 66 mg/kg. In addition, seven of these dogs smoked nine cigarettes per day, five days per week for six years. A malignant pleural and/or peritoneal mesothelioma developed in six of these dogs, and adenocarcinoma of the lung developed in four, one of which had areas of squamous differentiation. The first animal died of a malignant tumor six years after the onset of exposure, and the last animal died eight years after the onset.

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TWO TYPES OF NEOPLASIA in humans have been definitely associated with inhalation of asbestos fibers: carcinoma of the lung and pleural mesothelioma. Two other types, gastrointestinal carcinoma and peritoneal mesothelioma, may have such an association. The relationship between carcinoma of the lung and asbestos inhalation was first noted in the United States by Lynch and Smith in 1935,¹ but the magnitude of this risk was compiled by Selikoff² in a study of 632 insulation workers with more than 20 years elapsed since the onset of asbestos exposure. These men had a death rate from cancer of the lung or pleura 6.8 times that of the United States white male population of similar age. In a later report,¹² he found the risk of death from carcinoma of the lung in asbestos workers who smoked cigarettes to be 92 times that of men who neither smoked nor had been exposed to asbestos dust, but he found no cases of cancer of the lung among the 87 asbestos workers who had never smoked cigarettes regularly. In the majority of instances, lung cancer in persons exposed to asbestos is peripheral in location and is an adenocarcinoma, although squamous cell carcinoma of the larger bronchi can also occur.

The increased risk of developing carcinoma of the lung in humans who are cigarette smokers is now

well known, but considerable difficulty has been encountered in producing carcinoma of the lung from cigarette smoke in large animals. Auerbach *et al.*³ and Hammond *et al.*⁴ claim to have found invasive bronchioalveolar tumors in 8 of 12 dogs killed after 2.4 years of smoking. These dogs gradually increased their rate of smoking unfiltered cigarettes to nine per day and continued at this rate for 1.8 years. None of these tumors had metastasized at the time the dogs were killed.

Several forms of asbestos have been administered to a variety of small animals, but at the time this study was initiated, there was no report in the medical literature on the combined effect of asbestos installation and cigarette smoke in large animals. It seemed to the authors that such a combination might be used to develop a model for the production of cancer of the lung in dogs.

Method

Preparation of Asbestos

A supply of high grade industrial crocidolite (blue asbestos) was obtained from the North American Asbestos Company. The asbestos was washed three times with distilled water. Each time it was passed through a 16 mesh screen and collected on Whatman #52 paper. Aliquots of 2.5 g of the washed asbestos with 500 ml of distilled water were homogenized in a blender for 30 minutes and then examined by using phase-contrast microscopy and an ocular micrometer. The fiber length varied from 2 to 90 μ m in length and 0.2 to 2.0 μ m in diameter. The asbestos

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