Screening for Bladder Cancer in High-Risk Groups: Delineation of the Problem

Paul A. Schulte, PhD

Since 1895, various exogenous chemicals and occupations have been identified as risk factors for bladder cancer. The aromatic amines are among the most notable chemicals. To date, numerous groups of workers and, in some cases, community residents, who are at increased risk of bladder cancer have come to the attention of health officials and have sought guidance concerning screening for bladder cancer. Most of these persons are asymptomatic, but they may not have attained the average length of preclinical latency for aromatic amine-induced cancer. Although the principal public health strategy for combatting occupational exposure to carcinogens is primary prevention, screening is another strategy that can be used for those already exposed to known or suspected carcinogens. Screening also can be used to assess whether or not environmental controls are needed or need to be improved. For more than a decade the question of screening has been problematic with regard to occupational groups where known exposures have been documented. The question facing government, labor, industry, and academia is what to recommend with regard to screening high-risk groups.

A state-of-the-art conference on bladder cancer screening for the general population in 1977 determined that there was a lack of good evidence on which to base a recommendation of screening for bladder cancer.[1] Using the then-available data, the conferees concluded that early detection did not lead to improved survival and reduction of mortality. However, during the past decade, there have been exciting advances in the epidemiology, pathology, detection, and treatment of bladder cancer.

From the Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH 45226-1998.

Address correspondence to: National Institute for Occupational Safety and Health, 4676 Columbia Parkway, MS R-13, Cincinnati, OH 45226-1998.

0096-1736/90/3209-789$02.00/0

The 1989 conference was organized to take stock of what is now known. The goal was to develop recommendations for screening of asymptomatic persons/groups who are at risk of bladder cancer.

The question of whether or not screening should be recommended for asymptomatic groups at high risk of bladder cancer needed to be addressed. For the most part, these groups are occupational but the question also pertains to community residents exposed to bladder carcinogens, to cigarette smokers and, clinically, to bladder cancer patients at risk of recurrent disease. Screening for bladder cancer was considered in 1977 at the State-of-the-Art Conference on Bladder Cancer Screening. The task of the 1989 conference was to determine whether there had been developments since 1977 that impacted on the question of screening for bladder cancer in high-risk groups. Based on old and new work, were we ready to develop a strategy for screening, or were we at the stage of evaluating current and future screening programs so that such strategies can be developed? With regard to workers, this is a recurring question for the National Institute for Occupational Safety and Health, corporations, labor unions, and clinicians. Other federal and state agencies have to deal with this question with regard to residents living near sources of bladder carcinogens.

The 1977 Conference

The primary mission of the 1977 conference was to determine whether or not sufficient information existed to demonstrate the value of any bladder cancer screening activity in terms of the outcome measures: morbidity and mortality from bladder cancer. Although the proceedings were not widely disseminated, certainly not in published form, a reading of transcripts[1] and summaries[2] of the meeting, provided by Drs George Hutchison and Gilbert Friedell, suggests the following series of questions and answers:

1. *Is bladder cancer a disease favorable to screening?* Yes, because it is a disease with serious consequences. It could be the target of a screening program if it is highly prevalent in the population to be screened. Although this is not the case in the general population, it is true in certain high-risk groups, particularly occupational. Although screening efforts in these groups may reduce bladder cancer mortality in the general population only 5–20%, they may be worthwhile.

2. *Is there a good screening test?* Again, a qualified "yes." Bladder cancer screening by Papanicolaou cytology, its limitations duly acknowledged, has the characteristics of a good screening test: high sensitivity and specificity, low cost, and little inconvenience and discomfort. These detection characteristics, however, apply only to the use of the test to detect invasive or high-grade disease.

3. *Does the screening test have a high positive predictive value?* Yes. However, this will depend on the prevalence of bladder cancer in the group screened; the greater the prevalence, the greater the predictive value. High-risk groups have the greatest prevalence.

4. *Is there a favorable natural history and treatment for the disease?* No. As Dr. Hutchison noted with regard to the natural history, the question relevant to screening is whether or not the presumed 2-year lead time allows discovery at a stage that is more subject to effective treatment than would be the case 2 years later. In 1977, there was no evidence to show that lesions detected by screening differed in stage distribution from the stage distribution of symptomatic bladder cancer.

Finally, perhaps the most telling comment from the State-of-the-Art of the Bladder Cancer Screening Conference in 1977 was the conclusion of Dr Hutchison[1]: "If there was any message I learned clearly in these three days it was that screening for bladder cancer has not been adequately evaluated." In part, this was due to the paucity of data; in part it was due, as John Bailar[1] observed, to mixing of incidence and prevalence data; lack of adjustment for age; inadequate consideration of tumor stage, tumor grade, or multicentricity; and little information on the nature and quality of treatment. Moreover, where comparisons were made between screened and unscreened groups, comparability of populations was not shown. As Dr Whitmore[1] observed: "It is conceivable that when one compares a symptomatic group to a cytologically detected group of patients, you're talking about a different population of patients."

Developments in Bladder Cancer Research and Treatment, 1977 to 1989

The 1977 conference found that there was a shortage of data on screening, and what there was had not been adequately evaluated. The steering committee from the conference concluded, after a review of evidence from past and ongoing screening and surveillance programs, that the data did not demonstrate any improvement in the survival of such patients as a result of screening in the asymptomatic state.[2,3] Thus, for more than a decade since the conference, there has been uncertainty regarding what to recommend for asymptomatic workers and persons at increased risk of bladder cancer as a result of community exposures. During this time there have been developments that impacted on this question,[3] including increased understanding of the epidemiology and pathology of bladder cancer coupled with advances in prognostication and treatment.[4–6] We now can identify not only numerous occupational high-risk groups, but also subgroups. These may be defined in terms of exposure factors, such as the presence of aromatic amine adducts to DNA or hemoglobin, behavioral factors such as cigarette smoking, and genetic factors such as metabolic phenotypes.[3,5]

Understanding of the pathology of bladder cancer also continues to improve. It is now routine to distinguish two separate overlapping pathways, the papillary and nonpapillary, and to know the implications for progression from each.[7–9] The identification and description of carcinoma in situ by pathologists and the recognition of its clinical features and diagnostic implications by clinicians represent further advances in the effort to control invasive epithelial cancer.[10] However, despite this understanding and, as Dr Mostofi discussed at the 1989 meeting, there continues to be a problem in how we define and classify "bladder cancer."

Nowhere has research on bladder cancer expanded as it has in the area of potential detection techniques.[8–12] The relative accessibility of the bladder, coupled with rapid advances in molecular biology, have led to a vast array of techniques to define bladder cancer earlier in its natural history. Many of these techniques, such as the use of monoclonal antibodies, quantitative fluorescence image analysis for DNA hyperploidy, oncogenes, and the autocrine motility factor, were discussed at this meeting. However, the utility of these advances becomes academic if the effectiveness of therapy is not improved by diagnosis at earlier stages. This remains to be proven.

An example of the increasing effectiveness of treatment is improved 5-year survival rates in white men (53% in 1960; 63% to 74% in 1976 to 1981).[13] These statistics overshadow other, less pleasant realities, such as a racial differential that shows a 54% (up from 24%, 1960 to 1963) 5-year survival for blacks, 1976 to 1981, compared with 74% in whites. Also, despite improved survival, bladder cancer is a recurrent disease. This factor affects the quality of life but is not evident in survival statistics. These issues, notwithstanding the survival rates, probably do not reflect newer improvements in treatments, such as the use of intravesical instillation of adriamycin and Bacillus Calmette Guérin immunotherapy.[14–18]

Based on the analysis of differences in survival rates between patients treated for localized disease and patients treated for more advanced disease, Hill,[19] in Canada, estimated that a 13% reduction in mortality rates could be achieved in the general population by early detection. Such an analysis suggests that reductions could be greater in high-risk populations, because by targeting them it should be possible to initiate treatments in a more timely manner than would otherwise

occur. In addition, this would suggest that black workers also could show significant gains because poor access to health care and the lack of timely treatment lead, in part, to disproportionately poorer survival rates. Improvement in these areas could enhance survival rates for black workers.

Indeed, in light of the potential advances, screening may be too narrow a view of the matter. What may be required is a comprehensive management plan for asymptomatic high-risk persons and groups.[4,6] The question for the 1989 conference was: In reality, have there been significant developments in the areas of epidemiology, pathology, detection, and therapy? Will they have an important impact on what is recommended for high-risk groups?

Regarding occupational and environmental bladder cancer, we have witnessed decades of discovery of bladder carcinogens.[20–25] Although it is most likely that there remain undiscovered bladder carcinogens and etiologic questions, it is well known which major classes of chemicals and occupational groups should be suspected. Emphasis now appears to be on cancer control. Can we effectively utilize the knowledge we have for groups at high risk of bladder cancer? This translates to two specific questions: (1) can we use preclinical markers to define populations at high risk, and (2) can clinical intervention result in decreased morbidity and mortality? The importance of these questions is not only for the clinical outcome, but also for the impact on environmental controls. Screening in occupational groups must be evaluated also in terms of whether or not it indicates any information about workplace exposures that can lead to primary prevention. This is one of the characteristics that distinguishes the considerations of screening in the occupational environment from those in the general population.

Despite almost 12 years of "advances" since the 1977 conference, few screening (or management) programs have been established for high-risk persons. Many of these persons at risk do not know of their risk. Many of the same questions about a paucity of screening data remain.[26,27] The main reason for this impasse is that there have been few validation studies of various detection techniques and no randomized clinical trials to provide data on bladder cancer screening. Are such trials a viable possibility? What form would they take? Is now the time to propose such trials or should other types of studies be considered?

A recent review by both the National Cancer Institute (NCI)[28] and the International Union Against Cancer[29] cited the absence of clinical trial data as the major obstacle to recommendations on bladder cancer screening. As the NCI report indicates: "At this time, there is no general agreement on the extent of the impact of bladder cancer screening in reducing mortality."[27] It appears that if a controlled trial for a screening modality or screening "plus" treatment modality is ever to be developed, it will have to be in high-risk groups such as those discussed at the 1989 conference. Such a trial was recommended at the 1977 conference, but no action has been taken.

Finally, although screening may be appropriate for high-risk groups only, valuable lessons on mechanisms, natural history, diagnosis, and therapy obtained in high-risk groups will pertain to the general population. It is estimated that in the general population there were 40 000 new cases of bladder cancer and 10 000 deaths in the United States in 1989.[13]

The 1989 Conference

Against this history and anticipated future, this meeting had the potential to address the following questions:

1. Which screening tests are effective for early detection?
2. Which tests need validation studies?
3. Does early detection of bladder cancer allow for more effective, less morbid, lower cost therapeutic intervention?
4. Should bladder cancer screening be recommended for high-risk groups and, if so, what should be the content of the recommendation?
5. Should there be a controlled clinical trial to establish the therapeutic efficacy of early detection and intervention for bladder cancer?

We asked these questions against the backdrop of presentations given at this meeting. Some illustrate the specific types of problems that confront government, industry, and labor, and for which recommendations are necessary. These problematic situations range from the situation described by Dr Marsh of a group of workers exposed to the confirmed human bladder carcinogen 2-naphthylamine to that described by Dr Ward of workers exposed to 4,4′-methylenebis(2-chloroaniline), which is an animal bladder carcinogen and, thus, suspect for humans. In the last session of this conference, the audience and the panel were asked to consider all that had been presented and, thereby, attempt to arrive at some recommendations that might meet the needs in the situations described.

Timeliness is essential in addressing the situation, since many persons at high risk have not experienced the average period of latency (20 years; range 4 to 40 years) for occupational and environmental bladder cancer. Efforts should be made to minimize the burden of bladder cancer to persons at risk by bringing the most advanced scientific knowledge to bear on the problem. We took a step forward at this conference by critically reviewing current knowledge and providing conclusions about what is known and by deciding in which direction to proceed.

References

1. State-of-the-art conference on bladder cancer screening. Transcript. Chantilly, Va: ACE-Federal Reporters Inc.; Dec 7, 1977.
2. Friedell GH, Greenfield RE, Hilgar AG. Introduction: urinary bladder cancer. *Semin Oncol.* 1979;2:145–148.
3. Schulte PA, Ringen K, Hemstreet GP. Optimal management of asymptomatic workers at high-risk of bladder cancer. *J. Occup Med.* 1986;28:13–17.
4. Cartwright RA. Screening workers exposed to suspect bladder

carcinogens. *J. Occup Med.* 1986;28:1017–1019.

5. Cartwright RS, Glashan RW, Rogers HJ, et al. Role of *N*-acetyltransferase phenotypes in bladder carcinogenesis: a pharmacogenetic epidemiological approach to bladder cancer. *Lancet.* 1982;ii:842–846.

6. Ellwein LB, Farrow GM, Friedell GH, et al. An assessment of the impact of urine cytology screening using a computer-based model of bladder cancer. *Urol Clin North Am.* 1984;11:585–598.

7. Zoler ML. Note valuable bladder cancer prognostic data obtained by urinary cytology, random biopsies. *Urol Times.* 1984;12:2.

8. Mostofi FK. Markers of bladder cancer. *JNCI.* 1988;80:1184. Editorial.

9. Javadpour N. Cell surface antigens and chromosomal abnormalities in bladder cancer. In: Javadpour N, ed. *Bladder Cancer.* Baltimore, Md: Williams & Wilkins; 1984:75–85.

10. Utz DC, Farrow GM. Carcinoma in situ of the urinary tract. *Urol Clin North Am.* 1984;11:735–740.

11. Hemstreet GP, West SS, Weems WL, et al. Quantitative fluorescence measurements of AO-stained normal and malignant bladder cells. *Int J Cancer.* 1983;31:577–585.

12. Goldfarb M, Shimizu K, Peruchio M, et al. Isolation and preliminary characterization of a human transforming gene from T24 bladder carcinoma cells. *Nature.* 1982;296:404–409.

13. Smart CR. Bladder cancer survival statistics. *J Occup Med.* 1990;32:926–928.

14. Reynolds RH, Stogdill VD, Lamm DL. Disease progression in BCG-treated patients with transitional cell carcinoma of the bladder. (Abstracted.) Presented at the American Urological Association Annual Meeting. May 1985, Atlanta, Ga.

15. Lamm DL, Thor DE, Winters WD, et al. BCG immunotherapy of bladder cancer: inhibition of tumor recurrence and associated immune responses. *Cancer.* 1981;48:82–88.

16. Pinsky CM, Camacho FJ, Kerr D, et al. Treatment of superficial bladder cancer with intravesical BCG. In: Terry WD, Rosenber SA, eds. *Immunotherapy of Human Cancer.* New York, NY: Elsevier-North Holland; 1982:309–313.

17. Marshall MV, Griffin AC. Chemoprevention: a new field with much promise. In: Shaw CR, ed. *Prevention of Occupational Cancer.* Boca Raton, Fla. CRC Press; 1981:175–184.

18. Koontz WW, Jr. Intravesical chemotherapy and chemoprevention of superficial, low grade, low stage bladder carcinoma. *Semin Oncol.* 1979;6:217–219.

19. Hill GB: Epidemiologic considerations. In: Javadpour N, ed. *Bladder Cancer.* Baltimore, Md: Williams & Wilkins; 1984:5–36.

20. Hueper WC. *Occupational and Environmental Cancers of the Urinary System.* New Haven, Conn: Yale University Press; 1969:118–180.

21. Johnson WM, Parnes WC. Beta-naphthylamine and benzidine identification of groups at high-risk of bladder cancer. *Ann NY Acad Sci.* 1979;29:277–284.

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

23. Samuels SW. The management of populations at high-risk in the chemical industry. *Ann NY Acad Sci.* 1982;381:328–342.

24. Silverman DT, Hoover RN, Mason T. Employment in motor exhaust-related occupations and bladder cancer. *Am J Public Health.* 1984;74:52–56.

25. Stasik MJ. Carcinomas of the urinary bladder in a 4-chloro-*o*-toluidine cohort. *Int Arch Occup Environ Health.* 1988;60:21–24.

26. Jacobs R. A review of the effectiveness of urinary cytology as a screening technique for occupational bladder cancer. *J Soc Occup Med.* 1987;37:24–26.

27. Baxter PJ. Occupational bladder cancer and the hospital clinician. *Br J Ind Med.* 1989;46:73.

28. National Cancer Institute. *Cancer Control Objectives for the Nation: 1985–2000.* Washington, DC: NCI Monographs, no. 2, 1986; 29.

29. Prorok PC, Chamberlin J, Day NE, et al. UICC workshop on the evaluation of screening programs for cancer. *Int J Cancer.* 1984;34:1–4.

The Packaging Challenge

We create a huge industry putting food in cans for dogs, and then allow people to "take them for walks" so that they can defecate on the public streets. We spend, as a community, nearly thirty pounds per year for each man, woman, and child, on packaging materials, and occupy some of our most lively minded citizens to design and manufacture the packages—then we find them littered over our beaches and countryside, and use nineteenth-century methods to remove them from our homes.

—From *Dirt: A Social History as Seen Through the Uses and Abuses of Dirt,* by T. McLaughlin. New York, NY: Dorset Press; 1971;167–168.