Final Discussion: Where Do We Go from Here?

Moderator: William Halperin, MD. Panel Members: Raymond A. Cartwright, PhD; George M. Farrow, MD; Leon B. Ellwein, PhD; Thomas J. Mason, PhD; Fathollah K. Mostofi, MD; Charles R. Smart, MD; Willet F. Whitmore, Jr, MD.

The purpose of the concluding session was to reach consensus among conference participants on a strategy for screening high-risk occupational groups for bladder cancer and to define areas where views were divergent. To reach this goal, in preparation for the conference, the organizers (Drs Halperin, Schulte, and Ward) developed a simple model that defined several situations in which screening might be used and chose screening tests for those situations. After listening to the conference sessions, the organizers modified the model. On the final morning of the conference two of the organizers (Drs Halperin and Schulte) met with a panel that the organizers had chosen from among the conference participants to discuss the model and modify it, based on the comments of the panel members. In the final session of the conference, the model was presented to all participants. After remarks by the panel members, comments were made by other participants. A transcript of the session, edited for style but not substance by the conference organizers and circulated to panel members and other conference participants who had commented from the audience, is presented here.

While these comments should help clarify what the following pages represent, several disclaimers would be appropriate. First, an often-heard phrase, the views presented here are those of the participants and not necessarily the institutions with which they are affiliated. In particular, the views do not represent the policy of the National Institute for Occupational Safety and Health (NIOSH), the institution that sponsored the conference. Second, response to the strategy presented here and development of alternatives might have been different had the conference participants been different. By and large, the participants were scientists, not ethicists, lawyers, economists, risk assessors, or decision theorists.

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Opening Remarks

Dr William Halperin: Emphasis on the value of screening should be both a salutation and a valedictory for a conference on screening. The value in screening is in its role as prevention of occupational disease.[1] There are three kinds of prevention; when we think about the efficacy of screening in prevention, we have to think about the three kinds of prevention.

This conference generally has dealt with secondary prevention. Secondary prevention is the early detection of disease, before the onset of clinical signs and symptoms, at a stage when the disease is reversible or more easily treatable. The beneficiary of secondary prevention is the patient who is found to have treatable or reversible disease on screening. Secondary prevention is the usual role for screening tests when employed by public health practitioners in the community or by clinicians doing periodic examinations. This is the usual clinical mode of thinking and is familiar to us as clinicians.

Screening also has a role in primary prevention. Primary prevention involves an intervention that precludes the initiation of the disease process; for example, immunization against infectious disease, or, in the occupational setting, control of exposure. One difference between screening in the community and screening for occupational disease[2] is the potential for screening data to lead to reduction of exposure, which is primary prevention. Use of screening data for primary prevention requires that the data for all those screenings be tabulated, and not simply added to each patient's medical record for his [or her] personal benefit, which is adequate for secondary prevention. There are various ways in which results of screening programs may be useful in primary prevention. For example, detection of a positive result may suggest that there are failures of control of exposure to a known hazard or that a suspected hazard should be more adequately regulated. Many occupational diseases have long latencies, particularly cancers, so that the earlier there is recognition that control of exposure is inadequate, the earlier controls may be instituted and the initiation of the disease process prevented. In this context, it is not necessary that the disease be more easily treatable or reversible, although that would be desirable. The beneficiary of screening is everyone exposed to the occupational blad-

der carcinogen, if the screening program leads to a reduction in exposure.

The third type of prevention, tertiary, is the appropriate clinical care of persons with disease, whether it be clinically evident at the time of detection or found by screening techniques. As new therapeutic methods are developed that are more effective in early stages of disease, so change the incentives for early detection for the purpose of treating the patient. Hence, tertiary and secondary prevention are linked. There is a relationship between clinical care and primary prevention. It is often the astute clinical practitioner who recognizes that there is an excess of disease in a population, which on further evaluation leads to the recognition of a hazard. The collection of clinical data from an occupational population, and their analysis, may lead to screening of the work force both for reasons of secondary prevention, that is, to benefit the person screened, and for purposes of primary prevention, that is, to determine whether or not control of exposure has been adequate. The collection, analysis, and use of health information, whether it be clinical data or screening results, is known as surveillance.

The model is presented in the Figure. Exposure has been dichotomized into "high," suggesting levels that have been encountered in occupational situations where the hazard is present in concentrated form, and "low," suggesting well-controlled occupational exposure or environmental exposure where the hazardous material has been diluted in the environment. On the other axis, carcinogens are dichotomized as "known," for which there is a body of data demonstrating that the agent is a human carcinogen, and "suspect," based upon toxicological studies, structure, etc. Toluidine is an example of a suspect carcinogen, since there are experimental evidence of carcinogenicity and structural similarities with known carcinogens; β-naphthylamine is an example of a known human carcinogen. Dichotomizing carcinogens into known and suspect and exposure into high and low provides four situations for discussion of strategies.

The first category is known carcinogens at high levels of exposure. The panel agreed that there should be cytologic examination and a red blood cell (RBC) analysis every 6 months. Because this category is for known carcinogens, doing RBC analysis for low-grade tumors to provide data by which to define the substance as a carcinogen is not an intellectually plausible argument.

Known Carcinogen	Suspect Carcinogen	
Cytology every 6 mo RBC test every 6 mo to ensure acceptability	Cytology every 6 mo RBC test every 6 mo to catch low-grade tumors	HIGH EXPOSURE
Cytology after 2 yrs then every 5 yrs	Cytology depending on circumstances	LOW EXPOSURE

Figure. Scenarios for screening programs. Educational and psychosocial support would be included in each scenario. Frequency of screening would be modified depending on the degree of exposure, strength of carcinogenicity, and latency since first exposure.

The exposure is de facto to a known carcinogen. So why include RBC analysis, which is likely to identify low-grade rather than aggressive tumors? The answer is a practical one based on the experience of conference participants. In a screening program that uses cytology but not RBC analysis, the likelihood of low-grade tumors being missed by the screening is high. The discovery of these tumors may reduce confidence in the screening program. We opted, as a very practical step to ensure the acceptability of the screening program, to include RBC analysis in the category of high exposure to a known carcinogen.

For suspect carcinogens when exposure is high, the screening approach should be cytologic examinations and analyses for RBCs at 6-month intervals. The rationale for the analysis for RBCs is to detect low-grade tumors. The motivation for seeking the low-grade tumors is both to provide information by which to define whether there is human evidence that the suspect carcinogen really is a carcinogen, which may lead to its control—primary prevention—and to benefit the person tested—secondary prevention. Within this category, the panel agreed that level of exposure and latency, interval from first exposure to the date of screening, should be used to modify the frequency of screening. The panel also agreed that for every category there was a need for education and psychosocial support for the population, not just for those who were offered and agreed to screening. The third situation is that of low-level exposure to a known carcinogen. The panel concurred with a recommendation for cytology at more infrequent intervals than for high-level exposures to known carcinogens. For example, after initial screening, screening could be repeated after 2 years, and then at 5-year intervals. The frequency of the screening should be based on available information concerning the known carcinogen. These recommendations suggest a less intensive screen that is used to search for disease in a high-exposure occupational group. RBC analysis on voided urine is not recommended for this category. This recommendation is based on the expected low incidence of disease in a population exposed at low levels and the consequent prediction that most persons found to have RBCs in their urine would not have a cancer associated with the exposure of interest.

The last category is low-level exposure to a suspect carcinogen. The panel was equivocal on whether there should be any screening. Screening was expected to be of less value to the population than education and psychosocial support of those persons with low-level exposure. The panel suggested resources that might otherwise be used for screening in this population be directed to studying a population with high-level exposure to the same agent, in an effort to determine whether the agent is a carcinogen. Surveillance for disease in the community would also be appropriate. A finding of increased rates of disease would lead to increased screening efforts.

These recommendations are narrowly focused on the decisions whether to utilize cytologic and RBC screening techniques. Screening, however, must be seen as only

part of a continuum of techniques useful for the prevention of occupational disease. For example, in each scenario presented, it is assumed that efforts for primary prevention, such as control of exposure and environmental monitoring, would be in place. Because the populations of concern will already have had exposure, it is assumed also that educational efforts and other psychosocial support efforts[3] will help to ameliorate the social and psychological consequences that accompany recognition that a population has been exposed sufficiently to a known or suspect carcinogen to warrant screening efforts. Also, it is assumed that the recommendations must be modified according to the particular situation. It is expected that higher levels of exposure, and exposure to more potent carcinogens, will lead to more intense screening efforts.

Dr Raymond Cartwright: I have two additional points to make. The elements of an effective screening program are twofold. One element is the screening test or method. I showed that in a high-risk population, the Papanicolaou method can create lead time. However, in that particular study, the experience of death came to the exposed population very quickly. That was the result not of the failure of the test but of the failure of therapy. Any screen must be accompanied by effective therapeutic regimes.

Second, I want to emphasize the point that bladder cancer in these circumstances is two sorts of disease—one I'm interested in; the other I'm not interested in. I'm not interested in superficial bladder cancer, which seems to me to be well controlled and treated when it appears symptomatically or by whatever means. I am interested in the invasive lesion that kills people. This seems to be a different beast from the other sort of bladder cancer. To my way of thinking, what we're looking for is the invasive disease because that's the one we want to prevent to stop the mortality.

Dr George Farrow: I would like to say from the outset that I would be interested in seeing a screening program implemented, but only as an investigative project, not necessarily with the hope of providing early intervention and reducing cancer mortality. I think that bladder cancer is really not the optimum disease for a screening program. For one thing, much of the disease does not have serious consequences, making it difficult to offer to a cohort of screenees the hope of some reduction in mortality. In addition, we've heard that there is not really a very good screening test available for the low-grade, low-stage form of the disease. Urine cytology or quantitative immunofluorescence assay (QFIA) is a very good test for the high-grade or lethal form of the disease.

Finally, the thing that concerns me the most about bladder cancer is the fact that we don't now have a handle on a high-risk population. We can say that people who work in a chemical factory are at very high risk, but unfortunately the majority of these people, at least from the data that I'm familiar with, have gotten their cancers, in most instances, after they've terminated their employment, usually through retirement, and are living in Arizona or Florida and are not readily amenable to or accessible for screening. Any screening program would have to take into account those people who were employees in the factory or the chemical plant but who have terminated employment. They would have to be accounted for in any cohort until death or perhaps until they were well into their 70s or 80s, to get an idea, even in an investigative way, of the true incidence of cancer in that group.

[Unidentified Panelist]: I believe that there is one disease. Some of them progress on to superficial malignancies that are invasive or noninvasive. The noninvasive can become invasive and the invasive superficial can become deep, and the deep can kill. Therefore, I don't really know that not looking for more superficial ones is beneficial. I would be inclined to screen for bladder cancer whatever it is, whatever its type.

[Unidentified Panelist]: I share Dr Farrow's position. Screening programs should, overall, be regarded as still investigational. I am not saying that such investigations should not be pursued, but I think that screening programs should be regarded as investigational. I have several reasons for my uncertainty. First, I'm not convinced that screening has a favorable effect on survival. Our experience with superficial bladder tumors indicates that our results are very good in the management of these tumors. It is true that some progress and do give rise to a population of killing cancer. We do not know how to predict that progression and until we do, we are not going to be in any better position to handle the diagnosis of the disease in the screening participants than we are in the patients who are symptomatic at presentation. I do not see any convincing evidence that we are going to improve the survival with superficial disease. As far as concerns patients with deeply infiltrating tumors, I think that there is a prospect of recognizing this disease at an earlier stage, but when we define it at an early stage, it becomes superficial disease and then we are faced with this uncertainty about how it is to be treated and whether it is the type that is going to be progressive. So, we are just compounding our problem in the management of superficial disease by diagnosing the killing disease earlier.

The other thing that is lacking is an estimate of the proportion of patients with occupational cancers who present with superficial *v* invasive disease. If patients with occupational cancers have superficial disease, then there is no special problem. Wait until they have symptoms, and treat them. I do not see any palpable evidence that they are going to be any worse off than if detected by a screening test.

Relative to the point that Dr Farrow made regarding workers developing bladder tumors long after they retire, I think that it would be helpful and practically useful to have information on the relationship of bladder tumor incidence, level of exposure, and latent period. If the latent period for a certain level of exposure indicates that the median time to development of a tumor is 8 to 12 years, the screening program should be started 5 or 6 years after a person begins to be exposed.

Dr Leon Ellwein: I like the point about primary and secondary prevention. For secondary prevention we

need to focus on the high-grade lesions. Cytology is certainly a candidate for that. Considering low-level exposure, when screening for the purpose of primary prevention, if you are screening in the environment, you might as well use age and sex as predictors and then choose older white men who smoke. They will have as high a risk as any other group we can find. When screening as an early warning in an occupational setting, I think the problem arises when we start to pick up some early cases. The next questions, of course, are: What's the culprit? What's the agent? Is there going to be consensus on it? Can we remove it? Then we get into a new set of issues and problems that are bigger than the ones we started out with. In trying to look all the way down to the end in terms of action that changes something, we're just asking for a whole other set of issues and problems. One final point relating to molecular biology and the promising new techniques and methods to find change even earlier. If we find change too early we only give ourselves another set of dilemmas, another set of questions. This is particularly true if we tell a urologist, "This patient is positive," and the urologist performs cystoscopy on the patient and can't find anything. We are then faced with all those persons who are positive on screening but negative on clinical examination. I don't know what we'd do with them—perform cystoscopy until we actually find something or until the patient gets upset and leaves us, I suppose. These are some of the remaining issues. None of them, of course, is clear and they don't really have any answers.

Dr Thomas Mason: I'd like to pick up on two points. Obviously, as an epidemiologist, I am interested in what data are required. I would argue that what is sorely missing is a uniform, readily accessible, and verifiable minimal set of information on persons likely to have been exposed such that we can, indeed, pool across a number of occupation-exposed cohorts. I believe in the concept of screening among persons at high risk. I believe in the concept of chasing that tail of the distribution looking for an indication of a response. Most chemical carcinogens are dose dependent in initiating tumors; however, there are some very curious things with regard to bladder carcinogens—there are some big differences between the benzidine-exposed and the β-naphthylamine-exposed and workers exposed to other compounds. What we really need is a consensus regarding an approach with comparable, not necessarily exactly the same, protocols being followed. Each protocol should include the same core set of information to facilitate follow-up. If the bottom line is mortality, there should be a way never to lose track of cohort members once they're enrolled. If they are in areas with population-based cancer registries, not limited to the SEER network but including other places that have reasonably good incidence registries, they do not have to be lost to us for morbidity. If we keep track of cohort members, we have an opportunity to collect biological materials to pursue the most provocative new advances. I am very optimistic about what has happened in the last 18 months, and I think there are some very provocative questions that we can now address. Also, as an epidemiologist, I am a hoarder. I want biological specimens that I can bank because I don't think any of us are clever enough right now to anticipate the questions that we'll be able to address in the next 5 years.

Dr Fathollah Mostofi: It seems to me that there are two categories of vesical carcinogenic agents: those that are well known to be carcinogenic and those that are suspect. For the latter group, we certainly need additional and definitive data. Such data must be collected before we can make any recommendation. I believe the starting point should be the education of general practitioners and urologists to take a detailed history of possible industrial exposure, not only for the immediate workplace but for many years earlier. Education should also be directed to the public.

Some mechanism has to be established to monitor persons who are working in known industrial risk environments. I understand that immediately after the Second World War the Russians did establish a survey system whereby those working in industries dealing with known bladder carcinogens had an annual urinalysis. If this was positive for blood, these workers were followed by cystoscopic examination and if they had persistent hematuria, they were moved to other jobs. I do not know whether this procedure was actually followed, but some such system might work in the United States. Because everyone should have a complete annual physical examination, this procedure should be practical and feasible, and I hope it can be done.

Dr Halperin: In summary it would appear that there is still general agreement on the strategies discussed earlier (Figure). It would be valuable to recapitulate some of the comments made by panel members. First, screening for bladder cancer should be viewed as a research endeavor whose benefits for persons or for the populations screened are not yet delineated. Second, coordination among researchers conducting bladder cancer screening projects may improve chances of resolving important remaining questions. Third, techniques for screening are evolving; it would be wise to bank serum and urine samples. Fourth, screening programs for populations exposed to low levels of occupational carcinogens, who are probably at low risk, should consider other factors such as age and smoking status, known risk factors for bladder cancer, in selecting participants for screening. Fifth, the natural history of bladder cancer remains unclear; hence, the value to the individual of detecting superficial *v* invasive lesions is unclear. Sixth, recommendations for screening should be tailored to the extent of exposure to the carcinogen and the expected potency of the carcinogen. The frequency of screening should be related to the time since first exposure and should continue after exposure has ceased, even if employment has ceased. Seventh, the efficacy of a screening program will depend on the efficacy of the screening tests and of the therapeutic intervention that is available for those persons found to have disease. Eighth, primary and secondary prevention should be considered as motivations for conducting screening.

Next we will turn our attention to research needs. I will try to summarize suggestions and comments that have been made over the last 2 days. These are shown in the Table. We have heard clearly that we need a series of studies that compare different modalities. With screening tests such as QFIA or Papanicolaou smears and earlier markers, we need clear-cut comparisons of one modality *v* another so we have some idea of sensitivity and specificity of these various approaches. We heard somewhat about biological risk factors. Rather than exposures, these are genetic risk factors, such as acetylator status. Clearly, the amount of research in this area is relatively limited. Natural history of bladder cancer remains to be defined. We do not know what the progression of certain stage and grade disease to other stage and grade disease is. Standardized approaches and collaborative approaches to conducting numerous small screening projects may increase our chances of obtaining information on which to base better informed decisions. Finally, some conference participants have called for a randomized clinical trial testing the value of early intervention for bladder cancer.

Dr Mostofi: I agree with what has been said. I think there is a great need for research. I could talk about the areas of research that we need to do for the early detection of bladder, but I think that we ought to forget about morbidity, mortality, and so forth, and talk about what research we do need to understand the natural history of bladder cancer.

Dr Mason: My primary interest at the moment has to do with enhanced susceptibility and measures of susceptibility to known or suspect carcinogens. I would argue that an area that really needs to be pursued in this is debrisoquine metabolism, because it characterizes individual susceptibility to the carcinogenic effect of cigarette smoking in subsets of the populations that we are working with. I think that much can be learned, and there's no question that cigarette smoking does, indeed, play a role. That, along with acetylation and other such personal characteristics, I think, can be best addressed in these well-characterized populations.

Dr Ellwein: On the research agenda, I think that the first item in the Table, and the way you've characterized it as modality *v* modality *v* modality, is a high priority. This should be pursued, not in terms of randomized trials of each modality, but by doing three or more modalities each time we screen to determine the performance of each with respect to the others in whatever groups we're studying: high risk, low risk, whatever setting. Our goal should be to understand what these tests do, so that if appropriate populations are identified, we will know how our tests stack up when it comes time for deployment.

TABLE
Research Needs

1. Comparison of screening modalities (including early markers).
2. Identification of occupational populations with substantial exposure.
3. Evaluation of risk factors for increased susceptibility:
   - P-450
   - Caffeine metabolism
   - Debrisoquine
4. Clarification of natural history of superficial and invasive tumors.
5. Collaboration to develop standardized questionnaires and methods.
6. Pooling of data.
7. Banking of specimens for further testing.
8. Studies in clinical populations exposed at pharmacologic doses: cyclophosphamide
9. Effectiveness of psychosocial support approaches.
10. Evaluation of the acceptability of and compliance with screening modalities.

Dr Whitmore: It's a little outside the range, perhaps, of screening questions, but I would suggest that epidemiologic studies address the question of whether there are different risk factors for the two types of bladder cancer. I think there are two types, superficial and deep. It's true that the superficial type sometimes becomes deep but most of the deep cancers appear as deep initially, and I think they are different diseases. It may well be that the intensity of the stimulus or the duration of the exposure or some other factor may be different in these two groups. The latent periods may be different and there may be differences in their biology that would dictate different strategies in their follow-up or screening.

Dr Farrow: You could define high risk, actually, in one of three ways. One would be that a group of people exposed to a certain agent have an increased death rate from bladder cancer; that certainly would be a high risk. You could also say that those who get tumors at a much earlier age, although their incidence of the disease is not greatly increased over a control population, are at high risk. When Dr Theriault discussed cases in the aluminum smelting works—although I didn't catch the age of the population—he noted that patients were developing bladder tumors at a much earlier age than one would anticipate. Third, you might say that an increased risk would have to do with developing a more aggressive form of the disease. That is to say, perhaps some types of exposure give you high-grade cancer and others give you low-grade cancer. We know, for example, that cyclophosphamide, which is a well-known bladder carcinogen with more than 40 cases reported, almost always gives a very highly anaplastic, lethal form of cancer and it doesn't give a mixture of papillary and low-grade tumors. That type of information could be part of an interesting investigation that would characterize very carefully those types of cancer with respect to all the parameters that we know occur in occupational situations.

Dr Cartwright: I think there's a very good case now to be made for a continued follow-up of those long-term survivor patients who received cyclophosphamide therapy for whatever reason. We've already started this in a private way, in Yorkshire, in those children who received cyclophosphamide for malignant disease. I think that could be a very useful and worthwhile series of studies. It would have to be done on a national or international basis to get enough numbers to be useful.

Dr Lawrence Fine: NIOSH is in the process of developing guidelines for medical screening for occupationally exposed populations, including those exposed to

suspected or known bladder carcinogens. Although the final guidelines have not been adopted yet, they are likely to recommend screening only when it can be justified on the basis of benefit to the patient. The recommendations in the NIOSH guidelines are likely to be more conservative than those presented in Figure. Specifically, the guidelines will recommend only urinary cytology. However, the NIOSH guidelines are general recommendations for use in small or large populations and under circumstances where screening may not be analyzed from a sophisticated scientific basis.

In reference to the Figure, I'd like the panel to comment on the value of screening tests for the detection of hematuria. Consider the nonexperimental setting, a setting where we're not really doing research, we're not making recommendations because the data will be useful for deciding more about screening or the natural history of cancer, but where we're recommending it as a service activity, a setting that NIOSH and other public health authorities find themselves in frequently. I was not convinced that there really was a solid case for adding screening for RBCs. Using just cytology, of a thousand people you obtain 40 rigid cystoscopies. Once you add anything else, you greatly expand the number of invasive procedures. Given the uncertainty about whether detecting low-grade tumors is, in fact, useful—not from the point of view of research, but in terms of saying to the individual patient, "This is in your benefit to detect these low-grade tumors"—it seems to me that the resources that you have to use in a screening program and the amount of morbidity associated with the screening program itself go up very sizably when you add RBC screening to the protocol. From the comments I've heard here, particularly those of the clinicians, many do not seem very positive about doing RBC screening. Are we at a point, in the nonresearch setting, the service setting, where we want to say that if you're exposed to a suspected bladder carcinogen—and in America this means about 100,000 people—that we recommend RBC screening? Because, as someone on the panel mentioned, if we say *that*, we are really saying to men over 70 who are cigarette smokers that they should do the same thing, because they are clearly at the same level of risk as a 45-year-old who has worked with a suspected carcinogen. I would like some more discussion of how strong the support is for RBC screening.

Dr Farrow: In regard to the sensitivity of various screening tests, the way most of these reports have been put together has been, as in my own case, a one-shot test. A patient came in, a voided urine was obtained, whatever happened to be in his bladder at the time was examined, and the results were correlated with outcome. In a sense, it was like a screening test, only performed on symptomatic patients. On the other hand, if one really wanted to improve the results dramatically, and I think they could be improved dramatically with voided urine cytology, one could concentrate on the patient in a more intensive way. In other words, obtain much better specimens, be certain that they are prepared very quickly and were examined in a very timely manner by a higher level of expertise than perhaps some screening programs have done. I believe that the sensitivity of urine cytology as it is practiced now could be greatly improved. I like the blood test because I think that although it is not nearly as specific, it is, perhaps, a little bit more sensitive in the sense that it picks up disease that urine cytology might not pick up because of restrictions of size or rate. I would like to see some sort of program where the two are done together but in which urine cytology testing would then be concentrated—whether it would include QFIA or some other modality—on those patients in whom non-negative findings resulted from either the initial hematest or the initial urine cytology. I think that once a patient is identified as having an abnormal finding, it's not necessary to go immediately to cystoscopy. I think that's a complete misconception. I think that those patients can be considerably better worked up and categorized before the need for any form of intervention.

Dr Messing: I also like the RBC analysis for its high degree of sensitivity, but I would like to suggest that there's a problem with a very wide-ranging cytology screening program in a population with low yield. It's a very practical problem of dealing with cytology or cytotechnology screeners and cytopathologists who are going to be looking at negative specimen after negative specimen after negative specimen and who will soon be lulled into a kind of never-never land where they're going to miss the very rare specimen that's positive. To avoid that, I would suggest that a two-tier system of screening be considered in which RBC search was done first and those persons who had microhematuria, and only those persons, perhaps on one of three tests, if necessary, go to cytology. If the cytology is positive or suspicious they then go for investigation of possible bladder cancer. If it's negative, one might want to repeat the test, maybe a month later. If cytology is still negative, then I would suggest that they be referred to a physician to look for causes of hematuria unrelated to possible bladder cancer.

Dr Melamed: Would you like to comment on the issue of home analysis for RBCs, given the issue of lulling the laboratory practitioner into the expectation of negativity?

Dr Messing: You mean the question of whether looking for microhematuria would face the same problem?

Dr Melamed: Might the person being tested be more careful in looking for a positive on the dipstick than the laboratory workers on the urine sent there?

Dr Messing: I'll answer the last question first. We've done this too many times now. It's not only me, there have been articles for the past 20 years. There are articles every year in the throwaway medical journals that say, "is microscopic urinalysis ever needed, since the dipstick is just as good?" Paper after paper says that if you are just looking for hematuria, the dipstick—be it Ames, Boehringer-Manheim—is just about as good and in many ways much more accurate than other methods.

In addition, in our study in our prepilot training, the only factor that demonstrated that someone couldn't do a dipstick test was a postgraduate degree. Everyone

else who read the instructions got it right, including very elderly, very feeble people. As long as you could see you'd get it right. The second you start to think about it and try to outsmart the test, it's a big disaster. So I think there is no question that most people could do it as accurately as someone who is specially trained.

Finally, there's the issue of expense. These dipsticks can be bottled in another way. If enough people are doing it, you can probably get five for a dollar rather than the $15 it costs to do a microscopic urinalysis in Madison. There's an issue of how repetitive hematuria testing is, that there is a minimum number of negative tests above which you don't have to work someone up. But if you wait for a urinalysis to confirm your positive dipstick test, I think the evidence is again overwhelming that that's going to be a potential problem.

In answer to whether hematuria should go, I guess I agree with Dr Farrow that it really would be more sensitive than the single cytology. Cytology tests, depending upon what part of the country you're in, cost a lost of money to do and have potential problems. I know that in a big study you can get a reduced fee, but no one in the whole conference has addressed expenses but obviously they are not small issues, particularly when we've heard about testing textile workers and how companies are hesitant to foot the bill for a lot of things. They are certainly going to be more hesitant to foot the bill for a bigger expense than for a lesser one.

I want to ask Dr Whitmore one thing, because I've always respected you and I'm just a little surprised to hear you say that we're not sure what to do with superficial bladder tumors and heterogeneous disease. And that in some people it probably won't make a difference and in other people it progresses. While this is all true, I think it would be hard to deny, particularly when many of the data come from your own institution, that virtually all muscle-invading and deeper bladder cancer arises on the urothelial surface. That doesn't only come from your institution but from common sense. If you detect it at that stage it probably is not terribly different from that small percentage of high-grade or anaplastic superficial disease that we now occasionally are lucky enough to find early. For those patients, with standard treatments—transurethral resections, thiotepa—70% progress to muscle invasion or death within 5 years. Intravesical instillations, particularly with BCG and our awareness, have markedly reduced that rate. I think there *is* a treatment for the tumor that's destined to become invasive, before it's invasive, if it could be caught. I don't think I'm being overly biased by saying that.

Dr Whitmore: I prefaced my remarks about the superficial tumors by saying that I was making general remarks about a heterogeneous group of tumors. For example, the high-grade T1 lesions have a distinctly ominous prognosis and we tend to handle them more aggressively, although there are exceptions in the management of those as well. I don't mean to imply that there are no guidelines for the more aggressive treatment of superficial tumors. I'm simply saying that for many of these lesions conservative therapy is adequate, although there is a large range of variation in physician opinion regarding the definition and management of these lesions.

Dr Robert Hurst: I think we need to go back to first principles. I'm hearing a lot of comments that indicate that people are viewing us as being stuck where we are, as opposed to doing the research to get us where we need to be. Study after study, for example, has shown that most conventional screening approaches detect muscle-invasive disease too late. There is a small percentage, as Dr Messing mentioned, in which the urologist is lucky enough to find it, and these probably result in cures. Clearly, an important area of research is the identification of potentially muscle-invasive disease in a preclinical phase. This is clearly not done effectively by conventional approaches with cytology or hematuria. Whether this is the fault of the test or the way it is being used is not clear. Along with this—and although I am sympathetic to Dr Whitmore's dilemma of what to do with patients who are positive on a screening test in whom no disease can be detected—my sympathy is tempered by the knowledge that ultimately achieving cures must address this group of patients. BCG with carcinoma in situ has certainly given us the hope that this group can be dealt with. If they are identified, I think this will drive studies of how to treat them effectively. For example, would BCG be an effective treatment for dysplasias? Would retinoid therapy be an effective treatment for these kinds of early biochemically defined lesions? I don't know. Our inability to effectively identify these people precludes effective clinical trials.

Second, low-grade tumors need to be detected and healed. For one reason, 10% to 20% progress. That's a small percentage, but of a large number of patients. Low-grade tumors are probably the largest group of bladder cancers. So, 20% of that group is not an insignificant number of people, and detecting patients likely to progress is important to reducing mortality. Besides that, detecting a low-grade tumor at an earlier stage minimizes the morbidity that results. If it can be removed by endoscopic means as opposed to open surgery, I, as a potential patient, would much prefer endoscopic removal to resection or extensive surgery.

A recurrent tumor probably arises within a field of damaged urothelium. Thus, we need to understand field disease much better and to be able to predict from the biochemical characteristics of the cells from the damaged field the likelihood that a recurrent tumor will be more highly malignant. Certainly, we also need, if we are going to develop screening programs, objective quality-controllable, machine-sensible approaches. Machines do not get bored by looking at large numbers of negative samples. Finally, I believe, we need endpoints other than mortality to measure detection and treatment efficacy. If we could find some objective biochemical or cytological criteria we could get answers earlier and we could get answers with smaller numbers. I noticed that for a clinical trial on bladder cancer screening, Dr Smart would require, as best I could read, 750,000 people. That's quite a considerable number, and I don't think it's one that is realistically achievable in any way. The

numbers certainly could be reduced by finding other kinds of endpoints.

Dr Ringen: Some very practical things should be noted with regard to the large groups of workers who have been exposed to bladder carcinogens. They deserve better medical care than is being offered at the present time. When we deal with asbestos workers, we are practical about criteria for screening and surveillance. We decide that 20 years has to have elapsed since the worker's first exposure, we limit the number of tests that they can get, and so on. We have to do these things for cost reasons. We can do the same thing for populations exposed to bladder carcinogens, if somebody is willing to make some practical, epidemiological decisions about who's really at risk in these populations. From the Augusta project and other US projects and Dr Cartwright's experience in England, we have a pretty good idea about who we want to follow within these populations. I think most reasonable people are prepared to agree on a protocol, much like the one Tom Mason has put together, as a reasonable standard. This protocol would first use the basic dipstick analysis and then a more extensive cytometric analysis or something like that to follow up before you go into any kind of cystoscopy. With regard to new studies, I would like to make two points. We have an awfully hard time sustaining the studies that we have already started. In fact, at this time, nobody is following those workers in Augusta who had positive cytology and positive cytometry. The Public Health Department in Augusta is supposed to be doing something, but we know it's not doing a decent job of it. It seems to me that we have a responsibility to continue those studies for the sake of the workers and for the sake of research: we can learn a lot from following these existing populations. Consider the remarks that Dr Hurst and Dr Whitmore made about people already identified cytometrically or cytologically as being positive or atypical. It seems to me that we ought to try to make recommendations regarding therapy as well as following them. Let's do something for these workers, because if we don't, in all likelihood, they will end up being diagnosed at a very late stage.

Finally, I think that doing more case-control studies is very important. There is one particular type of case-control study that virtually has not been done in bladder cancer. We need case-control studies for risk factors for secondary prevention. When Dr Smart presented his data on black and white differences for bladder cancer, some startling things stood out. Part of the reason for the relatively low incidence rate among blacks must have to do with detection. Blacks don't get bladder cancer detected as readily as whites. I believe that the reason we've seen an apparently much more rapid growth recently in the incidence of bladder cancer among blacks is that blacks have gradually improved their access to medical care. At the same time, the higher mortality rates among blacks compared with whites has to do with the response of the medical care system. The medical care provided to blacks appears to be of lower quality than the medical care provided to the white population in general. This does not necessarily all have to do with racial discrimination; it may be due to socioeconomic issues as well. I think what we see in the black population is something that we would see in the low-income white population also, if we had data on the low-income white population. Another important area of research might be to use the tumor series of the National Bladder Cancer Project that was started in the late 1960s. It is unfortunate that they collected these enormous tumor series without collecting risk factor data as well. Nevertheless, I still think that there is something in those tumor series and that it would be worthwhile going back and determining whether one could identify risk factors—why the disease occurred in these people and what kind of medical care was given. Such analyses may not be possible, but it's something that nobody has tried to follow up on.

Dr Melamed: In terms of the value of cytology for detection of carcinoma in situ, I think we should point out that the disease, to my knowledge, was never diagnosed or found in the absence of coexisting invasive cancer until cytology was used as a technique to examine patients. It's a very effective technique. I recognize the limitations of cytology as well as most, but it's a very effective technique for identifying carcinoma in situ and we shouldn't dismiss it.

With respect to low-grade papillary tumors and the importance of their detection and removal for the prevention of invasive cancer, it's clear that invasive cancers, for the most part do not come directly from those papillary tumors. The papillary tumors are signals of a urothelial abnormality and high risk of developing invasive cancers, but you do not remove the likelihood of invasive cancer appearing elsewhere in the bladder when you remove a low-grade papillary tumor. So, the detection importance in terms of preventing morbidity and death is to identify the appearance of a high-grade lesion, whether it is associated with that papillary tumor, independent of it, or elsewhere in the bladder, and that involves screening the high-risk patients, I think, primarily with cytology. The screening programs that are planned here do not address the question of prevention of death from disease. We can do all of these screening programs as they've been outlined and we will never know whether the screening has done any good at all. We'll find some patients with disease; we'll either cure them or we won't cure them; we have nothing to compare them with. So, we get nothing in terms of patient benefit information from these screening programs.

The other reason for carrying out the screening programs is to assess the value of screening techniques in terms of how effective they are for detection of disease. I think we have to understand that we know quite a bit about exfoliative cytology already. There's been a 30-year history of its use. It's been applied in many institutions. The data that we have from these places are consistent. We know a lot about cytology and its successes and failures in cancer detection. The techniques that are new and about which we may get information from applying them in a screening test—and I include QFIA and autocrine motility factor among those tech-

niques—are better evaluated in a situation where there is a large expected population of disease, not in a situation where you're going to detect two to three cases per thousand. They ought to be applied and evaluated in a situation, perhaps a hospital population, where there are patients with a history of tumor, an expectation of recurrent tumor, and control populations with known non-neoplastic disease in large numbers, and the opportunity to repeat the test a sufficient number of times so that there is good evidence of the value of the technique before one goes to the expense and trouble of using it in a detection program where it may not give you any information at all in terms of sensitivity because you're looking at only two or three cases per thousand. That doesn't make sense to me.

Mr Eric Frumin: I would like to respond to the dilemma that was posed earlier by the clinicians who say, "Goodness, if we find this out then what do we do." This is a problem in occupational medicine and in prevention; these are not neatly described circumstances over which one has much control. One just fastens one's seatbelt and goes for the ride. If one is going to be presented with social problems or clinical difficulties in terms of making recommendations to patients, so be it. From the perspective of the workers who are confronted with the unknown, having been told that they are at risk, they need some concrete guidance, as best as that can be, and I'm encouraged by this discussion this afternoon: after lo, these many years of awaiting such guidance, we're getting there.

I think one research need that should be addressed is the extent to which screening methods and the organization of screenings deal with the behavioral issues and not just the laboratory issues. These detailed clinical issues are very important for the patients involved and for the clinicians, but we have major behavioral questions that need to be addressed. Something tells me that when we look back 5 years from now, that we're going to find the answers to the laboratory questions before we find the answers to the psychosocial questions: how do you get people to cooperate and participate and show up and not refuse the more advanced methods that we are making available to them, and how do you overcome their fears of disease? If we can, at the same time as we still don't know how effective by measures of mortality the screenings are going to be, go forth with what we *do* know and try to look as objectively as possible at the important behavioral questions, then we'll be prepared to use these screening methods that we're putting so much time and effort into developing, when they're ready.

Dr George Hemstreet: I support the remarks that have been made about the detection of low-grade papillary lesions and believe that urologists are equipped to handle these lesions in a systematic way. In the past 5 years, remarkable advances in immunotherapy for carcinoma in situ have impacted significantly on the nonsurgical management of these lesions, with initial response rates of 75%.

Regarding the model presented by Dr Ellwein, probably most urologists in this room would agree that immunotherapy and systemic chemotherapy are altering patient survival rates, but these are not reflected adequately in current survival data. Because it may be 5 to 10 years before we have another consensus conference, we should assume an aggressive posture regarding screening programs based on the current and projected effectiveness of bladder cancer therapy rather than on survival rates of 5 years ago. For that reason, I strongly support some of the remarks of our National Cancer Institute colleague, Dr Smart, who seems to have intuitively put his finger on the "magic button." Bladder cytology—whether it is conventional Papanicolaou or machine-sensible QFIA—is more sensitive than and equally as specific as any test used in most screening programs, including mammography, Hemoccult, and cervical cytology. The best positive predictive value will be reflected in high-risk cohorts such as occupationally exposed persons and smokers over 55 years old. We can predict that the cost of screening will be markedly reduced over the next 3 to 4 years with high-speed automation and the development of gene probes. The end result will be more effective control of this disease just as we have experienced with breast and cervical cancer. With regard to testing persons for hematuria, I support Dr Messing's multiple dipstick approach. Undoubtedly, we are currently missing some low-grade tumors with conventional cytology and QFIA, but this will improve with the addition of monoclonal antibodies, which can be integrated into automated systems. Final evaluation of sensitivity and specificity of these new markers will require an additional 2 to 3 years.

Epilogue

Over the past decade, we have been involved in numerous epidemiologic investigations of populations exposed to known or suspect bladder carcinogens. Concurrently, we have been asked for advice by others responsible for the medical care of populations similarly exposed, and our opinions have been sought on drafting regulations for the screening of workers exposed to suspect or known bladder carcinogens. If no other facts are secure, it is clear that many issues having to do with bladder cancer, notably the natural history of the disease and the efficacy of alternative screening modalities, are not certain.

Hence, in 1987 we determined that a state-of-the-art conference on bladder cancer was in order. We come away from this conference with the realization that this was a valuable endeavor and that it should be repeated at intervals. More specifically, we are impressed that occupational populations exposed to known and suspected carcinogens exist, that although it is not proven that screening will be to their benefit, they clearly should not be ignored. They deserve information and education about their situation, and given the optimism about improving therapy and new diagnostic techniques that are within our capacity, these populations deserve the opportunity to participate in screening programs. As has been so well described by others at this confer-

ence, these screening programs should not be offered with the assurance that they offer medical benefit, but rather they should be presented realistically as service projects and conducted with scientific rigor so that a body of information can evolve that will make it possible to determine whether these programs offer benefit to the workers exposed.

This ongoing effort will require continued interchange, sharing of protocols and new screening tests, and periodic meetings among researchers in the field. Specifically, studies should plan to use multiple modalities for screening, and each study should have an intrinsic longitudinal component so that the long-term consequences of test results can be interpreted. Collaboration clearly is necessary with colleagues who are conducting similar studies in clinical populations that have been exposed to suspect bladder carcinogens at pharmacologic doses. We look forward to progress in prevention of bladder cancer through secondary prevention and to our next meeting, which we are planning for 1995.

Paul Schulte, PhD
William Halperin, MD, MPH
Elizabeth Ward, PhD

Cincinnati, Ohio, 1990

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