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Bladder Tumors in Two Young Males Occupationally Exposed to MBOCA

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MBOCA (4,4′ methylenebis (2-chloroaniline) is a structural analogue of benzidine and is carcinogenic in mice, rats, and dogs. MBOCA has not yet been demonstrated to be carcinogenic in humans and is not regulated as an occupational carcinogen in the United States. We report two noninvasive papillary tumors of the bladder identified in a screening study of 540 workers exposed to MBOCA during its production at a Michigan chemical plant from 1968 to 1979. Both tumors occurred in men under 30 years old who had never smoked. Although the prevalence of grade 1–2 tumors among asymptomatic males in this age group is unknown, the incidence of clinically apparent tumors on U.S. males aged 25–29 is only 1 per 100,000 per year. The detection of the two tumors in young, nonsmoking males is consistent with the hypothesis that MBOCA induces bladder neoplasms in humans.

Key words: 4,4′ methylenebis (2-chloroaniline), bladder cancer, occupation

INTRODUCTION

MBOCA (4,4′ methylenebis (2-chloroaniline)) is a structural analogue of benzidine, an aromatic amine known to cause bladder cancer in humans [Case and Hosker, 1954]. In addition to their chemical similarity (Fig. 1), MBOCA and benzidine have similar potency to induce bladder tumors in beagle dogs, the species considered to be the best animal model for humans [Stula et al., 1977]. MBOCA also is carcinogenic in mice and rats [NIOSH, 1978]. Despite its recognized carcinogenicity in animals, and its structural resemblance to benzidine, MBOCA has been unregulated as an occupational carcinogen in the United States except for a brief period, 1973–1974, when an OSHA standard was promulgated and then remanded for procedural reasons [Ward et al., 1987]. An estimated 9,000–18,000 U.S. workers are employed in plants that use MBOCA to cure isocyanate-containing polyurethane

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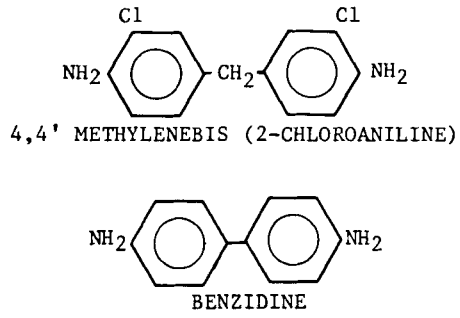

Fig. 1. Chemical structure of MBOCA and benzidine.

products [EPA, 1983]. MBOCA has not been produced in the United States since 1979, but it is imported, largely from Japan.

Investigators at the National Institute for Occupational Safety and Health (NIOSH) are studying bladder cancer incidence among 540 workers who produced MBOCA at a Michigan chemical plant from 1968 to 1979.

MBOCA production at this plant ranged from 184,137 kg to 580,684 kg per year [Harger, 1979, in Committee on Amines, 1981]. Although there are no measurements of MBOCA concentrations within the plant during its production, extensive contamination of the surrounding community has been documented [Committee on Amines, 1981]. Urine samples obtained from plant workers several months after production ceased had detectable MBOCA levels that ranged as high as 50,000 ppb [Vander Kolk, 1979]. A search of the toxicologic literature for other chemicals listed in the company catalogue did not reveal any known bladder carcinogens. However, we do not have complete information on products which were manufactured under contract for other companies.

The first phase of the study involved microscopic cytologic examination of two morning urine samples obtained from workers who had been employed at the plant during the years when MBOCA was produced. Three hundred seventy of the 540 eligible workers submitted urine samples for examination (the remainder either could not be contacted or declined to participate). Although no suspicious or positive cytologic changes were found, one 28-year-old worker with microscopic hematuria was found to have a bladder tumor (case 1).

We subsequently offered cystoscopy to 77 workers observed to have at least five red blood cells per low power field or a cytologic diagnosis of atypia in the initial examination, and to 83 workers whose job histories suggested that their exposure to MBOCA was among the highest of the 452 workers for whom detailed job histories were available. Sixty-seven of these workers agreed to have the examination. Case 2 was identified by biopsy in a young male. We report the two cases of bladder tumors here.

CASE 1

A 28-year-old man was asymptomatic until June, 1986, when he was found to have seven red blood cells per low power field in a urinary screening examination and normal cytology. Intermittent, low-level hematuria was present in several urine

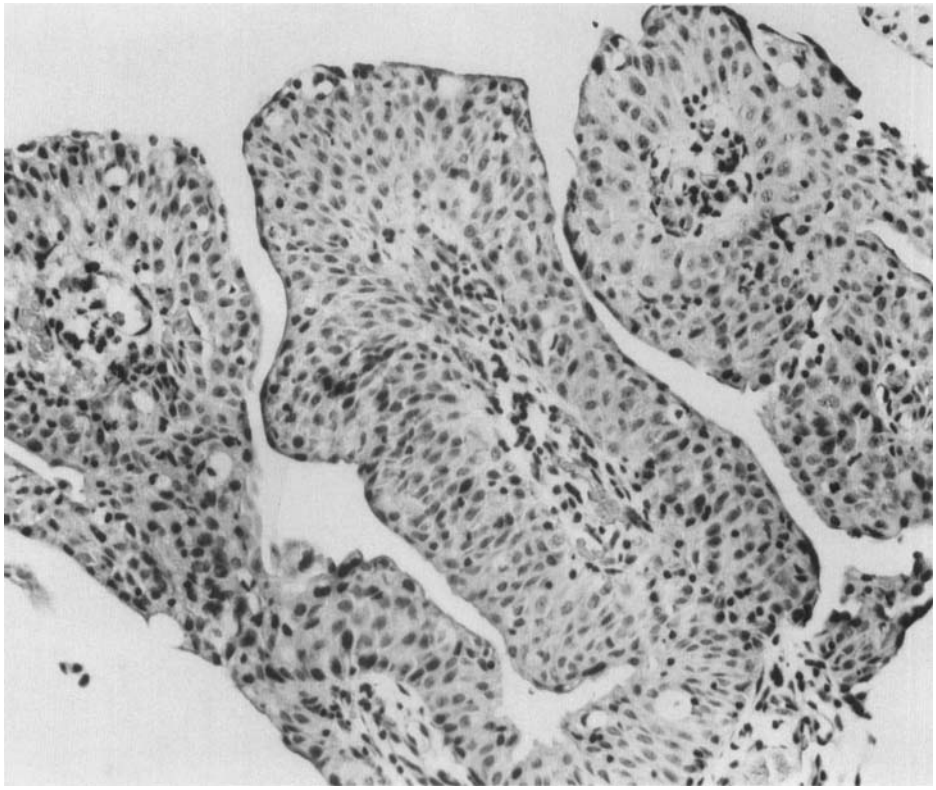

Fig. 2. Case 1. Small papillary tumors, grade 1–2, of the urinary bladder. Note scattered nuclear abnormalities. X200.

samples collected subsequently by his personal physician, and the patient was referred for urologic evaluation. Cystoscopy in July, 1986, revealed a small, papillary tumor in the left lateral wall.

Intravenous pyelogram showed a normal upper urinary tract. The tumor was excised by transurethral resection. The pathologic diagnosis, which was confirmed by one of us (L.K.), was noninvasive, papillary, transitional cell tumor, grade 1–2 of the bladder (Fig. 2).

The patient, who had never smoked, worked at the MBOCA production plant for 1 year in 1978, 8 years prior to diagnosis. He worked as a pipe fitter and maintenance man. He estimates that he worked directly on the MBOCA process for about 4–6 hours per week. He wore gloves when necessary to protect his hands from acids and burns. Aside from his employment at the MBOCA production facility, he has not been employed in occupations with exposure to potential bladder carcinogens.

CASE 2

A 29-year-old man was asymptomatic when he participated in the NIOSH screening program in April, 1987. His screening results were negative, with one red

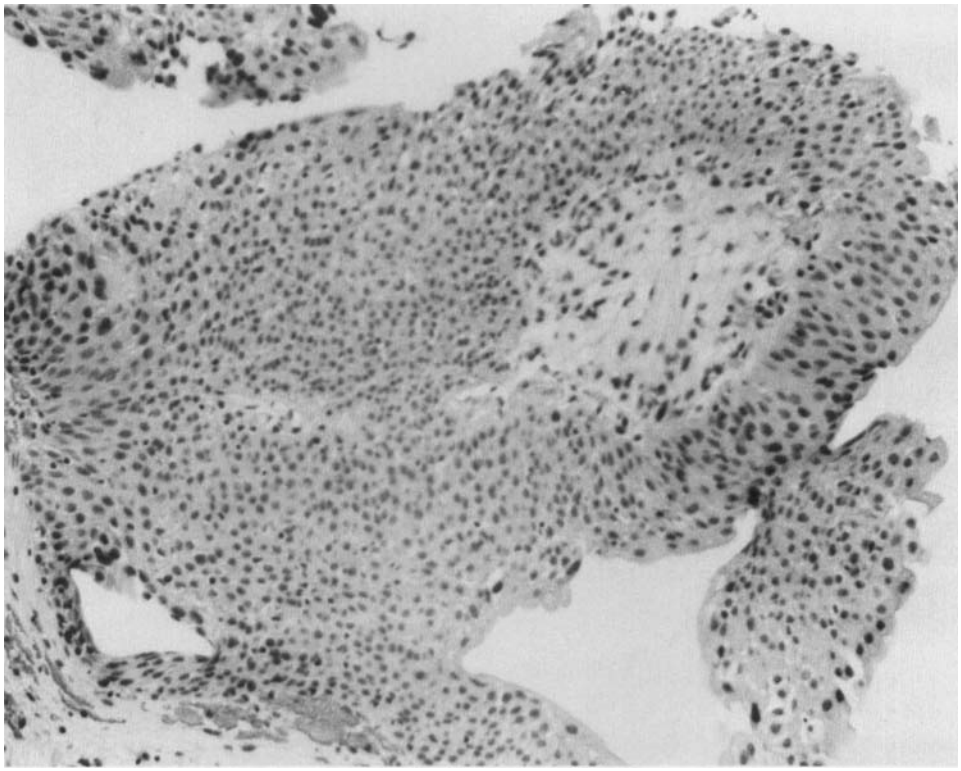

Fig. 3. Case 2. Tiny papillary tumors, grade 1, of the urinary bladder. This photograph shows a point of fusion of two adjacent lesions. X200.

blood cell per low power field and normal cytology. However, he was subsequently offered cystoscopy because of his history of exposure to MBOCA. A single frond of bladder epithelium was biopsied. The pathologic diagnosis, which was confirmed by one of us (L.K.), was papillary urothelial neoplasm, grade 1 (Fig. 3).

The patient, who had never smoked, worked at the MBOCA production plant for 9 months in 1976, 11 years prior to diagnosis. He operated an oven in which MBOCA was dried, and he also packed MBOCA into barrels. These were the jobs at the plant with the greatest potential MBOCA exposure. He reportedly used a respirator and wore gloves and overalls while working with MBOCA. Aside from his employment at the MBOCA production facility, he has not been employed in occupations with exposure to potential bladder carcinogens.

DISCUSSION

We report two cases of tumor of the bladder among workers exposed to MBOCA, an industrial agent that is already implicated as a potential bladder carcinogen by chemical and toxicologic evidence. The tumors detected on cystoscopy were small, low-grade, noninvasive lesions that would not have been detected without systematic screening. Although there is disagreement about the nomenclature

for such tumors, there is general consensus about their malignant biologic potential. The terms "transitional cell papilloma" and "grade 1 transitional cell carcinoma" are used interchangeably to designate a tumor composed of transitional epithelial cells arranged in a papillary frond-like growth on a basement membrane with delicate intervening stroma of reticulin fibers and vascular channels [Greene et al., 1973]. These tumors uncommonly invade, rarely metastasize, and are associated with patient survival approaching that in the general population [Murphy et al., 1984]. Individuals diagnosed with noninvasive papillary tumors have a 30–60% probability of having a recurrence, and about a 10% probability of developing carcinoma in situ or invasive carcinoma [Lerman et al., 1970]. The probability of recurrence is higher in those patients presenting with multiple, rather than solitary, papillomas [Lerman et al., 1970]. Subsequent tumors frequently arise at a location distinct from a preceding papillary lesion [Thompson, 1960, Brawn, 1984]. One possible explanation for the recurrence and multicentricity of these tumors is that they arise from a widespread, premalignant field change in the bladder mucosa [Farrow, 1979]. In a population exposed to a potential bladder carcinogen, we would expect that an increased prevalence of noninvasive papillary lesions might occur earlier in the latency period than the diagnosis of invasive carcinomas.

After the diagnosis of the second tumor, we decided to expand the scope of the study to include all workers employed at the company during the time MBOCA was produced. To date, 203 of the 540 MBOCA-exposed workers at this plant have undergone cystoscopy. The prevalence of grade 1–2 papillary neoplasms is 1.0% (two out of 203) among individuals who have been cystoscoped and 0.4% (two out of 540) among the population as a whole. We know of no comparison group of asymptomatic individuals having been cystoscoped; therefore, we cannot directly compare the frequency among the MBOCA workers to an "expected" prevalence. However, the incidence of clinically apparent bladder tumors in U.S. males aged 25–29 is only 1 per 100,000 per year [SEER, 1977]. The detection of the two tumors in young, nonsmoking males is consistent with the hypothesis that MBOCA induces bladder neoplasms in humans.

Urinary cytology was negative in both of the cases subsequently detected by cystoscopy and biopsy, which is consistent with the previous observation that urinary cytologic screening is of little value in detecting low-grade, papillary neoplasms [Farrow, 1979; Koss, 1985]. Despite this limitation, urinary cytology is valuable in following groups at high risk of bladder cancer because abnormal cytology may precede by several years the cystoscopic diagnosis of higher grade tumors [Koss, 1969].

Although screening may be of some benefit to workers exposed to an occupational bladder carcinogen, the more appropriate public health intervention is reduction or elimination of exposure to substances that are implicated as potential carcinogens by toxicologic evidence. There are as yet no published studies documenting the carcinogenic potential of MBOCA in humans. A study by Linch, which did not detect an excess of bladder cancer, was based on a small number of workers studied a relatively short time after first exposure to MBOCA [Linch, 1971]. Another study of workers at a chemical plant that produced MBOCA and a variety of other chemicals is nearing completion in Great Britain [Cartwright, 1987].

Workers exposed to MBOCA's structural analogue, benzidine, have mortality rates from bladder cancer 19 times greater than the general population [Case and

Hosker, 1954]. Given the toxicologic data on MBOCA, the epidemiologic data on related aromatic amines, and the identification of these two cases, we believe that it would be judicious to treat MBOCA as a potential occupational carcinogen [NIOSH, 1978].

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Note Added in Proof:

In April, 1988 a third worker with a "non-invasive, Grade 1, papillary transitional cell carcinoma" was identified by cystoscopy. This person is a 44-year-old male whose prior cytology and urinalysis results were negative. He worked in MBOCA production for 1.5 months in 1972, in direct daily contact with MBOCA. He is a former cigarette smoker who held other jobs in the chemical industry following employment at the MBOCA-production plant.