21.3

Bladder Cancer*

William Halperin • *Paul A. Schulte*

Occupational exposure to aromatic amines has been known to cause bladder cancer since Rehn identified the first few cases in workers in the new organic chemical industry in 1895. Since that time, numerous occupations and specific substances have been associated with an increased risk of bladder cancer (Tables 8 and 9). Beyond the certainties that specific aromatic amines have been demonstrated to be human occupational bladder carcinogens, and that a broad range of occupations are at risk of bladder cancer, a well-informed approach to the prevention and management of bladder cancer depends on appreciating various controversies involved in its primary and secondary prevention and treatment. The reader is referred to a report of a national conference held in 1989 (Schulte et al, 1990) to delineate these issues from which most of the material for this chapter is drawn.

ETIOLOGY

Epidemiology

Occupation contributes a substantial fraction of all cases of bladder cancer occurring in the general population. In Massachusetts, where working with bladder carcinogens in the leather industry was common, 20% of bladder cancer was attributable to occupation. A more recent study in 10 areas in the United States found that 21% to 25% of white male cases and 11% of white female cases were attributable to occupation. This is a sizable number given that there were 47,000 new cases and 10,200 bladder cancer deaths in 1989. In 1989, bladder cancer represented about 5% of all new cancer cases and approximately 2.2% of all cancer deaths. Predictably, this attributable fraction may be higher or lower in populations with greater or lesser past exposure to occupational bladder carcinogens. This approach addresses the contribution of occupational bladder carcinogens to the societal burden of bladder cancer.

To assess the effect of exposure to particular bladder carcinogens, a cohort or group of workers with that exposure in the past must be identified and their current health status determined. The exposure must have taken place early enough to allow for the expression of disease, if it is to occur, and the population studied must be large enough to ensure that the study does not produce false-negative results. An example of a study that inquires into the effect of bladder carcinogens on specific populations with known exposures is an investigation of the last producer of beta-naphthylamine in the United States.

All workers who ever worked in this facility were identified and assembled into a cohort. The vital status of all members of the cohort was determined. Not surprisingly, two workers were determined to have died of bladder cancer; based on United States mortality rates, 0.7 deaths were expected, yielding a standardized mortality ratio of only 2.9. In contrast, when inquiries were made as to whether workers ever had a bladder cancer for which they were treated and surviving workers were screened, 13 cases were found as compared with 3.3 expected. Beta-naphthylamine clearly causes bladder cancer, but mortality rates do not always clearly reflect morbidity. The risk in populations previously exposed to bladder cancer will depend on the degree of their exposure and sufficient time since exposure for the disease to develop.

There is no known distinctive histologic feature for occupational bladder cancer. However, in heavily exposed cohorts, cases regularly occur at an age 15 years younger than that of the general population, in which the rate of bladder cancer increases substantially with age. Usually, the interval from first exposure to onset of symptoms is decades long; however, occupational cases have occurred surprisingly early after exposure, which substantiates the argument that cases with only a few years of latency should not be discounted as occupationally induced.

The most important nonoccupational cause of bladder cancer in developed countries is cigarette smoking, with a relative risk of about twofold accounting for approximately 30% to 40% of cases and, with occupation, explaining part of the 3:1 male predominance. The contributions of coffee drinking and alcohol consumption to bladder cancer are equivocal. In developing countries, chronic infection (infection with *Schistosoma haematobium*, in particular) is important. Exposure to bladder carcinogens, such as cigarette smoking, in the personal environment does not preclude a contribution from occupational exposures, for which the relative risks may be substantially higher than for smoking.

Exposure to Bladder Carcinogens

Many more chemicals have been associated with bladder tumors in animal studies than have been shown to be human carcinogens by epidemiologic study or regulated as such (compare Tables 8 and 9). NIOSH maintains a Registry of Toxic Effects of Chemical Substances (RTECS), which lists approximately 200 animal bladder carcinogens. When this list is cross-indexed with sample surveys of industry that were conducted from 1972 to 1974 and again from 1981 to 1983, a large number of workers were found with greater than 4 hours per day of potential exposure to the cited chemicals; it is estimated that 700,000 persons were exposed in the 1980s. When the requirement for exposure is relaxed to some potential, the numbers increase to 1.8 million in the 1970s and 3.5 million in the 1980s. Caution must be used in extrapolating information from the surveys because they are based on inspection and interview, and no sampling was performed. Also, these estimates may be high in that not all animal bladder carcinogens (Table 9) may have the same effect in humans. The reciprocal caution also is in order because human bladder carcinogens may not similarly affect

TABLE 8 Occupations Associated with Increased Risk of Bladder Cancer in Males*

Occupation	Industry	Increased morbidity relative risk (CI)	Increased mortality relative risk (CI)	Other risks controlled for	Reference
Announcers	Communications	1.5 (0.8–2.7) ↑ ↑		Smoking	Silverman et al, 1989
Armed services		1.8 (1.2–2.7)			Howe et al, 1980
Blasters		1.7 (0.9–3.3) ↑ ↑		Smoking	Silverman et al, 1989
Bootblacks		1.9 (0.8–4.4) ↑ ↑		Smoking	Silverman et al, 1989
Butchers	Meat processing	1.3			Malker et al, 1987
Carpenters		11.1 (3.3–37.0)		Current smokers	Schumacher et al, 1989
Carpenters		1.4 (1.1–1.8)		Smoking	Silverman et al, 1989
Checkers	Manufacturing	1.4 (1.1–1.8) ↑ ↑		Smoking	Silverman et al, 1989
Chemical workers	Manufacturing	2.2 (1.7–3.0)			Boyko et al, 1985
Cleaners		3.5 (1.6–7.7)		Age, alcohol, smoking	Brownson et al, 1987
Construction workers		1.6 (1.1–2.5) ↑ ↑		Smoking	Silverman et al, 1989
Dental technicians		2.5			Malker et al, 1987
Drill press operatives		↑ ↑			Silverman et al, 1989
Drivers	Transportation	5.3 (2.3–12.2)			Isovich et al, 1987
Drivers	Railroad	6.5 (2.5–16.9)		Among smokers	Isovich et al, 1987
Drivers	Transportation, road	1.3 (1.1–1.6)		Sex, age, smoking	Hensen et al, 1987
Drivers		1.2 (1.1–1.4)		Smoking	Silverman et al, 1989
Drivers, locomotive	Transportation, rail	3.0 (1.2–8.8)			Claude et al, 1988
Drivers, taxi	Transportation, road	1.5 (1.2–2.0) ↑ ↑		Smoking	Silverman et al, 1989
Drivers, taxi	Transportation, usual occupation	6.3 (1.6–29.3) ↑ ↑		Age, smoking	Silverman et al, 1986
Drivers, truck		2.5 (1.4–4.4)		Age, smoking	Silverman et al, 1983
		2.1 ↑ ↑			
Drivers, truck	Transportation, road	1.2 (1.0–1.4) ↑ ↑		Smoking	Silverman et al, 1989
Drivers, truck	Transportation, road	1.8 (1.1–2.8) ↑ ↑		Smoking	Claude et al, 1988
Drivers, truck	Transportation, road	1.5 (1.1–2.0)		Age, smoking	Silverman et al, 1986
Drivers, truck	Transportation		2.0 ($p<0.05$)		Baxter and McDowall, 1986
Dry cleaning workers	Dry cleaning plants		3.0 (1.3–5.9)		Brown and Kaplan, 1987
			2.7	White males	
			5.0	Black males	
Dyers, printers	Textile	4.4 (1.2–16.8)		Smoking	Silverman et al, 1989
Dyers	Textile	4.6 (1.1–31.6)		Latency ≥ 8 yrs	Risch et al, 1988
Dye mfg. workers	Dyeworks	3.5 (2.2–5.3)		Smokers, nonsmokers	Cartwright, 1982
		4.6, 1.9			
Dye mfg. workers	Dyeworks	2.7 (1.9–3.8)			Boyko et al, 1985
Entertainers	Communications	1.5 (0.8–2.7) ↑ ↑		Smoking	Silverman et al, 1989
Examiners	Manufacturing	1.4 (1.1–1.8) ↑ ↑		Smoking	Silverman et al, 1989
Firemen		↑ ↑			Silverman et al, 1989
Food counter or fountain workers		2.6 (1.4–5.1)		Age, smoking	Schoenberg et al, 1984
Food counter or fountain workers		1.4 (0.9–2.1) ↑ ↑		Smoking	Silverman et al, 1989
Furnace operator		↑ ↑			Silverman et al, 1989
Guards		4.0 (1.3–16.4)			Howe et al, 1980
Inspectors	Manufacturing	1.4 (1.1–1.8) ↑ ↑		Smoking	Silverman et al, 1989
Janitors		3.5 (1.6–7.7)		Age, alcohol, smoking	Brownson et al, 1987
Janitors		3.5 (1.2–9.9)		Smoking, exposure	Claude et al, 1988
Laborers	Manufacturing	12.3 ↑ ↑			Silverman et al, 1989
Lumbermen		1.3 (1.0–1.5) ↑ ↑		Smoking	Silverman et al, 1989
Machinists		1.2			Malker et al, 1987
Machinists, metal		1.1 (1.0–1.3)		Smoking	Silverman et al, 1989
Machinists, metal		2.7 (1.1–7.6)			Howe et al, 1980
Machinists		1.3 (1.0–1.7)		Smoking	Silverman et al, 1989
Mechanics		3.5 (1.4–9.1)		Age, alcohol, smoking	Brownson et al, 1987
Mechanics		1.2			Malker et al, 1987
Mechanics		1.2 (1.0–1.4)		Smoking	Silverman et al, 1989
Mechanics		1.8 (1.2–2.8)		Smoking	Silverman et al, 1989
Mechanics, auto	Trucking service	10.2 (2.1–68.6)		Smoking	Silverman et al, 1989
Metal filers, polishers, sanders, buffers		1.5 (1.0–2.2) ↑ ↑		Smoking	Silverman et al, 1989
Metal workers		1.2 (1.0–1.4)		Smoking	Silverman et al, 1989
Mining machine ops	Mining	2.9 (1.1–7.5)		Age, alcohol, smoking	Brownson et al, 1987
Mining workers	Mining	2.0 (1.2–3.3)		Smoking	Claude et al, 1988
		3.2 (10–19 yrs)			

TABLE 8 Occupations Associated with Increased Risk of Bladder Cancer in Males* *(Continued)*

Occupation	Industry	Increased morbidity relative risk (CI)	Increased mortality relative risk (CI)	Other risks controlled for	Reference
Operators (dusty jobs)	Chemical manufacture	1.4 (0.8–2.7)		Age, smoking, location	Zahm et al, 1987
Painters			1.7 (1.0–2.7) 2.1 (1.0–3.9)		Guberan et al, 1988
Painters		1.4 (1.1–1.9)		Sex, age, smoking	Jensen et al, 1987
Painters, artistic			2.6 (1.5–4.4)		Miller et al, 1986
Painters		1.5 (1.2–2.0) ↑ ↑		Smoking	Silverman et al, 1989
Petroleum processors	Petroleum extraction	2.4 (1.1–5.5)		Smoking	Silverman et al, 1989
Potroom workers	Aluminum smelting	5.9 (2.4–14.3)			Armstrong et al, 1986
Powdermen		1.7 (0.9–3.3) ↑ ↑		Smoking	Silverman et al, 1989
Printers	Printing	3.1 (1.4–6.8)			Cartwright, 1982
Printers		2.1 (1.0–4.3)		Smoking	Silverman et al, 1989
Print machine ops	Printing		3.1 (1.1–8.9)	Age, alcohol, smoking	Brownson et al, 1987
Produce graders, packers	Food processing	3.2 (1.1–9.3)		Smoking, educ.	Silverman et al, 1989
Salesmen	Service, construction	2.2 (1.2–4.1) ↑ ↑		Smoking	Silverman et al, 1989
Tailors	Textile	2.7 (1.1–6.6)			Claude et al, 1988
Tailors		3.9 (1.3–14.2)		Latency ≥ 8 yrs	Risch et al, 1988
Telephone and telegraph operators	Communications	1.9 (0.9–4.0) ↑ ↑		Smoking	Silverman et al, 1989
Turners		2.3 (1.0–5.6) ↑ ↑		Smoking	Claude et al, 1988
Upholsterers	Textile	2.7 (1.1–6.6)			Claude et al, 1988
Watchmen		3.5 (1–10 years) 12.3 (10–19 yrs)		Smoking	Claude et al, 1988
Watchmen		4.0 (1.3–16.4)			Howe et al, 1980
Weavers	Textile	2.7 (1.1–6.6)			Claude et al, 1988
Weavers	Textile	3.5 (1.3–9.3)		Smoking	Silverman et al, 1989
Welders		2.8 (1.1–8.8)			Howe et al, 1980
Welders, oxyacetylene	Shipyards		3.7 (1.2–8.6)		Merlo et al, 1989
Woodworkers		1.3 (1.0–1.5) ↑ ↑		Smoking	Silverman et al, 1989
Writers	Communications	1.5 (0.8–2.7) ↑ ↑		Smoking	Silverman et al, 1989

*Only occupations explicitly mentioned in a study are included.

↑ ↑, Dose response demonstrated

animals, and the number of chemicals that have been tested and hence have any potential for being on the RTECS list is small. These estimates also do not consider turnover among employees, which would lead to a greater number of persons exposed than is suggested by estimates from specific points in time.

CLINICAL ASPECTS

Pathology

One problem in the pathology of bladder tumors is the somewhat ambiguous line between the benign and the malignant. This distinction should be viewed as a region where borders shift between pathologists, between institutions, and given the circumstances, even of the patient who is biopsied. Several problems have been defined; most notably distinguishing between a papilloma, a papillary tumor with delicate fibrovascular stroma covered by a layer of epithelial cells indistinguishable from normal bladder mucosa, and a papillary carcinoma. Some so-called benign papillomas display effects of inflammation and reactive or regenerative conditions so that they are classified by some pathologists as anaplastic, although most of them do not behave as malignant tumors. To make the situation more complicated, some tumors do become aggressive. Second, different pathologists observing the same anaplastic findings may have different interpretations of the grade of the tumor, which is an estimate of its likely aggressiveness. Third, there can also be variation between clinical and pathologic systems used for staging bladder tumors, which reflects the depth of infiltration of the tumor. Another problem in pathology is consistency and accuracy in distinguishing carcinoma in situ from atypia or dysplasia among nonpapillary, noninfiltrating, or flat lesions. The use of biochemical, molecular, and genetic characteristics of cells is beginning to provide pathologists with a way to reduce these uncertainties. Strong associations of various markers with progression, invasiveness, and metastatic potential may provide a way to distinguish between pathologic subtypes of bladder cancer in the future.

Therapy

Strategies for diagnosis and therapy of bladder cancer do not differ from the general knowledge of therapy of bladder cancer resulting from nonoccupational etiologies. There are some promising advances in therapeutic approaches. These include newer surgical techniques that preserve sexual function, systemic chemotherapy, intravesicular instillation of chemotherapeutics, and instillation of Bacille Calmette-

TABLE 9 Known, Suspected, and Possible Bladder Carcinogens Based on Animal Studies and Human Epidemiology

Compound name	Evidence of carcinogenicity			Compound name	Evidence of carcinogenicity		
	EPA	NCI/ NTP	IARC		EPA	NCI/ NTP	IARC
acenaphthene, 5-nitro	+		Group 2B	2-imidazolidinone, 1-(5-nitro-2-thiazolyl)-	+		Group 2B
acetamide, N-fluoren-2-yl-	+	+		isothiocyanic acid, allyl ester		+	Group 3
acetamide, N-(4-(5-nitro-2-furyl)-2-thiazolyl)-	+		Group 2B	melamine		+	Group 3
acetic acid, nitrilotri-	+	+		methanesulfonic acid, methyl ester	+		Group 3
acetic acid, nitrilotri- trisodium salt		+		2,7-naphthalenedisulfonic acid, 4-amino-3-((4'-((2,4-diaminophenyl)azo)(1,1'biphenyl)-	+	+	Group 2A
acetic acid, (2,4,5-trichlorophenoxy)-	+		Group 2B				
acetohydroxamic acid, N-fluoren-2-yl-	+						
p-acetophenetidide	+	+	Group 2A	2,7-naphthalenedisulfonic acid, 3,3'-((4,4'-biphenylylene)bis(azo))bis(5-amino-	+	+	Group 2A
ammonium, (4-bis(p-dimethylamino)phenyl) methylene)-2,5-cyclohexadien-1-yli	+						
				2,7-naphthalenedisulfonic acid, 3-hydroxy-4-((2,4,5-trimethylphenyl)azo)-,D	+		Group 2B
aniline	+		Group 3				
aniline, N,N-dimethyl-p-phenylazo-	+	+	Group 2B				
aniline, 4,4'-(imidocarbonyl)bis (N,N-dimethyl-HCl	+			2-naphthol, 1-((2,5-dimethoxyphenyl)azo)-	+		Group 2B
o-anisidine, HCl	+	+	Group 2B	2-naphthol, 1-(phenylazo)-		+	Group 3
o-anisidine, 5-methyl-	+	+	Group 2B	2-naphthol, 1-(o-tolylazo)-	+		Group 2B
p-anisidine, 2-methyl-		+	Group 3	2-naphthylamine	+	+	Group 1
2-anthracenamine	+			2-naphthylamine, N,N-bis(2-chloroethyl)-	+	+	Group 1
9,10-anthracenedione, 1,4,5,8-tetraamino-	+						
				19-nor-17-alpha-pregna-1,3,5(10)-triene-20-yne-3,17-diol	+	+	Group 2A
benz[*a*]anthracene	+	+	Group 2A				
benzidine	+	+	Group 1	2H-1,3,2-oxazaphosphorine, 2-(bis (2-chloroethyl)amino)tetrahydro-, 2-oxide	+	+	Group 1
benzidine, 3,3'-dichloro-	+	+	Group 2B				
benzidine, 3,3'-dimethoxy-	+	+	Group 2B				
benzisothiazolin-3 one, 1,1-dioxide (saccharin)	+		Group 2B	phenol, 4-amino-2-nitro-	+	+	Group 3
				phenol, (1,1-dimethylethyl)-4-methoxy-	+		Group 2B
benzisothiazolin-3-one, 1,1-dioxide sodium salt (sodium saccharin)	+		Group 2B	m-phenylenediamine, 4-chloro-	+		Group 3
				o-phenylenediamine, 4-chloro-	+		Group 2B
p-benzoquinone, dioxime		+	Group 3	phosphorodiamidic acid, N,N-bis(2-chloroethyl)-N'-(3-hydroxypropyl)-		+	
4-biphenylamine	+		Group 1				
4-biphenylamine, 3,2'-dimethyl-		+					
biphenyl, 4-nitro	+		Group 3	1-propanol, 2,3-dibromo-, phosphate (3:1)	+	+	Group 2A
2-biphenylol, sodium salt			Group 2B				
bracken fern			Group 2B	propene, 1,3-dichloro-		+	Group 2B
1-butanamine, N-butyl-N-nitroso	+	+	Group 2B	purine, 6-((1-methyl-4-nitroimidazol-5-yl)thio)-+	+		Group 1
1-butanol, 4-(butylnitrosoamino)-	+		Group 2B				
p-cresol, 2,6-di-tert-butyl-	+		Group 3	5H-pyrido(4,3-b)indole, 3-amino-1,4-dimethyl-	+		Group 2B
cyclohexanesulfamic acid, monosodium salt (cyclamate)			Group 3				
				5H-pyrido(4,3-b)indole, 3-amino-1-methyl-			Group 2B
dibenz(a,h)anthracene	+	+	Group 2A				
7H-dibenzo(c,g)carbazole	+		Group 2B	serine, diazoacetate (ester)	+		Group 2B
dimethylamine, N-nitroso-	+	+	Group 2A	4,4'-stilbenediol, alpha,alpha'-diethyl-, dipropionate, (e)-			Group 2B
diphenylamine, N-nitroso-	+	+	Group 3				
dipropylamine, N-nitroso-	+	+	Group 2B	toluene, 2,4-dinitro-		±	Group 2B
estradiol	+	+	Group 2A	o-toluidine	+	+	Group 2A
flavone, 3,3',4',5,7-pentahydroxy-	+		Group 3	o-toluidine, hydrochloride	+	+	Group 2B
fluoren-2-amine	±			o-toluidine, 4-(o-tolylazo)-	+		Group 2B
formamide, N-(5 nitro-2-furyl)-2 thiazolyl)-	+			undecanoic acid, 11-amino-		+	Group 3
				urea, N-methyl-N-nitroso-	+	+	Group 2A
formic acid, 2-(4-(5-nitro-2-furyl)-2-thiasolyl)hydrazide	+		Group 2B	vincaleukoblastine		+	
hydroxylamine, N-2-naphthyl-	+						

An RTECS search for substances associated with bladder tumors produced this list. Notations indicate how compounds were rated by the EPA Gene-Tox Program, NCI/NTP Carcinogenesis Bioassays, and IARC Monographs. IARC Classification: Group 1, definite human bladder carcinogen; Group 2A, probable human bladder carcinogen; Group 2B, possible human bladder carcinogen or animal carcinogen, lacking data in humans; Group 3, lacking evidence.

From Ruder A, Fine L, Sundin D. National estimates of occupational exposure to animal bladder tumorigens. J Occup Med 1990; 32:797–805.

Guérin (BCG) vaccine. Technology also is advancing with the advent of flexible cystoscopes and lasers. However, variations in pathologic grading and staging, as well as variations between studies in the means of identifying cases, make evaluation of alternative therapeutic techniques difficult. Cases found by screening may inherently be more indolent than those that are clinically apparent; hence, trials with the same approach in these different groups may suggest survival differences that are artifactual. Patients with bladder cancer require particularly thorough follow-up because these patients are at increased risk of developing subsequent tumors. A difficult situation requiring frequent and thorough follow-up is the asymptomatic patient with abnormal cytology with no discernible lesion. The one difference in populations with

bladder cancer due to an occupational exposure is the ability to control further exposure and to identify co-workers similarly exposed for screening and education.

Survival

The survival of patients with bladder cancer depends on the grade of anaplasia of the tumor and the stage of tumor invasion at time of diagnosis. Five-year survival rates range from 88% for localized disease in whites to 8% for distant disease in blacks. Blacks fare more poorly than whites for each grade and stage and usually are diagnosed at a more advanced stage. The survival of bladder cancer cases has increased by 45% over the past 35 years and is probably not due to better early detection because survival has increased for each category of stage as well. On the other hand, early detection may be contributing to the 51% increase in the disease over the past 35 years.

PREVENTION

Techniques for Early Detection

Urine cytology is the accepted technique for detection of bladder cancer in asymptomatic individuals. Cytology for bladder cancer has a sensitivity of about 67% and a specificity of 96%, which is comparable to screening tests for cervical cancer, breast cancer, and colon cancer. These data do not distinguish between different forms of bladder cancer. Essentially, two forms of bladder cancer have been described—an indolent form and an aggressive form. Indolent tumors begin as superficial, noninvasive growths and remain so, although some become more aggressive. At the first recognition of clinical symptoms, 60% to 80% of tumors are of advanced stage; hence, the importance of preclinical detection. Bladder cytology is effective in detecting preclinical stages of aggressive tumors and is substantially less effective in detecting low-grade tumors. There is widespread agreement that superficial well-differentiated papillary tumors rarely can be diagnosed definitively from voided urine cytology. In summary, cytology may be used to detect aggressive tumors, but these tumors may be advanced by the time they are discovered by this method. Cytology is less effective for low-grade tumors, which although they are less aggressive, would be desirable to find.

Hematuria screening, by urinalysis or by dipstick, may be a more effective method than cytology for detecting early stage bladder tumors. The dilemma with testing for hematuria is that although almost all bladder tumors eventually cause hematuria, an infrequent examination may not be adequately sensitive. Although more frequent examinations increase the sensitivity of the test for bladder cancer, this method decreases the specificity of the test because other nonmalignant conditions causing hematuria will be detected. The debate then focuses on the predictive value of a positive test result for hematuria or the probability that a positive test result will reflect bladder cancer rather than another problem. It has been suggested that 5% to 10% of patients with hematuria have bladder cancer and 10% to 20% have some other serious urinary tract disease. As a condition becomes more prevalent in a population, the predictive value of a positive test increases. Exposure of an individual to an occupational carcinogen, as well as the individual's age and other risk factors for bladder cancer, should ensure a higher underlying prevalence of bladder cancer and thus increase the predictive value of a screen for hematuria.

Cystoscopy was used in the 1930s and 1950s as a screening test for bladder cancer in occupational groups at high risk for bladder cancer due to exposure to aromatic amines. In the group studied in the 1930s, 4.7% were found to have bladder cancer; 11% were found to have bladder cancer in the group studied in the 1950s (Prout 1990). A higher yield would be expected on the first screening, when old and new tumors would be detected (prevalent cases), than on subsequent screenings, when only new or incident tumors would be found. In comparison to other noninvasive screening tests, cystoscopy is more onerous in terms of cost and personal discomfort. Current use of cystoscopy should be reserved as a diagnostic test in individuals who had positive results on cytology and hematuria in a high-risk population.

Individual variation in metabolism of bladder carcinogens may identify some workers at particularly high risk. In a series of studies in England (Cartwright et al, 1982), a disproportionate number of cases of bladder cancer were found among dye workers who also were slow acetylators. Acetylator status is recognized as affecting the metabolism of some therapeutic drugs such as isoniazid but has not been confirmed to affect metabolism of occupational carcinogens. If acetylator status is confirmed as a risk factor for bladder cancer, simple tests for acetylator status may be used, along with history of occupational exposures to carcinogens, age, and smoking status as predictors of risk in determining who should be screened for bladder cancer or screened with a different frequency.

Other tests for screening and diagnosis of bladder cancer are now being developed or evaluated. In addition to variations in metabolic phenotypes such as *N*-acetyltransferase, there are other genetic factors and acquired factors, such as recessive alleles for oncogenes, mutated tumor suppressor genes, and growth factors, that may place individuals at increased risk for bladder cancer independent of occupational exposure. These genetic factors could add to other occupational risks for bladder cancer or multiply those risks. It is likely that the rapid pace of research will result in the identification of new predictive or prognostic markers in the near future.

A number of new techniques are being tested for use in bladder cancer screening. Quantitative fluorescence image analysis, which measures DNA, has been used as a screening technique in various high-risk groups. This approach uses exfoliated bladder cells. Flow cytometry is an automated technique for detecting bladder cancer based on abnormal DNA content of bladder cells. Flow cytometry may be improved by combining its use with monoclonal antibody markers, which could be used to distinguish bladder cancer cells from other cells and distinguish tumor cells among other bladder cells. Flow cytometry generally requires bladder washings, but attempts are being made to use voided urine, which will enhance its utility as a screening test.

Screening Programs

There are two reasons for screening a population exposed to a known or suspect bladder carcinogen. First, individuals

may be screened so that their tumors can be detected early when they are more readily treated, resulting in less morbidity and higher survival rates. This type of screening is for the personal benefit of the individuals. The second rationale for screening is to detect disease in a population at the earliest time possible in order to ensure that more primary methods of disease prevention, such as engineering controls and use of personal protective devices, are effectively incorporated to prevent exposure. The two motivations should be kept in mind in appreciating a consensus view that was reached at the end of the 1989 conference on screening for bladder cancer in high-risk groups. For populations exposed to known carcinogens at high levels, cytologic examination and testing for hematuria was recommended at 6-month intervals. The rationale for including hematuria was to ensure the acceptability of the screening program by ensuring that low-grade tumors are detected that otherwise may be missed by cytology. For low-exposure groups, as may be found in patients suffering from conditions as a result of environmental exposures, cytology was recommended 2 years after the first exposure, then every 5 years thereafter. For a suspect carcinogen, at high-exposure levels, cytology was recommended every 6 months, as well as measurement of hematuria to detect low-grade tumors. The argument for detecting low-grade tumors, even though there may be limited personal benefit for the individual because most such tumors are less aggressive, is to provide information that exposure has not been adequately controlled. The panel was not enthusiastic about any recommendations for a suspect carcinogen at low levels of exposure.

When weighing the benefits of a strategy of early detection, be it for the personal benefit of the worker or for the benefit of the workforce, it is necessary to consider the extent to which false-positive findings will be involved. A screening modality that leads to a disproportionate number of unnecessary follow-up and diagnostic procedures may not be cost effective or personally desirable. Moreover, the lengthening of the lead time, although possibly providing an extended opportunity for therapeutic intervention, also could provide a longer period of anxiety and distress for the worker.

Bibliography

Armstrong BG, Tremblay CG, Cyr D, Theriault GP. Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. Scand J Work Environ Health 1986; 12:483–493.

Baxter PJ, McDowall ME. Occupation and cancer in London. An investigation into nasal and bladder cancer using the Cancer Atlas. Br J Ind Med 1986; 43:44–49.

Boyko RW, Cartwright RA, Glashan RW. Bladder cancer in dye manufacturing workers. J Occup Med 1985; 27:799–803.

Brown DP, Kaplan SD. Retrospective cohort mortality study of dry cleaning workers using perchloroethylene. J Occup Med 1987; 29:535–541.

Brownson RC, Chang JC, Davis JR. Occupation, smoking and alcohol in the epidemiology of bladder cancer. Am J Public Health 1987; 77:1298–1300.

Cartwright R. Occupational bladder cancer and cigarette smoking in West Yorkshire. Scand J Work Environ Health 1982; 8:79–82.

Cartwright RA, Glashan RW, Rogers HJ, et al. Role of *N*-acetyltransferase phenotype in bladder cancer. Lancet 1982; ii(8303):842–845.

Case RAM, Hosker ME, MacDonald DB, Pearson JT. Tumors of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediaries in the British chemical industry. Br J Ind Med 1954; 11:75–104.

Claude JC, Prenzal-Beyme RR, Kunze E. Occupation and risk of cancer of the lower urinary tract among men. A case-control study. Int J Cancer 1988; 41:371–379.

Cole P, Hoover R, Friedell GH. Occupation and cancer of the lower urinary tract. Cancer 1972; 29:1250–1260.

Cole P, Monson RR, Haning H, et al. Smoking and cancer of the lower urinary tract. N Engl J Med 1971; 248:129.

Farrow G. Urine cytology in the detection of bladder cancer: a critical approach. J Occup Med 1990; 32:817–821.

Grant DM, Tang BK, Kalow W. A simple test for acetylator phenotype using caffeine. Br J Clin Pharmacol 1984; 17:459–464.

Guberan E, Usel M, Raymond L, et al. Disability, mortality and incidence of cancer among Geneva painters and electricians: A historical prospective study. Br J Ind Med 1988; 46:16–23.

Halperin W, Ratcliffe J, Frazier T, et al. Medical screening in the workplace: Proposed principles. J Occup Med 1986; 28:547–552.

Hoar SK, Hoover R. Truck driving and bladder cancer mortality in rural New England. J Natl Cancer Inst 1985; 74:771–774.

Howe GR, Burch JD, Miller AB, et al. Tobacco use, occupation, coffee, various nutrients and bladder cancer. J Natl Cancer Inst 1980; 64:701–703.

Hulka B. Principles of bladder cancer screening in an intervention trial. J Occup Med 1990; 32:812–816.

Hurst R, Jones P, Rao JY, Hemstreet G. Molecular and cellular biological approaches and techniques in the detection of bladder cancer and enhanced risk for bladder cancer in high-risk groups. J Occup Med 1990; 32:854–862.

Iscovich J, Castellrito R, Esteve J, et al. Tobacco smoking, occupational exposure and bladder cancer in Argentina. Int J Cancer 1987; 49:734–740.

Jensen OM, Wahrendorf J, Knudsen JB, et al. The Copenhagen case-referent study on bladder cancer. Risks among drivers, painters and certain other occupations. Scand J Work Environ Health 1987; 13:129–134.

Malker HSR, McLaughlin JK, Silvermann DT, et al. Occupational risks for bladder cancer among men in Sweden. Cancer Res 1987; 47:6763–6766.

Merlo F, Costantini M, Doria M. Cause specific mortality among workers exposed to welding fumes and gases: A historical prospective study. Sangyo Ika Daigaku Zasshi 1989; 11(Suppl):302–315.

Messing E, Vaillancourt A. Hematuria screening for bladder cancer. J Occup Med 1990; 32:838–846.

Miller BA, Silverman DT, Hoover RN, et al. Cancer risk among artistic painters. Am J Ind Med 1986; 9:281–287.

Mostofi F, Davis C, Sesterhenn A. Current understanding of pathology of bladder cancer and attendant problems. J Occup Med 1990; 32:793–796.

Prout G. Historical and modern role of cystoscopy and bladder mucosal biopsy in detecting bladder cancer in a high-risk population. J Occup Med 1990; 32:834–837.

Risch HA, Burch JD, Miller, et al. Occupational factors and the incidence of cancer of the bladder in Canada. Br J Ind Med 1988; 45:361–367.

Ruder A, Fine L, Sundin D. National estimates of occupational exposure to animal bladder tumorigens. J Occup Med 1990; 32:797–805.

Schoenberg JB, Stemhagen A, Mogielnicki AP, et al. Case-control study of bladder cancer in New Jersey. I. Occupational exposure in white males. J Natl Cancer Inst 1984; 72:973–981.

Schulte P, Halperin W, Ward E, Ruder A, eds. Bladder Cancer Screening in High Risk Groups. J Occup Med 1990; 32:787–945.

Schulte PA, Ringen K, Hemstreet GP. Optimal management of asymptomatic workers at high risk of bladder cancer. J Occup Med 1986; 28:13–17.

Schulte PA, Ringen K, Hemstreet GP, et al. Risk assessment of a cohort exposed to aromatic amines. Initial results. J Occup Med 1985; 27:115–121.

Silverman DT, Levin LI, Hoover RN, Hartge P. Occupational risks of bladder cancer in the United States: I. White men. J Natl Cancer Inst 1989; 81:1472–1483.

Smart CR. Bladder cancer survival statistics. J Occup Med 1990; 32:921–925.

Stern FB, Murthy LI, Beaumont JJ, et al. Notification and risk assessment for bladder cancer of a cohort exposed to aromatic amines: III. Mortality among workers in the last B-naphthylamine manufacturing facility in the United States. J Occup Med 1985; 27:495–500.

Whitmore W. Current therapy of bladder cancer. J Occup Med 1990; 32:921–926.

Zahm SH, Hartge P, Hoover R. The National Bladder Cancer Study: Employment in the chemical industry. J Natl Cancer Inst 1987; 79:217–222.

Textbook of CLINICAL OCCUPATIONAL and ENVIRONMENTAL MEDICINE

LINDA ROSENSTOCK, M.D., M.P.H.
Director, National Institute for Occupational Safety and Health
Director, Occupational and Environmental Medicine Program
Professor of Medicine and Environmental Health
University of Washington
Schools of Medicine and Public Health and Community Medicine
Seattle, Washington

MARK R. CULLEN, M.D.
Professor of Medicine and Public Health
Director, Occupational/Environmental Medicine Program
Yale University School of Medicine
New Haven, Connecticut

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo

W.B. SAUNDERS COMPANY
A Division of
Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Textbook of clinical occupational and environmental medicine /
[edited by] Linda Rosenstock, Mark R. Cullen.

p. cm.

Includes bibliographical references and index.

ISBN 0–7216–3482–6

1. Occupational diseases. 2. Industrial hygiene. 3. Industrial toxicology. I. Rosenstock, Linda. II. Cullen, Mark R. [DNLM: 1. Occupational Diseases. 2. Occupational Medicine. 3. Environmental Pollutants. 4. Environmental Exposure. WA 400 T3543 1994]

RC964.T38 1994 616.9′803—dc20

DNLM/DLC 93–8640

Textbook of Clinical Occupational and Environmental Medicine ISBN 0–7216–3482–6

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1