

# Nasal Cancer in a Worker Exposed to Formaldehyde

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• **Formaldehyde has not been established as a human carcinogen. Toxicological studies have, however, demonstrated that formaldehyde causes squamous cell carcinoma of the nasal cavity in rats. A case of squamous cell carcinoma of the nasal cavity occurred in a 57-year-old man who had 25 years of occupational exposure to low concentrations of formaldehyde in the textile-finishing industry.**  
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SQUAMOUS cell carcinoma of the nasal cavity developed in a 57-year-old man who worked in the textile industry. As a textiles engineer, he had experienced 25 years of occupational exposure to low concentrations of formaldehyde.

Formaldehyde, known to physicians throughout the world as a tissue preservative and disinfectant, is a basic feedstock of the modern chemical industry. More than 6 million pounds of aqueous formaldehyde are produced annually in the United States. It is estimated that in the United States, at least 1.6 million workers are exposed to formaldehyde, of whom 57,000 are exposed for four or more hours per day.

Cancer of the nasal cavity and sinuses (International Classification of Diseases 160, eighth revision) is relatively rare. The annual incidence for males is approximately eight per 1 million in the United States (Con-

necticut); few cases occur in males before age 50 years, and rates increase with age. Approximately half of nasal malignant neoplasms are squamous cell carcinoma. Other histologic types include adenocarcinoma, adenoid cystic carcinoma, and melanoma.

Various occupational exposures have been associated with cancer of the nasal cavity and paranasal sinus. These include nickel, chromium, isopropyl alcohol, mustard gas, cutting oils, and wood dust. Nasal cancer has also been associated with employment in several industries, including furniture making, shoemaking, and coal mining, and with several occupations, including furnacemen in the gas, coke, and chemical industry, furnacemen and laborers in foundries, and textile workers.

Evidence that formaldehyde is carcinogenic stems from three experiments in which rats were exposed by inhalation to high concentrations of formaldehyde vapor. The first study, conducted at New York University,<sup>1</sup> was designed to test the effect of ambient bis(chloromethyl) ether (BCME) that might be produced in environments in which both formaldehyde and hydrochloric acid were present. Rats were exposed to a mix-

ture of 14.6 ppm of formaldehyde and 10.6 ppm of hydrochloric acid. Bis(chloromethyl) ether is a combination product of formaldehyde and hydrochloric acid that causes lung cancer and tumors of the olfactory nasal epithelium in rats and oat cell carcinoma of the lung in humans. Twenty-five of the 100 rats had nasal squamous cell carcinoma; this tumor was not observed in the 100 control animals in this study or had it ever been observed in 2,000 control animals previously tested in the laboratory. None of the exposed animals had either lung cancer or cancer of the olfactory nasal epithelium develop, which was expected if the effect were caused by BCME.

In a second study conducted at New York University,<sup>2</sup> nasal squamous cell carcinoma developed in ten of 100 rats exposed to 14.2 ppm of formaldehyde alone, in 12 of 100 rats exposed to a combination of 14.3 ppm of formaldehyde and 10.0 ppm of hydrochloric acid, and in none of 100 animals exposed to 10.2 ppm of hydrochloric acid alone or in 100 control animals. This study intimates that the squamous cell carcinoma seen in both studies at New York University resulted from the exposure to formaldehyde and not from exposure to BCME.

In a study conducted at Chemical Industries Institute of Toxicology, Research Triangle Park, NC,<sup>3,4</sup> 240 rats were exposed to 15 ppm of formaldehyde vapor. At 18 months, 36 had squamous cell carcinoma of the nasal cavity; at 24 months, 103 of 240 rats had experienced this tumor. Two

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of 240 rats exposed at 6 ppm experienced nasal squamous cell carcinomas. No squamous cell carcinomas developed in 240 rats exposed at 2 ppm or in any of the 240 unexposed control animals.

Results of exposure studies in mice are less definitive. One study in which the nasal epithelium was not examined reported squamous and atypical metaplasia of the trachea and bronchus.<sup>5</sup> In another study, although two mice experienced squamous nasal cancer after an exposure at 14.3 ppm, these results were not statistically significant.<sup>3,4</sup>

Despite this strong evidence that formaldehyde is an animal carcinogen, no clinical or epidemiologic data link formaldehyde exposure with excess respiratory tract cancer in man. Three epidemiologic studies<sup>6-8</sup> have been conducted to assess the effect of formaldehyde on human cancer incidence. No case of nasal cancer and no increased incidence of respiratory tract cancer were observed in these studies. Each of the three epidemiologic studies, however, was limited in its ability to detect an excess of nasal or respiratory cancer because of limited sample size, limited duration of exposure, and insufficient verification of the levels of exposure.

The first epidemiologic study was a proportional mortality analysis of embalmers,<sup>6</sup> which did not detect any cases of nasal cancer or show a significant excess in overall cancer proportion (proportionate mortality ratio [PMR], 108) or respiratory cancer (PMR, 102). The proportions of skin cancer (PMR, 253), kidney cancer (PMR, 256), and brain cancer (PMR, 245) were substantially elevated. The chance of this study to detect a threefold excess of nasal cancer was only 12%. Although embalmers may be exposed to formaldehyde in excess of 1.4 ppm, their total exposure will depend on the frequency of embalming. In addition, this study was based on the mortality of embalmers who were recently relicensed and may have failed to include some embalmers with diseases likely to cause retirement but cause death only later in retirement.

The second epidemiologic study was a retrospective cohort mortality analysis of chemical production workers<sup>7</sup> who had exposure to numerous agents, including formaldehyde. This

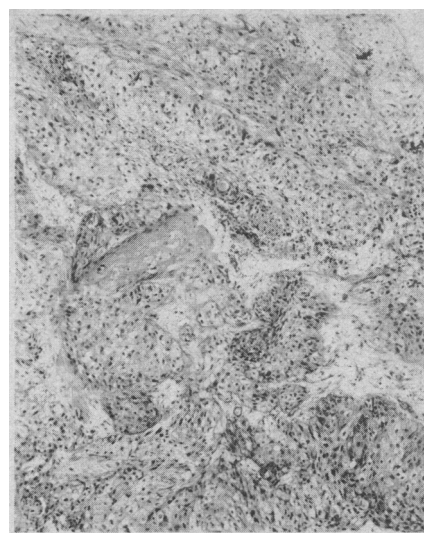
study had only a 7% chance of detecting a threefold excess of nasal cancer because of the small size of the deceased population (146 persons). Furthermore, the duration of follow-up of the cohort was brief; only 19 deaths of cancer would have been expected to occur in the group of workers followed up for more than 20 years since first employment. Since occupational cancers do not commonly develop before 20 years after the first exposure, even if the exposure started with first employment, this short follow-up period further weakens the findings from this study.

The third epidemiologic study was a proportional mortality analysis of workers exposed to formaldehyde in the production of resins.<sup>8</sup> This disclosed no deaths caused by cancer of the nasal cavity. Because of the small numbers of deaths, the ability of this study to detect a threefold excess of nasal cancer was 8%. In addition, the mean length of exposure to formaldehyde was only 4.5 years. Only four deaths of cancer were expected in workers with five or more years of exposure and 20 or more years of latency. For a study to provide convincing results, this latency and exposure category would have to be substantially larger.

### Report of a Case

**Occupational History.**—After graduation from high school in 1943, the patient worked for six years as a taxi driver. He changed jobs in 1949 and built aircraft engines until 1954. In that capacity, he heat-treated metal parts in an oven, soldered engine parts for about two years, and quenched hot engine parts in an exhaust-ventilated oil bath for about three months. This job did not involve the welding or grinding of metal parts that might produce metal dusts.

In 1954, the patient became a maintenance man in the fabric-finishing industry. In the finishing of fabric, a textile is permeated with a formaldehyde-based resin to provide crease resistance. In the process, formaldehyde resin of either the urea or melamine type is mixed with catalysts, wetting agents, and other ingredients in a 50- to 300-gal agitated open tank. The mix or liquor is then piped to a trough that contains 25 to 75 gal. Fabric from a roll passes on rollers through the trough, through a set of squeeze rollers to remove excess liquid, through a drying oven, and is then rerolled. A recent investigation at a fabric-finishing plant in the



Photomicrograph of nasal cavity with squamous cell carcinoma (hematoxylin-eosin,  $\times 100$ ).

United States detected formaldehyde vapor in air at concentrations of 0.2 to 1.2 ppm; exposures may have been higher in previous years, when more highly concentrated solutions were used. Textile finishing also involves exposures to caustic solutions, eg, sodium hypochlorite, as well as dyes, dye carriers, and antifoaming agents.

The patient became a plant supervisor in 1960 and a manager in 1967; his exposure to formaldehyde continued during his employment in numerous textile plants. Although fabric was dyed in some of the plants where he worked, he had no direct involvement with dyeing until 1965, when he became a manager of a finishing and dyeing operation. He worked in the industry until his retirement in 1979.

**Clinical History.**—The patient experienced infrequent right-sided midfacial and right-sided nasal discomfort in 1972 at age 47 years. In 1975, he began, occasionally, to experience right-sided epistaxis. In late 1978, the frequency of his facial pain increased, and nasal obstruction developed. Examination showed bilateral nasal polyps in the middle meatus and a nasal tumor on the right side that extended posteriorly along the floor and lateral wall of the nasal cavity to the nasopharynx. Resection was undertaken in January 1979 by means of a right lateral rhinotomy. The operation included a right medial maxillectomy, right ethmoidectomy, and bilateral sphenoidotomy. After surgery, the patient received 6,000 rad to the right ethmoids, nasal cavity, and sphenoids in 30 sessions during two months. There is no clinical evidence of recurrence after three years. The patient, who had smoked the equivalent of 36 pack-years of cigarettes, had never complained of wheezing or shortness of breath. Other medical history included salmonellosis in 1973, a hemor-

rhoidectomy in 1975, and a cholecystectomy in 1978.

Histological slides prepared from biopsy and excision procedures showed keratinizing squamous cell carcinoma, with invasion of the underlying stroma (Figure).

#### Comment

The occurrence of this case of nasal carcinoma in an engineer with many years of occupational exposure to formaldehyde does not at all establish that formaldehyde causes cancer of the nasal cavity in man. Nevertheless, the similarity both in anatomic site as well as in the histological features between this neoplasm and those described in rats exposed experimentally to formaldehyde is noteworthy. A possible association with the exposure to formaldehyde should be sought in additional cases of nasal carcinoma.

The patient described herein was exposed to low concentrations of formaldehyde for 25 years while employed in the textile-finishing industry. His symptoms first appeared 21 years after his initial exposure to formaldehyde, a latency period similar to that seen in many studies of occupational carcinogenesis. He experienced other exposures that may have played a role in the development of his tumor. In particular, his exposures to quenching oils and to metal fumes while employed in the aircraft engine facility may be important, since, as previously noted, foundry work, nickel, chromium, and cutting oils have been associated with nasal cancer. Also, the patient smoked and had some contact with fabric dyeing.

Studies of smokers and dye workers have shown associations of these exposures with certain tumor types, but there is no proved relationship between these exposures and nasal cancer. Hoover, however, has noted a correlation between the mortality for nasopharyngeal and bladder cancer in US counties; bladder cancer is associated with dye manufacture.

Formaldehyde is a biologically plausible carcinogen, since it is a reactive alkylating agent. It would be expected to react at the surface of the respiratory tract. Other alkylating agents are known or suspect carcinogens.

The prospect that formaldehyde could be a human carcinogen causes deep concern in the public health and industrial communities. Obviously, no conclusions on the carcinogenicity of formaldehyde can be drawn from this one case. However, in the absence of definitive epidemiologic studies and in the presence of convincing toxicological data, a case of nasal cavity cancer in a worker exposed to formaldehyde should be considered a sentinel health event. Presently, each case of nasal cancer in a worker exposed to formaldehyde should be investigated and reported. In the absence of convincing epidemiologic studies, whether positive or negative, a series of case reports would bolster concern for the risk of formaldehyde exposure, whereas a dearth of reports would be reassuring. Case reports may also guide epidemiologists to appropriate industries or occupations for further study.

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