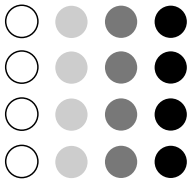


Defeating Prostate Cancer:
Crucial Directions for Research

Report of the Prostate Cancer Progress Review Group

August 1998

NATIONAL® CANCER INSTITUTE

FROM THE CHAIRMEN:

It is with great pleasure that we transmit the Report of the Prostate Cancer Progress Review Group to the Advisory Committee to the Director of the National Cancer Institute. This assessment of the Institute's progress in prostate cancer research was undertaken at the request of Dr. Richard Klausner, Director of the National Cancer Institute.

The overall goal of the Review Group was to develop a national plan consisting of a description of ongoing scientific activities and investigations relevant to prostate cancer and to provide to the Institute a list, in priority order, of scientific opportunities that should be pursued.

As co-chairs, we were pleased to serve with a committee of prominent members of the scientific, medical, industrial, and advocacy communities. Our colleagues represented the full spectrum of expertise needed to develop the comprehensive recommendations you will find in this report. We believe the hard work of this Review Group, which began its work in April 1997, has resulted in recommendations that, if pursued, will do much to eradicate morbidity and mortality due to prostate cancer, the leading site of new cancer cases and the second leading cause of cancer deaths in men in the United States.

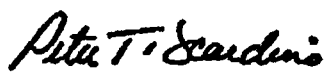
Our comprehensive assessment of the status of prostate cancer research, the depth and breadth of the Institute's investment in this research has provided us with a wealth of new scientific opportunities. We believe that this was, indeed, an opportune time to reassess the Institute's prostate cancer research portfolio and plan a research agenda for prostate cancer that will guide the prostate cancer research field into the next decade. We look forward to following the progress of the many recommendations made in this report and would be pleased to discuss our findings with the leadership of the National Cancer Institute.

Respectfully,

Donald Tindall, Ph.D.
Co-Chairman
Prostate Cancer
Progress Review Group

Peter Scardino, M.D.
Co-Chairman
Prostate Cancer
Progress Review Group

We the undersigned members of the Prostate Cancer Progress Review Group concur with the enclosed report.



Peter Scardino, M.D., Co-chair, PRG

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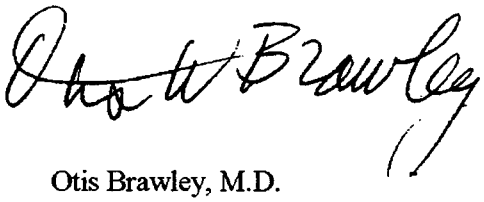

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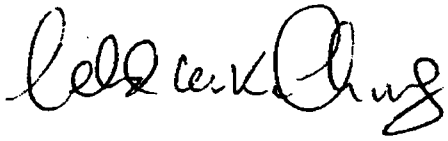

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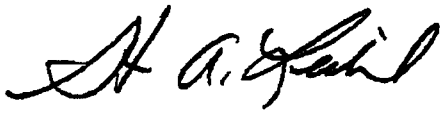

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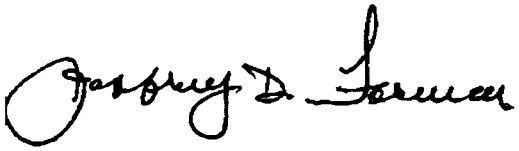

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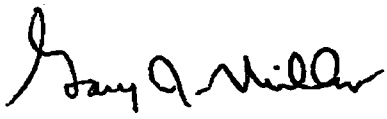

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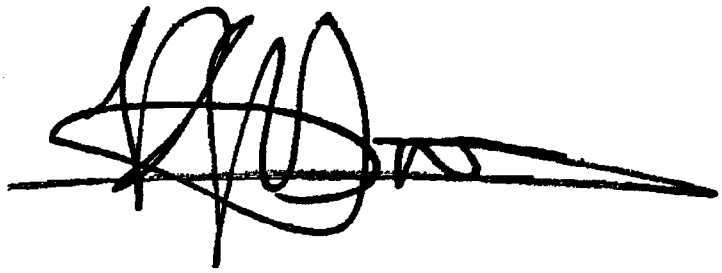

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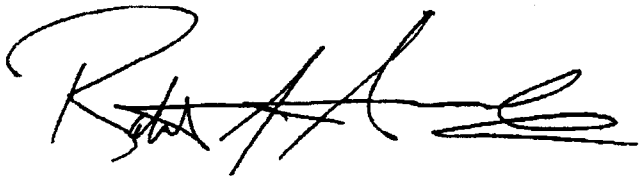

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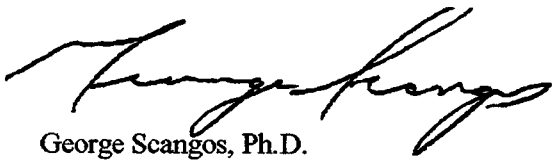

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We the undersigned members of the Prostate Cancer Progress Review Group concur with the enclosed report.

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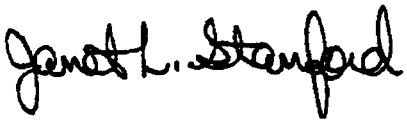

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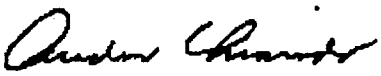

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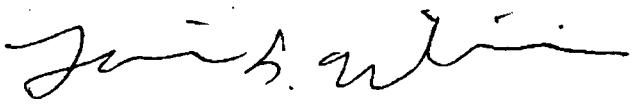
Executive Director, PRG



Lewis Williams, M.D., Ph.D.

ACKNOWLEDGEMENTS

Dr. Andrew Chiarodo served as Executive Director of the PRG and provided the crucial link between the members of the PRG and the members of the NCI Task Force. The work of the PRG would have been infinitely more difficult without Dr. Chiarodo's dedicated involvement.

The Progress Review Group benefited from the exceptional staff support and expertise of the Office of Science Policy (NCI), including Ms. Cherie Nichols, Chief, Office of Science Planning and Assessment; Dr. Susan Rossi, Senior Program Analyst; Ms. Kate Nagy, Program Analyst, Ms. Valerie Sasser, Program Analyst; Mr. John Tuskan, Program Analyst; Ms. Annabelle Uy, Secretary; and Ms. Marilyn Duncan, Program Assistant.

The members of the Task Force did an outstanding job with the large and complex task of reporting on the NCI research portfolio and the information they provided was central to deriving the estimates of funding support for the research topic areas of the PRG.

In addition, the PRG was fortunate to have the outstanding scientific writing expertise of Dr. Kathi Hanna and Dr. Miriam Davis. The United Information Systems (UIS) group provided excellent technical support to the prioritization effort and lastly, Ms. Sally Marshall provided gracious and helpful logistical support on behalf of the Cygnus Corporation.

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EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States. In 1997, an estimated 209,900 new cases of prostate cancer were diagnosed, and 42,000 men died of the disease. Despite significant advances in diagnosis and treatment, many patients still suffer from the sequelae of unresectable disease, including debilitation, pain, and premature death. The continuing challenge to the scientific and medical communities, therefore, is to develop successful preventive strategies to reduce the overall incidence of prostate cancer and to develop effective early detection strategies for all men and appropriate treatment strategies for men with prostate cancer, especially those with advanced lesions.

The National Cancer Institute (NCI) has supported a wide range of basic, clinical, and population-based research projects to elucidate the causes and biology of prostate cancer and to develop strategies and technologies for preventing, detecting, diagnosing, and treating prostate cancer. New data suggest that the application of these research results may save lives, as evidenced by the declining mortality rate for prostate cancer among some populations.

This ongoing research effort has provided a wealth of new scientific opportunities that if pursued may further advance our understanding of prostate cancer and our ability to care for men with this disease and those at risk of it. However, because research needs are growing, the limited resources available must be used optimally. This is an opportune time to reassess NCI's prostate cancer research portfolio and plan a research agenda for prostate cancer that will guide the field into the next decade.

The Prostate Cancer Progress Review Group is one of two pilot Progress Review Groups NCI has established to help sharpen the focus of its large, site-specific research programs. The Review Group's mission is to help NCI define and prioritize the national research agenda for prostate cancer by identifying new or unmet scientific opportunities; using an NCI analysis of its current research program and the ongoing activities as a baseline, providing expert opinions on how to address the opportunities and hasten progress against the disease.

After reviewing the portfolio of grants funded by NCI in 1997, the Review Group estimated that there are between 490 to 520 projects, totaling over $87 million, supporting research in prostate cancer (see Table 1). While the process of attribution of many scientific projects was difficult—since funded research projects often address diverse research topics as well as cancers in multiple tissues—the Review Group was able to identify the major focus of most projects and sort them according to the major research areas discussed in this report.

Table 1: Estimated NCI Support of Prostate Cancer Research

Topic Area	*Approximate Level of Support*	*Estimated No. Projects*
Biology	$11,500,000	70-75
Etiology/Prevention	$25,000,000	110-115
Detection/Diagnosis/Prognosis	$13,500,000	40-45
Systemic/Local Therapy	$18,500,000	135-140
Outcomes	$ 10,000,000	20-25
Resources	$ 8,500,000	115-120
TOTAL	$87,000,000	490-520

It is important to note that some projects overlap topic areas and are found in two or more categories. It is estimated that 25-30 of the projects identified did overlap in this manner and were relevant to more than one research topic area. It is estimated that there were 460 individual projects which, in part or whole, were relevant to prostate cancer. It should also be noted that the Models topic area is missing from Table 1. This was necessary because funding for models is distributed across many of the topic areas and could not be extracted from the database as a specific entity. While the dollar amount and number of grants attests to a substantial commitment of NCI to research in prostate cancer, the Review Group nonetheless identified key gaps in the research agenda and major new opportunities that, if supported, could move the pace of research in prostate cancer forward over the coming decade.

The Review Group examined the research portfolio and developed a ranked listing of priorities for research and the resources needed to support an expanded program of research. This report describes the research challenges and opportunities in each area and provides a hierarchy of research questions that should be addressed to advance the status of prevention, detection, diagnosis, and treatment of prostate cancer.

BIOLOGY, PROGRESSION, AND METASTASIS

Prostate cancer growth and development represents a continuum of biological processes, originating from early embryonic development, through growth and maturation, to aging and neoplastic transformation. To improve diagnosis, prevention, and treatment of prostate cancer, it is crucial to focus future research on the molecular, cellular, physiological, and pathological events that lead to uncontrolled growth and metastasis.

To define the molecular and cellular alterations associated with prostate gland growth and development requires knowledge of specific genes that may be switched on and off temporally at various stages of the organism's development. Because androgens have been recognized as key regulatory molecules that promote prostate growth, development, and differentiation, understanding androgen action in the prostate and the actions of other signals is essential. To understand the function

of key molecules, such as nuclear receptors and steroid-metabolizing enzymes, it is critical to determine the structure of these molecules. In addition, increased efforts are needed to identify and characterize partners of nuclear receptors that may function together either alone or together with other cell signaling pathways to control proliferative and differentiative signals in cells.

The process of prostate cancer metastasis is poorly understood. While prostate cancer is known to metastasize to the skeleton with very few exceptions, this natural history is not recapitulated in the established animal models. Key molecular determinants associated with increasing metastatic potential are unknown. Studies are needed to define metastasis-associated genes and their expressions in rodent and human cell or tissue models and validate such findings by correlation with prostate cancer in humans.

Prostate gland development, maturation, aging, and senescence in mammalian species are complex. In order to understand this process it is critical that we define the biochemical and molecular events which govern the continuation of prostate development from early embryogenesis to the onset of adulthood, through maturation, aging, and death.

At the levels of tissue organization and cell architecture and morphology, it is important to define the differentiative and proliferative potential of prostatic stem cells and to understand the biochemical and molecular mechanisms that guide cellular interactions governing normal and pathological prostate development. In addition, cell-cell interactions, which are crucial for orchestrating the ultimate outcome of organogenesis, morphogenesis, and functional differentiation of the tissues, need to be defined.

ETIOLOGY AND PRIMARY PREVENTION

It is important to understand what genes are important in the etiology of prostate cancer (e.g., inherited susceptibility genes and polymorphisms), as well as their etiologic role and function. NCI should support an infrastructure for more extensive collection of biological samples and clinical information obtained from families with apparently hereditary prostate cancer. When candidate genes are identified, NCI should support the development of "knock-out" animal models to investigate the function of such genes.

The prevention of prostate cancer is one of the most important goals of prostate cancer research. Prevention research stands to benefit greatly as more knowledge is gained about the molecular and cellular events underlying prostate cancer and how these events can be interrupted. It is important to determine which dietary elements correlate with altered risk of prostate cancer, and how risk may be reduced through chemoprevention. NCI should support more epidemiologic studies that include detailed prospective dietary studies coupled with extensive clinical databases.

To better understand the etiology of prostate cancer it is important to be able to identify men at increased risk for this disease, how environment and lifestyle influences this risk, and what chemopreventive measures may reduce risk. NCI should support targeted research and development of new

technology to identify risk factors and how the environment modifies those predisposing risks. An understanding of the interaction of genetic and environmental risk factors that determine incidence in high risk (e.g., African American) and low-risk (e.g., Asian) populations is also important.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Prostate-specific antigen (PSA) testing has greatly facilitated the diagnosis of prostate cancer. But it has not been demonstrated that PSA screening actually reduces morbidity or mortality from this disease. One of the most perplexing aspects of prostate cancer is that more cancers develop in men over age 50 than ever become clinically apparent or prove lethal. Consequently, men face a serious dilemma: if their cancer goes undetected, they could develop a debilitating, potentially lethal disease; however, if their tumor would have remained quiescent for the rest of their natural life, detection could lead to the adverse consequences of unnecessary treatment. Fortunately, screening seldom detects the small, clinically unimportant tumors.

Progress in early detection requires that tests used for detection be refined to ensure that, whenever possible, the cancers detected are clinically important, that is, to detect only those cancers with the potential to kill their host if left untreated without missing any clinically important cancers. In addition, prognostic "markers" must be further refined to accurately measure the biologic potential of a cancer, allowing therapy to be tailored to the risk posed by the individual cancer.

NCI should place major emphasis on the development, validation and application of biologic markers or determinants that can provide reliable prognostic information. This effort will likely require the formation of a new, dedicated multidisciplinary prostate cancer marker consortium involving multiple institutions committed to translational research in prostate cancer. Since no single marker is likely to prove sufficiently predictive, panels of multiple markers will be required, and analyzed with the sophisticated tools of modern medical informatics.

At the same time, NCI should continue to support clinical trials to determine whether screening for prostate cancer reduces the risk of dying from this disease and should substantially expand studies of the effects of early detection on morbidity and quality of life.

LABORATORY AND CLINICAL MODELS

Laboratory and clinical models are critical for defining the mechanisms of prostate cancer progression and for testing preventive and therapeutic regimens. Yet only a few laboratory and clinical models have been developed, all of which are encumbered by insufficient biological knowledge of the human cancer they strive to simulate. Better understanding of the basic biology of human prostate cancer will accelerate and refine the process of model development.

A laboratory model ideally simulates all of the properties of prostate cancer in humans; however, such a model is difficult to achieve in practice. A constellation of models (xenograft, transgenic, reconstitution, animal, *in vitro*, and mathematical) must be

developed to mimic distinct characteristics of human prostate cancer. Moreover, additional prostate cancer cell lines need to be developed. Each model then must be validated to permit a predictable level of extrapolation to humans.

The availability of new models will provide the means for testing new modalities of both prevention and progression of prostate cancer as well as methods of testing both chemopreventive and chemotherapeutic agents. Moreover, novel therapeutic protocols, such as gene therapy and immunotherapy, can be tested through such models.

STAGING AND TREATMENT OF LOCALIZED PROSTATE CANCER

Today, with systematic screening, we have the ability to detect almost all prostate cancers before they progress to become locally advanced or metastatic. What we do not have is the ability to determine reliably which cancers poses so little threat that active treatment can be deferred indefinitely. When treatment is indicated, it is generally safe and often effective. But each form of therapy—whether radical prostatectomy, external beam irradiation or interstitial seed implants—fails to cure some patients and each produces some undesirable side effects. Given the absence of results from randomized clinical trials, we have insufficient evidence that any one of these treatments is superior to another. We do not know how to predict how a given cancer will respond to a particular type of therapy, or how to select the most beneficial, least risky therapy for an individual cancer. Major progress against clinically localized prostate cancer will require new approaches.

Treatment may fail to control an apparently localized cancer either because malignant cells have already spread to distant sites or because some cells within the local tumor are not destroyed. Staging tests available today are not sufficiently sensitive to detect occult micrometastases in many patients. New techniques are urgently needed to detect metastatic cells and to determine their clinical significance. Even in the absence of such metastases, local treatment may fail because the cancer extends beyond the margins of surgical resection or because cells within the treated (e.g., irradiated) fields are not sufficiently damaged. Better indicators are needed to predict the response of individual cancers to different forms and intensities of therapy so that therapeutic options can be selected that are more appropriate to the characteristics of individual cancers. In addition, new therapeutic approaches need to be developed which improve cancer control or diminish the morbidity of treatment.

Prostate cancer, among the solid tumors, seems to be particularly suitable for gene therapy, since the organ is expendable, the primary tumor is accessible, and a circulating marker of response is readily available. Gene therapy has thus far been associated with low morbidity and could be applied repeatedly to palliate these slow growing cancers long enough for patients to live out their natural lives even if the cancer is not completely eradicated. In addition, occult micrometastases may be particularly susceptible to gene therapy strategies that augment the immunogenecity of tumor cells. Successful introduction of such novel approaches will require

support for a special clinical trials consortium, since gene therapy requires active collaboration of basic and clinical investigators incorporating multiple approaches and should emphasize mechanistic questions rather than simply documentation of response.

SYSTEMIC THERAPIES

Systemic therapies are required for tumors that can no longer be cured by local treatments, such as surgery or radiation therapy alone. Although prostate cancers represent a spectrum of diseases with a range of prognoses, defining optimal systemic treatments depends on understanding the natural history of the disease, and, ideally, on knowledge of the biologic determinants of the development and progression of disease in the individual patient. Although hormonal therapy presently is the only recognized systemic treatment for advanced disease, there are indications that systemic chemotherapy is active against prostate cancer and in patients with early-stage, poor-prognosis cancers.

A critical issue in developing systemic approaches is the design of clinical trials for prostate cancers. Clinical trial questions require specific endpoints designed to assess whether a particular approach should be continued. Trials for different disease states that address different questions require different outcome measures. Relevant endpoints include measures such as disease-specific survival, or in certain Phase I and II studies, the demonstration that a specific gene or gene product is inhibited.

Selection of an appropriate homogeneous patient population is essential for the success of a given clinical trial. Patient factors, such as comorbid conditions, the genetic background of the host, diet, and concomitant medications could affect immune function or influence the choice of treatments.

As our knowledge of the events associated with the development and progression of prostate cancer increases—in particular the events associated with the lethal hormone-independent variant of the disease—a number of promising mechanism-based approaches worthy of clinical testing have been identified. These include, among others, inhibiting signal transduction or specific steps in the cell cycle, blocking angiogenesis and other specific steps in the metastatic cascade, promoting apoptosis, inducing differentiation, as well as a variety of immunotherapeutic approaches. In addition, a number of chemotherapeutic agents have recently been evaluated and shown to produce efficacy in a significant proportion of patients. The combining of these approaches also is a critical area for investigation, but it will require substantial and sustained investment in the infrastructure needed to support clinical trials, develop clear endpoints, and follow up on treatment outcomes.

OUTCOMES RESEARCH

"Outcomes" includes both disease-specific and patient-focused endpoints used to describe the results of various interventions in the management of prostate cancer. Patient-focused outcomes include quality of life, treatment- and disease-related morbidity, economic impacts of care, and quality of and access to care. Methods to measure

patient-focused outcomes quantitatively have been developed, but there are few validated instruments appropriate for patients with prostate cancer and few adequate studies of the effects of the disease or its treatment on quality of life. Outcome measures are being used yet their meaningfulness may vary depending on the perspective by which the outcomes are measured—the patient's, the clinician's, the third party payer's, or society's. More data about all aspects of quality of life are needed to provide a more comprehensive perspective on the needs of the long-term cancer survivor.

Research is needed to develop better quality-of-life instruments to assess more accurately the impact of treatment and of the disease itself on patient-focused outcomes, how these may differ among different providers (for example, the community versus centers of excellence). Quantitative measurements are needed to measure how patients value tradeoffs between length of survival and quality of life. NCI should support efforts to standardize quality-of-life measurements within clinical trials, including screening and treatment trials. In addition, NCI should support the development of quantitative measures to describe and compare outcomes after different interventions.

RESOURCES NEEDED

Progress in prostate cancer is severely impeded by limitations in research funding, policies, and practices. Several major areas critically require investment and leadership: training and career development; an informatics network linking repositories and databases; clinical trials; translational research; laboratory and clinical models; new technology; and patient education.

The Review Group unanimously agreed that the education and training of investigators who will pursue research in prostate cancer should receive top priority. Training of young investigators will provide the foundation on which to build new research initiatives in the future.

There is a lack of databases serving the burgeoning needs of basic, clinical, and epidemiological researchers. The Review Group recommends that NCI support the development of new prostate cancer databases and bioinformatics to ensure that the vast amount of information that becomes available can be assimilated and exploited.

Prostate cancer research is hampered by an inadequate infrastructure for tissue acquisition, storage, and use. The limited tissue repositories available are not closely linked with appropriate clinical, pathological and epidemiological information. NCI should undertake or encourage the establishment of a National Prostate Cancer Repository to procure and distribute well-characterized tissue from prostate cancer patients, including samples obtained from autopsies and from patients in clinical trials.

The Review Group recommends the development and dissemination of new cell lines from human prostate cancer and new animal models. Research efforts should be supported to identify and characterize additional prostate cell-specific promoters in order to stimulate the further development of *in vivo* animal models that more accurately mimic human prostate cancer.

There is a lack of funding for the development and dissemination of new technologies for research in prostate cancer prevention, diagnosis, and treatment. The Review Group recommends that NCI facilitate the development and dissemination of reagents and data related to gene expression patterns from microarrays. Also, NCI should support regional centers that provide access to microarray/chip technology.

Finally, the Review Group recommends that NCI play a leadership role in the design of clinical trials (prevention, early detection, and treatment), establishing standardized systems for assessing prognostic markers, determining appropriate endpoints, and identifying response criteria. Also, NCI should develop a special prostate cancer trials consortium. This consortium should include institutions engaged in prostate cancer treatment and research.

These resources will provide the essential infrastructure to facilitate a multidisciplinary research agenda in prostate cancer and are common to many of the recommendations made throughout the report.

CONCLUSIONS

We have an unprecedented opportunity to make substantial strides in the treatment of prostate cancer. Recent advances in the understanding of biology of the disease will translate into new molecular targets. These, combined with improved throughput of compounds in the drug-screening process and better understanding of pharmacological activity of those compounds through array technology, should result in improved clinical activity of agents in the near future. Obviously, the challenge of moving compounds from pre-clinical to clinical status remains, as does the traditionally problematic process of interpreting clinical results. However, through a concerted effort on the part of the scientific community focusing on this disease, we should be able to overcome those barriers, discover the basic etiology of prostate cancer, understand its development and progression, design appropriate clinical trials, and develop regimens that have a positive impact on the lives of patients with prostate cancer.

Our nation will witness, in fact, lead a revolution in biology and medicine over the next generation that could provide the tools to allow mankind to control for the first time the complex constellation of diseases called cancer. More Americans die each year of cancer than have died in all the wars in our nation's history. An investment in biomedical research at this crucial period could bring the forces of modern biological and clinical sciences to the control of prostate cancer. It is our generation's responsibility to see that our children, and certainly our grandchildren, as they reach their golden years and wish to enjoy the fruits of a long life, will not have their lives cut short by the intractable growth and painful debilitating death from prostate cancer.

SECTION I.

BACKGROUND INFORMATION ON THE PROSTATE CANCER PROGRESS REVIEW GROUP

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RATIONALE FOR THE PROSTATE CANCER PROGRESS REVIEW GROUP

Prostate cancer is the leading site of new cancer cases and the second leading cause of cancer deaths in men in the United States. The National Cancer Institute (NCI) has supported a wide range of basic, clinical, and population-based research projects to elucidate the causes and biology of prostate cancer and to develop strategies and technologies for preventing, detecting, diagnosing, and treating prostate cancer. New data indicate that the application of these research results is saving lives, as evidenced by the declining mortality rate for prostate cancer among some, though not yet all, populations.

This ongoing research effort has provided a wealth of new scientific opportunities that, if pursued, may further advance our knowledge and ability to care for men with prostate cancer and those at risk of the disease. The growing number of research needs and scientific opportunities require that limited resources be used optimally. It is an opportune time to reassess the NCI's prostate cancer research portfolio and plan a research agenda for prostate cancer that will guide the prostate cancer research field into the next decade.

The Prostate Cancer Progress Review Group (the PRG or Review Group) is one of two pilot Progress Review Groups that have been established to help NCI sharpen the focus of its large, site-specific research programs. The other Progress Review Group is focusing on breast cancer. The Progress Review Groups are part of NCI's new overall planning framework, which also relies on Working Groups and Program Review Groups for evaluation, and planning of the research portfolio.

CHARGE TO THE PROSTATE CANCER PROGRESS REVIEW GROUP

The overall goal of the Review Group was to develop a national plan consisting of a description of ongoing scientific activities and investigations relevant to prostate cancer and a listing, in priority order, of scientific opportunities that should be pursued. Specifically, the Review Group was charged to:

- Identify and prioritize scientific needs and opportunities that are critical to hasten progress against prostate cancer.
- Review an NCI-prepared portfolio analysis of the current research program.
- Review recommendations from the research community generated through Prostate Cancer Roundtable meeting and Expert Panel reports.
- Review recommendations from the prostate cancer advocacy community and from stakeholders.
- Define and prioritize the research agenda.
- Develop an action plan encompassing both operational and strategic components of the NCI's prostate cancer enterprise, using the current research program as the baseline for recommended actions.

PROSTATE CANCER PROGRESS REVIEW GROUP MEMBERSHIP

The Review Group was selected from among prominent members of the scientific, medical, industrial, and advocacy communities to represent the full spectrum of expertise needed to develop comprehensive recommendations on NCI's prostate cancer research agenda. The membership was also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of prostate cancer research. (A roster of PRG members is presented in Appendix 1.)

ACTIVITIES OF THE PROSTATE CANCER PROGRESS REVIEW GROUP

The PRG first met in April 1997 to plan the Prostate Cancer Research Roundtable (described below). Following the Roundtable, the Review Group met frequently through May of 1998. These meetings were convened to review the Roundtable input and Expert Panel reports, receive stakeholder input, gather additional data, review the current NCI prostate cancer research portfolio, and discuss and prioritize key scientific questions and ultimately to develop recommendations for action.

The Prostate Cancer Research Roundtable was held in June 1997. (See Appendix 2 for the Roundtable Agenda; a list of participants appears in Appendix 3.) Over 100 members of the prostate cancer communities, including academic and industrial scientists, clinicians, and advocates, met in Chantilly, Virginia for intensive discussion. The Roundtable was an open forum designed to identify and formulate key scientific questions that should be addressed in the next 5 to 10 years in prostate cancer research. Attendees, nominated by PRG members, participated in an opening plenary session followed by discussions over a two-day period. Breakout groups were established to foster in-depth discussion in the following areas:

- Biology, Progression, and Metastasis
- Etiology and Prevention
- Early Detection, Diagnosis and Prognosis
- Laboratory and Clinical Models
- Staging and Treatment of Localized Prostate Cancer
- Systemic Therapy
- Outcomes
- Resources

At the conclusion of the Roundtable meeting, the breakout groups reported highlights of the discussions in a closing plenary session.

In addition, the PRG formed seven Expert Panels composed of experts in the following fields:

- Clinical Trial Design and Implementation
- Prognostic Marker Validation
- Radiobiology
- Screening and Early Detection
- Gene Therapy and Vaccines
- Gene Technology and Gene Identification
- Molecular Epidemiology

The Expert Panels examined in detail the opportunities, questions, issues, and resources that will enhance the field of prostate cancer research. The Expert Panels were encouraged to "be visionary" and to establish expectations of where the field could be, or should be,

in five years and beyond. Panels met between December 1997 and January 1998. (A roster of Expert Panel members appears in Appendix 4.)

To ensure that the professional and advocacy communities were fully represented, the PRG invited the input of 32 "stakeholder" groups— professional societies and advocacy groups who have an interest in prostate cancer research. Letters were sent to representatives of the groups encouraging participation, and a special web site was set up to collect feedback.

ASSESSING THE NCI PROSTATE CANCER RESEARCH PORTFOLIO: CAVEATS

The PRG used two separate mechanisms to assess the current NCI research portfolio in prostate cancer. The aim of the portfolio review was to describe the ongoing NCI prostate cancer research effort, which would then serve as a baseline for the PRG in formulating its recommendations. The NCI prostate cancer research portfolio was reviewed within the context of scientific questions and/or research areas. The first method used to review the portfolio was the formation of an internal NCI Task Force led by the Task Force Chairman who also served as the PRG Executive Director. The Task Force constructed a scientific outline based on the currently funded research projects within the extramural (grants and contracts) and intramural research programs. The NCI Task Force included leaders in intramural and extramural science from the NCI program, and other NIH staff. (The NCI Task Force roster can be viewed in Appendix 5.)

Each NCI Division designated at least one representative to the Task Force, which assessed the Division's scientific efforts with respect to prostate cancer. The NCI Task Force was charged to plan and conduct the portfolio review, prepare a handbook of cancer research and resources, and present this information to the PRG.

The PRG independently conducted a review of the NCI research portfolio using a prostate cancer keyword search strategy on a subset of projects funded in Fiscal Year 1997 to develop a "snapshot" of current NCI efforts in prostate cancer research.

Both the PRG members and Task Force members struggled with the task of categorizing projects to fit specific scientific areas and questions. Research projects are by their very nature large, complex undertakings that can have relevance to one or many scientific areas. An example of the type of dilemma that the PRG faced is how to adequately categorize the Prostate, Lung, Colorectal and Ovarian Cancer screening trial. The PLCO trial will enroll 74,000 men and is designed to answer the question "Does screening for prostate cancer with PSA (prostate specific antigen) and DRE (digital rectal examination) save lives?" However, in addition to testing screening for prostate cancer, the PLCO Trial is also studying screening interventions in men for lung and colorectal cancer. Further, the PLCO Trial is also collecting epidemiological information and biological samples which will be useful to investigators studying prostate cancer causation, biology and natural history. So how does one carve out what percentage of PLCO Trial funding is supporting prostate cancer research compared to other cancers, and how can one further divide

the funding among biology, etiology and screening?

This type of categorization issue was encountered repeatedly by the PRG. However, the members felt it was critical to describe to the best of their ability, the level of research support and funding to provide a baseline with which to make its recommendations. The result of this effort is an estimate of funding for prostate cancer research in fiscal year 1997 within six broad topic areas as is discussed at length in the Executive Summary of this PRG report. These estimates are given as the best possible estimate given the inherent complexity of the task and under the constraints of time and resources available.

REPORT DEVELOPMENT PROCESS

During the process of identifying research opportunities and the needs to advance research in prostate cancer, the PRG assembled over 400 scientific questions. These questions were derived from extensive deliberations of scientists, advocates, and clinicians at the NCI Roundtable on Prostate Cancer and were further supplemented by recommendations from Expert Panels and stakeholder groups. About 200 of the 400 scientific questions were chosen as having the appropriate "grain size" for prioritization; these are considered to be the "key scientific questions" addressed at length in this report. Each PRG member anonymously voted upon these 200 key scientific questions. At the outset of the prioritization process, a conscious decision was made to prioritize within but not between subgroups in order to avoid the tendency to vote in self-interest. Based on the voting results, the key scientific questions were prioritized into one of three categories. It is important to note that all of these questions are considered to be important in advancing the field of prostate cancer research. However, recognizing that not all areas can be implemented at once, the PRG prioritized the key scientific questions as follows:

Priority One

This area of research is critical for advancing the fields of research or public health

- and ready for immediate implementation;
- and/or responds to a recent development or breakthrough.

Priority Two

This area of research is important, but not as critical for advancing the fields of research or public health or may be technically less promising but still feasible.

Priority Three

This area of research is important, but already being addressed in some fashion;

- or not ready for implementation (although when ready, could become Priority I or II)
- or less critical for advancing the fields of research and public health.

Once the full Review Group prioritized the key scientific questions, the PRG subgroups prepared narratives on these scientific questions and developed recommended actions for inclusion in this report.

ABOUT THIS REPORT

Following this section, the Review Group presents a visionary statement of how best to move prostate cancer research efforts past current barriers and seize the opportunities that are emerging from past and ongoing research in prostate cancer. Section III contains detailed presentations of prioritized scientific questions and recommended actions
within the following eight categories of prostate cancer research.

- Biology, Progression, and Metastasis
- Etiology and Prevention
- Early Detection, Diagnosis and Prognosis
- Laboratory and Clinical Models
- Staging and Treatment of Localized Prostate Cancer
- Systemic Therapy
- Outcomes
- Resources Needed

SECTION II.

VISIONARY STATEMENT

VISIONARY STATEMENT

Prostate cancer is the most frequently diagnosed cancer in American men and the second leading cause of cancer deaths.[1] In some Western countries, it has become the leading cause of cancer deaths. As our population ages, the impact of prostate cancer on American men will increase; no other cancer rises in incidence and mortality rate with increasing age as rapidly as does prostate cancer.[2] It has been estimated that over 1 million American men now alive and over age 50 will eventually die of prostate cancer unless new treatments are developed to control this disease.[3] Unfortunately, prostate cancer has a disproportionate impact on certain segments of our population. For example, African American men are more likely to develop prostate cancer and twice as likely to die from it than are other Americans.[4]

Over the past decade, the incidence of prostate cancer has increased sharply as PSA testing has become widely available. With widespread awareness about prostate cancer and a greater willingness to discuss this disease publicly, more than 50 percent of men over the age of 50 report that they have been tested for prostate cancer within the past two years. Much of the increased incidence, therefore, has been related to the identification through widespread screening of a large number of prevalent, but previously undetected, cases in the population. The gradual decline in the mortality rate seen in the past five years may be related, in part, to the remarkable sensitivity of PSA in detecting prostate cancer earlier, when it can be controlled with surgery or irradiation therapy.

In recent years, real progress has begun to be made against human cancer. The mortality rate for all cancers peaked early in this decade and has begun slowly to decline. But with over 39,000 deaths expected from prostate cancer alone this year much remains to be done. Prostate cancer presents some unique challenges. Cells that have the appearance of prostate cancer can be found in the prostate gland of nearly half of all men over the age of 50. Yet the lifetime risk of a man being diagnosed with clinically apparent prostate cancer is only 11 percent and the lifetime risk of dying of prostate cancer is only 3.6 percent. Thus, some 3 cancers develop for every one that will prove lethal. The ultimate strategy for defeating prostate cancer calls for developing ways to distinguish the harmless (indolent) cancers from the potentially lethal, and developing effective ways to prevent or treat the potentially lethal cancers.

The growth of scientific knowledge presents our nation with a unique opportunity to advance the attack on prostate cancer and to accelerate the pace of progress against this disease. Taking advantage of this opportunity,

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[1] Landis, S.H., Murray, T., Bolden, S., Wingo, P.A. Cancer statistics, 1998. *CA: A Cancer Journal for Clinicians* 1998;48:6-29.

[2] Carter H.B. and Coffey D.S. The prostate: an increasing medical problem. *The Prostate*, 1990; 16:39-48

[3] Scardino, P.T., Weaver, R., Hudson, M.A. Early detection of prostate cancer. *Human Pathology* 1992;23:211-222.

[4] Parker, S.L., Davis, K.J., Wingo, P.A., Ries, L.A.G., Heath, C.W. Jr. Cancer statistics by race and ethnicity. *CA: A Cancer Journal for Clinicians* 1998;48:31-48.

however, will require a substantial commitment of people and resources dedicated to understanding and eventually eliminating prostate cancer.

The most important component of this effort is the development of a critical mass of multidisciplinary investigators – both physicians and scientists – committed to solving the problem of prostate cancer. Specific mechanisms of support are needed from the federal government to attract and nurture the research talent needed to carry out the necessary studies. Traditional training grant and fellowship programs are not sufficient to provide adequate numbers of basic and clinical investigators. To be effective, training programs must be durable with sufficient long-term funding. Trainees must be able to anticipate a reasonable level of sustained funding that would allow them to initiate independent research programs when they graduate. A long-term commitment to funding is the best mechanism to attract talented investigators to make a career-long commitment to prostate cancer research. Nothing is more important to the solution of prostate cancer than the attraction of adequate brainpower to solve this complex problem.

Over the past 10 years, remarkable progress in modern molecular and cellular biology has dramatically increased our understanding of the mechanisms that regulate the life and death of normal and malignant cells. Science is beginning to identify specific molecular pathways that can be used to characterize the biological potential or behavior of cancer cells and that promise to provide novel therapeutic targets. Innovative strategies, such as gene, cellular, or immunological therapies, promise to supplement the traditional surgical, radiation, chemotherapeutic, or hormonal approaches.

Exciting technological developments made possible by the revolution in information processing will provide new tools for characterizing cancers. Chip array technology will allow rapid assessment of literally thousands of genes from a single sample of malignant tissue. Medical informatics, by harnessing the power of the modern computer, can analyze millions of bits of data to provide individual genetic profiles. These will help delineate the risk of a given cancer to progress or to respond to different therapeutic interventions. Such risk "profiling" will lead to more efficient and productive clinical trials and will allow clinicians to tailor treatment to the threat posed by an individual cancer.

One of the most promising opportunities to improve the diagnosis and treatment of prostate cancer is the identification of familial and somatic genetic changes that initiate the development of prostate cancer and regulate its progression and metastasis. Information about genetics will help define new markers that can characterize the nature of each cancer and new targets for rational therapeutic intervention.

Prevention of prostate cancer is the ultimate approach to the control of this disease. However, effective prevention will require an understanding of its etiology. Risk factors identified by epidemiological studies, such as age, race, family history, dietary intake, androgenic status, and other factors need to be better understood with respect to the etiology of the disease. A better understanding of how genetic

predisposition and exogenous exposures interact to determine prostate cancer susceptibility is needed for the design of effective preventive strategies. Moreover, dietary factors may provide both preventive and therapeutic benefits.

Special attention to the biology of the normal and malignant prostate cell will open new, unexpected opportunities for improving the diagnosis and treatment of prostate cancer. It is especially important to understand the prostatic stem cell in its relation to the development of cancer. Many other malignancies exhibit a close relationship between the growth control mechanisms employed by stem and progenitor cell populations for a given lineage. These relationships should be explored thoroughly in prostate cancer as well.

A fundamental and universal feature of every prostate cancer that proves lethal is the development of androgen independence, yet the mechanisms of androgen resistance or independence at the cellular level are poorly understood. There has been an appropriate intensive molecular analysis of the androgen receptor in prostate cancer, but the complexity of the phenotype of androgen resistance needs far more attention in order to develop better agents to suppress recurrence of cancers after initial hormonal therapy fails.

Prostate cancer cell surface and internal antigens can provide a suitable target for imaging these cancers and for the development of new diagnostic agents and novel therapeutic interventions. Immunological strategies are proving successful with other tumors and offer enormous promise in prostate cancer as well.

With the developments in biology have come exciting new drugs that act through a variety of novel mechanisms– drugs like angiogenesis inhibitors, and those that block signal transduction mechanisms. Moreover, the field of experimental therapeutics is growing rapidly. Testing these and other novel therapies against human prostate cancer will require a much more extensive infrastructure to support translational research. Regardless of the effects in tissue culture or animal models, new diagnostic agents or therapeutic interventions must be tested in humans. Clinical trials are the essential bridge between science and medicine.

Many features of prostate cancer make the disease a good target for gene therapy. Among these features are its slow growth, enabling long-term control even if the cancer is not eradicated, the discrete and accessible nature of the prostate gland, and the fact that the response to therapy can be monitored throughout the course of the disease through PSA, biopsies, and scans. Prostate cancer, among the solid tumors, seems to be particularly suitable for gene therapy, since the organ is expendable, the primary tumor is accessible for applying treatment and monitoring the response, and a circulating marker of response is readily available. Gene therapy has thus far been associated with low morbidity and could be applied repeatedly to palliate these slow growing cancers long enough for patients to live out their natural lives even if the cancer is not completely eradicated. In addition, limited, occult micrometastases—the major cause of treatment failure—may be particularly susceptible to gene therapy strategies, which augment the immunogenecity of

tumor cells and thereby elicit systemic anti-tumor immunity.

A clinical trials mechanism that is adapted to the special means and opportunities in prostate cancer can play a major role in accelerating progress. While databases and tissue banks are being developed at individual centers, a national effort is justified to create databases of familial prostate cancer and of genetic changes in prostate cancer. An informatics network that links tissue, serum and nucleic acid repositories with detailed demographic, clinical, pathologic and epidemiological information would be an invaluable resource to investigators. Clinical trials have been hampered by the lack of uniform definitions of disease states, response criteria, techniques of intervention, and appropriate end points for clinical trials and outcomes. The National Cancer Institute is the most appropriate institution to provide the required leadership to define and standardize the methodology of clinical trials.

Ultimately, patients as individuals want to make their own choices about their health care. Modern outcomes research—the emerging discipline of clinical evaluative science—can provide patients, their families, and their physicians the tools to assimilate and manage the complex and seemingly conflicting data about their cancer. A major effort is needed to support this emerging scientific field, to develop quantitative approaches that can be refined as user-friendly tools and made applicable to the unique challenge of prostate cancer.

In summary, our nation will witness, and in fact lead, a revolution in biology and medicine over the next generation that could provide the tools to allow us to control for the first time the complex constellation of diseases called cancer. More Americans die each year of cancer than have died in all the wars in our nation's history. An investment in biomedical research at this crucial period could bring the forces of modern biological and clinical sciences to the problem of prostate cancer and lead to the control of this disease. It is our generation's responsibility to see that our children, and certainly our grandchildren, as they reach their golden years and wish to enjoy the fruits of a long life, will not have that life cut short by the intractable growth and painful, debilitating death from prostate cancer.

SECTION III.

PRIORITIES AND RECOMMENDATIONS

A. THE BIOLOGY, PROGRESSION AND METASTASIS OF PROSTATE CANCER

This section summarizes the views of the PRG with regard to the current status of research into normal and neoplastic prostate development, prostate tumor progression and metastasis, prostate tumor-host interactions, and genetic influences on prostate carcinogenesis and progression. Also reviewed are the roles of data collection and processing, the importance of a supportive infrastructure, and specific areas of research that, if studied in depth, appear most likely to contribute to the diminution, or even eradication, of human prostate cancer.

CURRENT STATUS OF THE FIELD

Understanding prostate cancer biology, progression, and metastasis are fundamental to improving our abilities to successfully prevent, diagnose, and treat human prostate cancer. To help discern the basic biology of prostate cancer, efforts must be devoted to analyzing the developmental, biological, and genetic aspects of prostate disease, emphasizing the identification of molecular mechanisms that can predict the risk of developing cancer and estimate a potential response to treatment.

Over the past decade our perception of normal and neoplastic prostate pathophysiology has improved dramatically. Several important details regarding the developmental, tissue, and cellular biology of the prostate gland have been characterized. For example, it is known that proliferation and development of prostate epithelium is initiated and subsequently maintained by angiogenic and surrounding mesenchymal stimuli through both autocrine and paracrine signals. Furthermore, several therapeutic modalities have been created as a result of an improved understanding of hormonal influences on prostatic tissue. The recognition that androgen receptors and metabolites are important in the regulation of prostate growth, differentiation, and neoplastic progression resulted in the development of the antiandrogens (e.g., flutamide, bicalutamide) and 5-alpha reductase inhibitors (finasteride) that are used clinically to treat prostate cancer.

Prostate cancer originates as a localized lesion. It subsequently progresses to acquire increased invasive, migratory, and metastatic potentials. Eventually, androgen independence develops and the tumor becomes refractory to conventional interventional therapies. The progression of clinical prostate disease from a localized tumor to a widely disseminated disease state probably occurs through alterations in proliferation, cell-cell adhesion, invasion potential, and critical interactions between prostate cancer cells and surrounding host cells at both primary and metastatic tumor sites. Unfortunately, contemporary methods of predicting how rapidly a given prostate cancer will acquire metastatic attributes and progress from an androgen-dependent to an androgen-independent state are unreliable. The evolution of prostate cancer from a malignancy

contained within the prostatic parenchyma to a systemic disease involving the seminal vesicles, lymph nodes, skeleton, and other distant organs involves fundamental changes dictated by genetic as well as epigenetic (environmental, behavioral, and dietary) influences. Supporting this contention are clinical and laboratory studies that demonstrate putative roles for hereditary factors, tumor characteristics (including DNA repair, cell cycle progression, and apoptotic potential), and host factors (comprising stromal-epithelial interactions, angiogenic influences, and host immune surveillance) in prostate cancer progression and metastasis.

Unfortunately, our understanding of the underlying mechanisms that dictate prostate development, carcinogenesis, tumor progression, and metastatic dissemination is still very rudimentary. The biochemical and molecular mechanisms that control cellular interaction during prostate organogenesis, morphogenesis, and functional differentiation remain undetermined. The differentiative and proliferative potentials of prostatic stem cells have not been defined. The inter- and intra-cellular signaling pathways that govern androgen receptor-mediated gene transcription and also communicate with other signal transduction pathways remain uncharacterized. Moreover, the specific target genes and gene products that are directly controlled by key signaling molecules during the various stages of prostate cancer development and progression have not been identified. Further research is needed into cellular signaling, cell surface receptor activity, and the interactions of prostate cancer cells with soluble and matrix-associated molecules that regulate prostate cancer growth, progression, and dissemination.

Tumor-host interactions are pivotal to the mechanisms of cancer cell invasion, migration, and metastasis. Such interactions are reciprocal, and reflect both the endocrine and immunologic status of the host, which can either foster or reject the survival of the neoplastic cells. The importance of understanding prostate cancer-skeletal interactions, in particular, is underscored by the strong propensity of prostate cancer to metastasize to the bone and the subsequent unique osteoblastic response observed in patients with metastatic disease. Hence, it will be necessary to identify the molecular and biochemical features of bone physiology and pathophysiology that influence interaction between prostate tumor and bone cells, and the subsequent characteristic osteoblastic reactions that are induced when tumor cells metastasize to the skeleton.

Recently, new technologies such as microdissection, microarray, and comparative genomic hybridization have been utilized to evaluate clinical specimens, enabling the identification, cloning, and characterization of prostate cancer progression-associated molecular markers that might someday be used to define and characterize the malignant potential of prostate cancer in individual patients. Despite the identification of these novel prostate cancer progression-associated biomarkers, validation of these findings, as well as discoveries of the molecular basis of cell communication and intra- and intercellular signaling, has not been performed with respect to progressively tumorigenic and metastatic clinical prostate cancer specimens. An intensified pursuit is needed to delineate the relevant and basic biological parameters discovered thus far and relate

them to such factors as: normal prostate development; prostate carcinogenesis; progression from an androgen-dependent to an androgen-independent state; acquisition of a metastatic phenotype; and interaction of prostate cancer cells with bone cells and other host factors. Novel genetic and molecular pathways that will allow us to stratify and classify disease status based on these molecular and biochemical parameters will facilitate our ability to significantly improve the prevention, diagnosis, and treatment of prostate cancer into the next millennium (see also Section C, *Early Detection, Diagnosis, and Prognosis*).

VISION

Identifying novel molecular and genetic markers associated with prostate development, carcinogenesis, tumor progression, and metastatic spread should foster many subsequent developments in prostate cancer management. These include the identification of underlying mechanisms of international and racial differences in prostate cancer development and progression; the separation of indolent and virulent forms of disease; improvements in diagnosing and monitoring patients; and the potential to predict the ultimate malignant potential of a prostate tumor while still at a localized state. The development of relevant human prostate cancer models that mimic the clinical characteristics of prostate cancer growth, including the acquisition of androgen independence and the propensity to metastasize to bone, is also crucial.

Prostate cancer is a heterogeneous and multifocal disease. To understand the clinical characteristics of prostate cancer, we must investigate the cellular and molecular basis of disease initiation and progression. Studies that will identify prostate cancer stem cells, elucidate the reciprocal interactions between prostate tumor and host or bone cells, and define hormone receptor structure, function, and interaction with other cognate cell signaling molecules, transcription regulators, and cell-cell and cell-matrix intercommunication must be pursued. Our ultimate goals are two-fold: to better understand key concepts of cancer biology, and to both prevent the development of prostate cancer and cure those men already afflicted. Hence, our investigative approaches should place a high priority on developing those aspects of basic research that are most appropriate to clinical prostate disease and most promising for translational application. Furthermore, as scientific thought is becoming more sub-specialized and individual researchers' interests and outlooks are becoming more focused, an interdisciplinary approach to prostate cancer research should be encouraged. To accelerate the study of human prostate cancer, therefore, several major research directions must be pursued as follows:

- First, strategies to identify genes and characterize novel genetic biomarkers that are differentially expressed or suppressed in the progression of prostate cancer to an androgen-independent and metastatic state must be developed. These novel genes will be evaluated and validated in clinical specimens of men in which the biological potential and responsiveness to hormonal, radiation, biological, and chemotherapies is known.

- Second, the search for intercellular signal transduction pathways that

govern ligand-dependent or independent activation of hormone receptors or other factors affecting androgen sensitivity, and their interaction with other cognate factors that may determine gene transcription and the differentiation of cancer cells, must be expanded and intensified. It is recognized that by delineating molecular pathways that control prostate development, differentiation, and senescence, exciting insights into the determinants of prostate cancer growth, proliferation, and apoptosis in response to physiological, pathological, and pharmacological perturbations (the hormonal status of the host, genetic background, age, and prior treatment history) will be developed.

Over the past few years, advances in basic prostate tumor science have improved our understanding of prostate carcinogenesis, metastasis, and progression. Now is the ideal time to act if we are to capitalize on the current momentum. However, such an endeavor will require an improved understanding of basic molecular and biochemical science, the creation and standardization of appropriate animal models, and reforms in the regulatory, financial, and proprietary infrastructure.

CHALLENGES AND OPPORTUNITIES

A substantial gap remains in our understanding of the basic cellular and molecular biology of the normal prostate, especially with regard to the events that govern the early stages of neoplastic cell transformation and the subsequent progression and acquisition of a malignant phenotype and metastatic potential. This lack of fundamental knowledge has impeded our progress in attacking prostate cancer in a rational fashion. Several factors have contributed to the absence of information regarding the continuum of normal prostate development, the multiple steps of carcinogenesis, and the ultimate acquisition of a malignant and metastatic phenotype. These include, but are not limited to, a lack of relevant animal models that closely mimic the development, transformation, and acquisition of androgen-independent and metastatic human prostate disease, and an absence in understanding of basic developmental processes, including the regulatory mechanisms of gene transcription and cell proliferation, differentiation, and senescence. Likewise, there is an incomplete identification and characterization of the molecular and biochemical factors involved of hormone-regulation and cell signaling. Insight into these processes is necessary if we are to fully understand how selective clones of transformed prostate cancer cells evolve from an androgen-dependent to an androgen-independent state and acquire proliferative and metastatic characteristics.

Because of the lack of understanding of the basic processes that underlie prostate cancer development, progression, and metastasis, our ability to prevent, diagnose, and assign prostate cancer patients to appropriate treatment modalities is significantly hampered. To improve therapeutic and management options for men with prostate disease, we must develop relevant models to study prostate cancer biology, progression, and metastasis, and to also expeditiously identify, isolate, clone, and characterize relevant genes or gene products that may serve as reliable

biomarkers of prostate cancer progression. Subsequently, this information needs to be applied through translational projects and disseminated to medical practitioners.

Overcoming these significant challenges, however, can also be viewed as a golden opportunity to help eradicate clinical prostate disease. For example, the development of new human prostate cancer cell lines and xenografts that closely mimic initial androgen dependency but are capable of progressing to an androgen-independent and metastatic phenotype will provide templates for translational research. New strategies to screen large quantities of cells in different physiological and pathological states for differences in gene expression affords us an opportunity to identify marker genes associated with each stage of progression. As a result, the causative genetic switches for each of the multiple steps from initial neoplastic transformation to disseminated, hormone-resistant disease can be identified and applied in the clinic. Future biochemical, pharmacological, molecular, and structural studies of nuclear receptors that are closely related to androgen receptors will yield new experimental strategies that will improve our ability to search for and identify those genes that may be positively or negatively regulated by such hormones.

In 1997, the overall funding for prostate biology, progression, metastasis, tumor-host interaction, and genetics and data processing was insufficient. Although additional funds were made available by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the National Institute of Environmental Health Sciences (NIEHS) to support the investigation of the biology of benign prostate gland growth, these funds were not necessarily applicable to neoplastic prostate diseases. This level of funding is inadequate in view of the importance of understanding the basic biology of normal and pathological prostate tissues. We recommend that the level of funding to prostate cancer biology studies be quadrupled with approximately equal funding distributed between investigators with interest in normal and neoplastic prostate development, progression, metastasis, and tumor-host interactions, genetic applications, and data processing, and infrastructure development and support.

RESEARCH PRIORITIES

Priority One

Members of the PRG identified the following investigative questions as having the highest priority. The high-priority assignments were made by the members of PRG because: 1) these questions are highly relevant to clinical prostate cancer, and any progress made in these areas will have a significant impact on cancer prevention and treatment; and 2) these questions are solvable, provided that adequate funding can be provided. (See Section I for further discussion of classifications.).

What are the potential roles of nuclear receptors, their interactive proteins, and ligand-metabolizing enzymes on prostate growth, tissue interactions, and development?

This important topic receives exceedingly low levels of NCI funding. The lack of funding could be misleading, however, because other NIH institutes, such as NIDDK and NIEHS may fund this general area of research.

Despite numerous research projects being performed by academic institutions and industry on the subject of nuclear receptors and drugs that may block receptor-ligand interaction, affect steroid metabolism, and interfere with prostate development, a lack of communication between academic and industrial centers on this topic has impaired development of this important research concern.

In addition, although many studies have been performed at the cellular and molecular levels to delineate steroid receptor action and any subsequent role in carcinogenesis, relationships between steroid hormone-induced gene transcription, growth, differentiation, and senescence at the organistic levels remain rudimentary.

The following are barriers to progress in this area: 1) lack of consensus on the most appropriate models and targets that should be pursued and validated; and 2) inadequacy of extrapolating data obtained from culture cells or cell-free systems to that of the prostate gland *in situ*.

Recommended Actions:

To understand the structure and activity of the well-defined molecules such as nuclear receptors and steroid-metabolizing enzymes, it is critical to obtain crystallography data on the molecules of concern. In addition, increasing efforts need to be devoted to identifying and characterizing partners of nuclear receptors that may function together either alone or crosstalk with other cell signaling pathways to control proliferative and differentiative signals in cells.

1. Expedite structural and pharmacological studies of important nuclear receptors and steroid-metabolizing enzymes.

2. Expedite human genome-based studies and the identification, cloning, and characterization of proteins relevant to normal and cancerous prostate cells. Such information may be valuable in assisting further progress in this area of research.

What are the molecular determinants that govern cancer invasion, migration, and metastasis?

While prostate cancer that metastasizes is known to metastasize with few exceptions to the skeleton, this natural history does not occur in the established animal models used in prostate cancer research. To date, there is no clear understanding or molecular insight to explain this discrepancy. Moreover, the treatment of men with advanced forms of metastatic prostate cancer has received limited research effort. Although it is likely that treating patients with metastatic disease could result in significant improvements in quality of life and survival, there are few data in the literature that yield any meaningful information in dealing with this extremely important question.

A key barrier is that no animal or cell culture models allow for the study of the complete stages of carcinogenesis from initiation to promotion and from promotion through the cascade of progression that ultimately results in the establishment of skeletal metastasis with osteoblastic reaction.

Recommended Actions:

1. Develop additional models to study cancer metastasis, particularly with respect to skeletal pathophysiology and its associated biochemical characteristics.

2. Because of the lack of animal models to study the complete cascade of prostate cancer development, progression, and metastasis, NCI should invite scientists to develop new models with a clear focus on prostate cancer metastasis. Because prostate cancer can spontaneously develop in the canine prostate, it is recommended that prostate cancer be more extensively studied in the dog. Both the natural history and pathology of canine prostate disease need to be determined, and a recommendation should be made to the scientific community regarding the appropriateness of this model for human prostate cancer.

3. Continue to define metastasis-associated genes and their expressions in rodent and human cell or tissue models and validate such findings by correlation with both primary and metastatic clinical prostate specimen.

What are the biochemical and molecular events that govern the continuation of prostate development from early embryogenesis to the onset of adulthood, maturation, aging, and death?

Considering the importance of this question, current NCI funding is inadequate. Members of the PRG noted that funding for this topic, along with other similar subject matters in the general areas of prostate development and early stages of cell transformation, is too low. One reason that funding for this general area of research interest is insufficient is because the traditional authority over research involving normal prostate development and carcinogenesis lies with NIDDK or NIEHS. Conversely, multistep carcinogenesis, tumor biology, and regulation of cancer growth and treatment programs are traditionally administered and funded by NCI. It is important to point out, however, that this area of research represents a foundation for future clinical research. Thus, expanded funding in this area with an emphasis on furthering our understanding of normal prostate development and the subsequent steps of carcinogenesis, cell aging, and apoptosis is warranted.

The genetic and molecular mechanisms involved in prostate gland development in mammalian species are complex. Knowledge of prostate development, maturation, aging, and senescence is limited. Difficulties remain in studying a continuum of development in man, beginning *in utero* and followed through to neonatal, prepubertal, pubertal, and adult periods.

Appropriate animal models must be established that recapitulate not only normal development but also its subsequent transformation by epigenetic and genetic modulations to express pre-neoplastic changes. Currently, consensus in the scientific community is lacking regarding the standardization of current cell and animal model systems and the identification of new and future directions on model development.

Furthermore, investigations into international differences in prostate cancer development and how this may be applicable to prostate development and its early stages of neoplastic transformation in humans are needed.

Recommended Actions:

1. A consensus conference should be co-sponsored by NCI, NIDDK, and NIEHS to coordinate their resources and reach unanimity regarding appropriate models for the study of normal prostate development and early neoplastic transformation. Emphasis should be placed on deciding the appropriateness of these models to predict multistep carcinogenesis in man.

2. A clearinghouse to streamline information already available and information of high priority should be made readily available to the scientific community through websites, brochures, and consensus reports.

What are the specific cell-cell interactions between and among developing epithelial cells, stromal cells, endothelial cells, neuroepithelial cells, and inflammatory cells?

Cell-cell interactions maintain a fundamental role in normal prostate development and subsequent multistep carcinogenesis. By identifying the principal cells that participate in these processes, we can then appropriately address the roles of nuclear receptors, steroid-metabolizing enzymes, and inter- and intracellular communication factors. This area is clearly underfunded by NCI. Cell-cell interaction occurs throughout development in multicellular organisms.

Investigators who devote their efforts to pursuing topics related to prostate development should keep abreast of progress made by basic scientists who focus on the study of basic developmental processes and cellular interaction in lower species (e.g., Nematode, Drosophila).

In addition, cell-cell interaction studies in the prostate have thus far been limited to stromal-epithelial interaction with particular emphasis on defining the roles of epithelial cells and their relationships with smooth muscle and fibroblast cells. To date, little attention has been paid to defining the possible roles of other cell types, such as endothelial cells, neuroepithelial cells, or inflammatory cells in overall neoplastic processes.

Prostate cancer research, by and large, is conducted under the auspices of the clinical discipline of urology. In order to expand this field and to attract a more sophisticated approach to studying prostate development, cellular interaction, and molecular mechanisms of the basic processes mentioned thus far, it is essential to expedite cross-fertilization between basic sciences departments and clinically based urology departments. An insufficient number of investigators are well-trained, conversant, and have combined knowledge and research expertise in multiple areas of research, such as developmental biology, cancer biology, prostate biology, and clinical urology. The lack of a multidisciplinary approach to prostate cancer research and the absence of such opportunities in the current climate of academic departmental organization. Consequently, little communication exists between the basic science and clinical disciplines in many academic institutions.

Recommended Actions:

Support research that emphasizes specific cell-cell interactions between and among developing epithelial cells, stromal cells, endothelial cells, neuroepithelial cells, and inflammatory cells.

What are the regulatory effector molecules that control reciprocal interaction between epithelial and stromal cells, clonal interactions between cancer epithelial cells, and the interactions between cancer cells and most immune-reactive cells?

While a large number of grants in this general area of cell biology have been funded, there are still gaps in our understanding of cellular interactions involving more than two cell types. Most of the funded studies devote their efforts to the investigation of interaction between two cell types; seldom are the interactions between three or more cell populations in the prostate gland evaluated.

Although a transgenic approach is extremely valuable, most of the funded studies also address the functions of one or two putative factors in the prostate gland. Moreover, significant limitations exist in all of the models utilized (e.g., cellular interaction may be significantly affected by host factors), thus limiting the validity of control studies.

Deletions of genes by "knock-out" and additions of gene functions by "knock-in" techniques could adversely effect the survival of animals, hence hampering the analysis of transgenic animals from embryonic to adult and geriatric periods.

In the absence of critical evaluations of the rules of cellular interaction and androgen receptor in normal prostate development and its neoplastic processes, it is impossible to draw general conclusions from the results in this critical area of research.

Improved models that can be used to evaluate the concept of cell-cell interaction and the roles of cellular interaction in cancer development and progression are needed. Assessing the molecular basis of such interactions is applicable to human cancer. Improved validation of data obtained from experimental models derived from human prostate cancer specimens could be crucial.

Recommended Actions:

1. Support research in the areas of multicellular interactions in the prostate gland and improve transgenic and other animal systems by introducing factors to the prostate gland in the hope of recapitulating the natural history of prostate development and its neoplastic transformation.

2. Support research in normal prostate development and general developmental processes in biology to accelerate discoveries in the understanding of multicellular interactions in the prostate gland and their underlying molecular basis.

Are there features of DNA damage, DNA repair, or cell cycle progression that are novel in prostate cancer cells?

This is a "hot" question in every area of cancer research. It is surprising to note that although this question was given high priority by the PRG, only two projects specific to prostate and this question are currently being supported by NCI.

Because cancer is believed to be associated with DNA damage and with increasing genomic instability, the understanding of DNA replication, repair, and regulation of cell cycle progression in cancer cells is crucial to the prediction of tumor responses to therapy. The challenges are to define whether there are prostate-specific features of DNA damage, repair, or regulatory checkpoints that are different from other solid tumors and whether one can take advantage of these features so that tumors resistant to hormonal, radiation, or chemotherapy can be rendered sensitive to such treatment.

In addition, prostate cancer cell lines and xenografts are difficult to establish. Many of the currently available models have fast tumor doubling times that differ from those of clinical samples. It is uncertain how information gained from these model studies may be applied and extrapolated to clinical disease.

No clear differences between the phenotypic and genotypic characteristics of prostate cancer cells and those of other human malignancies have been defined. Some members of study sections may be reluctant to view projects favorably that are only geared toward prostate cancer, since this area of research is also funded for other forms of tumors.

Recommended Actions:

1. Encourage a multidisciplinary approach to address the roles of DNA damage, DNA repair, and cell cycle progression that are distinctly different in prostate cancer cells than in other forms of malignancies. By expanding the investigation of this question to the prostate and by closely interacting with scientists and clinicians who may be interested in other forms of malignancies, we may be able to better understand why prostate cancer is less sensitive to radiation therapy and chemotherapy, which are often highly efficacious against the growth of other solid tumors.

What are the genetic and epigenetic determinants that affect progression of prostate cancer from the localized to disseminated state? What molecular markers are associated with such progression?

This important question appears to receive inadequate NCI support. This broad topic addresses fundamental issues of prostate cancer growth and progression: to identify the precise genetic loci that are responsible for the susceptibility of individuals to cancer

and the epigenetic constraints that may become activated in certain populations with defined genetic backgrounds (e.g. certain environmental factors may predispose to prostate cancer development and progression). For these reasons, the interaction between epigenetic and genetic factors deserves a substantial increase in support.

Mechanisms to translate information derived from animal models to human disease are not clearly defined. In addition, there is a lack of clearly identifiable human data to pin down the genetic and epigenetic factors that could influence prostate cancer development and progression. There also is a lack of consensus on how to interpret data produced from the studies of animal prostate cancers with human prostate cancers.

Recommended Actions:

Improved funding is needed to vigorously test the discoveries made in the understanding of the genetic, molecular, and tumor biological aspects of rodents to those of humans. In this same context, it is also important to evaluate and validate findings made in cell culture studies with animal models and pathological specimens obtained from men.

1. Support research to validate genetic and epigenetic molecular markers discovered by scientists in their investigation of tissue culture models and animal models, and to validate these markers by correlating them with clinical specimens with well-defined clinical data.

2. Support research to establish powerful methods that will allow "fast-track" discoveries (including identification, sequencing, cloning, and characterization of molecular markers), whether genetic or epigenetic, that will then be applied and validated in human prostate diseases.

Are there hereditary markers, angiogenesis switches, and/or biochemical and molecular determinants that predict progression?

This high-priority question receives moderate financial support. Unlike the previous topics, this question specifically focuses on the key genetic (e.g. hereditary markers) and epigenetic (e.g. angiogenesis) factors currently

under investigation as biochemical and molecular markers that serve to predict prostate cancer progression. Improvements in predicting and understanding tumor progression are important to improving patient management and reducing costs of health, since only one-third to one-half of the patients diagnosed with prostate cancer have progressive disease.

Despite intensive investigations into new genetic loci and biomarkers, their significance and value over existing molecular markers remains undetermined. There appears to be little incentive and few mechanisms available to test novel biomarkers or compare them head-on with existing molecular markers. An absence of comprehensive tissue and serum specimen banks with

corresponding clinical correlation impedes the opportunity for conducting thorough comparative studies.
In addition, there is an understandable reluctance among practicing urologists to accept novel biomarkers without substantiated testing by the scientific community and the significant cost of validating and marketing any new biomarkers for clinical use. There is currently no existing mechanism or financial support to conduct such comparative studies. This type of research is in general considered "service-oriented" and has traditionally been discouraged by the scientific community. Such investigations are not viewed by the scientific community as a high priority since these investigations do not generally result in publication or career advancement.

Recommended Actions:

Financial resources should be identified to perform the task of discovering new and better markers than PSA for the early diagnosis of patients who harbor fast-progressing and virulent forms of prostate cancer. Additionally, relevant biomarkers associated with disease progression can be utilized to monitor clinical responses of patients to various forms of treatment modalities.

1. Support "service-oriented" research and combine forces with industry (who will benefit most directly by the outcome of this type of research) to fund projects that may have merit in discovering new biomarkers predicting prostate cancer progression.

What are the critical housekeeping and regulatory genes that may be associated with human prostate cancer development and progression?

There is a lack of critical information regarding the applicability of discoveries of novel genes from cell culture and animal models and their applicability to human disease. An absence of genetic databases readily available to research institutions has impeded basic investigations in this area. In addition, the relevance of the information obtained from these studies to clinical specimens of human prostate cancer has not been validated. These resource issues are compounded by uncertainty about pending or future patent rights of investigators and their working institutions.

Recommended Action:

1. Support the collaborative pursuit of discovering novel genes expressed during prostate cancer development and its progression to androgen independence.

How do we define genetic susceptibility of individuals to prostate cancer, and how is such susceptibility associated with other forms of malignancies or diseases?

This question emphasizes the importance of genetic susceptibility of hosts to cancer development and progression. It is modestly funded by NCI.

Because prostate cancer disproportionately affects African Americans, there is a general consensus that devoting efforts to identifying the potential differences in genetic susceptibility between African Americans and other population groups will help answer questions about prostate cancer. New understanding may be acquired from the study of populations at extremely low prostate cancer risk (e.g. Asians, Africans, and Asian or African immigrants living in North America) and their changes in risk upon immigration to "Westernized" countries.

While genetics may be an important contributing factor to cancer initiation and development, the importance of environmental influences (epigenetics) cannot be emphasized enough. Both the scientific community and the public as a whole do not have a clear understanding of the interplay between the genetics of cancer and the environment, which may enhance or delay the rate of prostate cancer progression.

Research in this area is made difficult by the unavailability of genetically homogenous and relatively non-mobile populations for the proposed study and difficulties in obtaining funding for studies in low-risk populations (e.g., prostate cancer studies on Asian populations).

Recommended Actions:

1. Encourage international and immigration studies through RFA mechanisms to alleviate the lack of information in this general area of research.
2. Build a consensus and create collaborative consortia among geneticists, epidemiologists, molecular biologists, and urologists to design the most efficient way to approach this topic.

Priority Two

- What are the molecular and cellular mechanisms that control cell signaling and its subsequent influence on cell motility, migration, angiogenesis, and metastatic profiles?
- What genes are directly regulated by androgen receptors during prostate development?
- How do cells survive in the prostate gland upon androgen withdrawal?
- What other signaling pathways regulate prostate growth, development, differentiation, and apoptosis?

- What are the genetic polymorphisms that occur in the key regulatory molecules, such as androgen receptor, p53, cell cycle, regulatory molecules that control apoptosis, and senescence?
- What is the nature of prostatic stem cells?
- What are the molecular and cellular mechanisms that control the response of prostate cancer cells to alterations in androgens? What is the mechanism by which androgen antagonists, such as flutamide, switch from inhibitors to enhancers of prostate cancer cell growth during systemic therapy tumor progression?
- Can interactions between bone and prostate cancer cells be interrupted, and can androgen-independent and metastatic phenotypes be reversed?
- What are the genes, if any, that may explain international and racial differences in prostate cancer development, progression, and metastatic potential?

Priority Three

- How are indolent and virulent prostate cancer defined?
- What are the key determinants (either from metastatic cells or host cells) that influence tumor behavior and metastatic patterns?
- What is the role of the immune system in prostate cancer progression?
- What is the role of angiogenesis in metastasis?
- Are there genes that can be considered hereditary prostate cancer genes?
- Are there steps in prostate oncogenesis that recapitulate developmental events governing stem cell proliferation, migration, invasion, differentiation, or apoptosis?
- Are there molecular determinants that can distinguish high-risk groups (e.g., African Americans) from low-risk groups (e.g., Caucasians)?
- Do prostate cancer patients with soft tissue only disease (i.e., large lymph nodes or lung metastases, but not bone disease) have a phenotypically different disease?
- Can the identification of such genes be applied to the general population for the diagnosis, prognosis, and treatment of prostate cancer?
- What are the functions of other nuclear receptors, such as ER-beta, in the prostate?
- What are the molecular determinants of prostate cancer metastasis to the skeleton?
- How can genes be categorized? Should genes be categorized into high penetrance versus low penetrance genes, etc.?

B. ETIOLOGY AND PRIMARY PREVENTION

The age-adjusted incidence of prostate cancer now surpasses that of all other cancers among men in the United States. In addition, prostate cancer is the second leading cause of all male cancer deaths in the country, following cancer of the lung. This section addresses our effort to understand the causes of morbidity and mortality from this disease, and to learn how to prevent it.

Prevention provides an appealing approach to control of prostate cancer. The ability to block either the initiation of malignancy or its progression to metastasis will have a large impact on the magnitude of the disease burden. Effective prevention efforts require an understanding of prostate cancer etiology. However, despite years of effort, classical epidemiologic studies have revealed few risk factors for the disease. The paucity of established risk factors limits preventive efforts and highlights the need to better understand the biology of both normal and malignant prostate cells and tissues. In addition, better understanding of how genetic predisposition and exogenous exposures interact to determine prostate cancer susceptibility is needed to design effective preventive strategies.

CURRENT STATUS OF THE FIELD

The most extensively studied and documented risk factors for prostate cancer include:

- age
- race/ethnicity
- family history
- dietary intakes
- androgen production and metabolism, and
- other factors, such as vasectomy, benign prostatic hyperplasia, serum levels of type 1 insulin growth factor (IGF1), and living in the United States.

Age, race, and a history of prostate cancer in a close relative are well documented but poorly understood risk factors for prostate cancer. In contrast, the evidence to support etiologic roles for the other factors is less clear, with some studies showing positive associations, and others showing little or no altered risk associated with variation in the characteristic. The following is a brief review of the current state of knowledge concerning the roles of these factors in prostate cancer etiology.

Age

Prostate cancer is particularly common in elderly men. The average mortality rate among U.S. men aged 85 years or older is 629 deaths per 100,000 per year. Lung cancer, which is the second most common cancer in this age group, has a much lower mortality rate of 435 per 100,000 men. A distinctive feature of prostate cancer is that histologic cancer, which is a clinically unsuspected or incidentally discovered lesion, is frequently found in elderly men, particularly at the time of autopsy. Its prevalence has been reported at more than 40 percent in men aged 70 years or more.

It is not clear whether some physiological concomitant of aging is inherently necessary for prostate carcinogenesis and progression, or whether these processes are so slow that

they require many years to become clinically evident. This uncertainty indicates the need for better understanding of the natural history of prostate cancer. Does the steep rise with age of prostate cancer incidence reflect the rate of initial malignant transformation, or the rate of progression to clinical detection? The dramatic increases in prostate cancer incidence rates that occur in the seventh and eighth decades of life, combined with the almost ubiquitous occurrence of histologic prostate cancer in aging males has led to the speculation that the processes of aging and prostate carcinogenesis may be biologically related.

There is a critical need to find host and tumor markers that characterize those cancers most likely to progress to metastasis within the human lifespan. Moreover, we need to evaluate etiologic factors in terms of their potential contributions to risk. In particular, we need to know if there are exogenous exposures that promote progression to aggressive disease, and if so, whether interventions can be devised to block their effects.

Race/Ethnicity

Large variations in the incidence and mortality of prostate cancer have been observed among countries and racial/ethnic groups. African Americans have the highest mortality rates for prostate cancer in the world, followed by whites in Scandinavian countries. Asian men have the lowest mortality rates. The disproportionately high prostate cancer mortality rates in African Americans have been attributed to the poor prognosis of the disease in this group. Some studies have found African Americans more likely to present with regional or distant cancer than are Caucasian men, even after adjustment for socio-economic status. Other studies have observed greater proportions of poorly differentiated and advanced tumors and poorer overall, cause-specific, and disease-free survival rates in African Americans. In addition, there is evidence that stage-specific prostate cancer survival also is worse in African American men than in Caucasian men, even in equal-access health care settings.

The large racial differences in prostate cancer incidence and mortality provide important clues to the etiology of the disease. These clues should be exploited to further our understanding of prostate carcinogenesis. An important priority for future research is the establishment of cohorts of men at high, moderate, and low risk to be studied for genetic and lifestyle factors in relation to future prostate cancer occurrence, and for progression of disease once it occurs.

Family History

Epidemiological studies have found consistently that men who report a history of prostate cancer in a father, brother or son have a two- to three-fold increased risk of developing the disease, with higher risk estimates associated with multiple affected relatives or relatives affected at young ages. Segregation analyses support the possibility of inherited genetic factors as one explanation of this phenomenon. Moreover, the evidence suggests inheritance of rare, autosomal dominant alleles. Such inherited alleles have been estimated to account for some 43 percent of the disease in men aged 55 years or less, and some 9 percent in men of all ages. However, formal testing of

possible inheritance of genes on the X chromosome has not yet been reported. Several population-based studies have reported an excess risk of prostate cancer in men with affected brothers compared to those with affected fathers, consistent with the hypothesis of an X-linked mode of inheritance. In support of this possibility, there is evidence associating risk with polymorphisms of the androgen receptor (AR) gene on the X chromosome.

Linkage analysis in families with multiple cases of prostate cancer has found suggestive evidence for prostate cancer susceptibility loci on several chromosomes, including 1q, 4q, 5p, 7p, 13q and Xq. A putative hereditary prostate cancer gene, called HPC-1, has been localized to chromosome 1q24-25. Although the data are sparse, this locus may be more important in African Americans than in Caucasians. While two confirmatory studies have corroborated linkage to HPC-1, three additional studies have not. The disparity in these studies emphasizes the obstacles to gene identification in prostate cancer, which include a high phenocopy rate and the possibility of genetic heterogeneity.

To evaluate these results, the NCI-sponsored International Prostate Cancer Linkage Consortium (IPCLC) initiated a recent collaborative analysis of some 500 high-risk prostate cancer families. Preliminary results from this analysis do not support a major role for a hereditary prostate cancer locus in the region 1q24-25.

There is need for continued ascertainment of high-risk families, particularly African-American families, and for continued attempts to identify other hereditary prostate cancer genes. We also need to determine what fraction of familial prostate cancer aggregation can be explained by Mendelian inheritance of rare alleles of specific genes. The identification of such genes and determination of their function could provide insight into multiple facets of prostate carcinogenesis. This insight would provide a basis for the development of preventive, diagnostic, prognostic and therapeutic approaches to control of the disease. Research in this area could benefit not only carriers of high-risk alleles, but also the general population.

Dietary Intakes

Modification of dietary intakes is a potentially promising method of prostate cancer control. The plausibility of diet having a major role in the etiology of the disease is supported by the descriptive epidemiology of the disease: 1) the incidence of prostate cancer has been rising in Japan, where substantial dietary changes have occurred in the past three decades; 2) the incidence of the disease increases in Japanese and Chinese migrants to the United States; 3) the incidence of prostate cancer is positively correlated with other diet-related cancers, such as cancers of the colon and endometrium.

The main dietary component that has been associated with prostate cancer is fat. Overall, the epidemiological data are rather consistent in showing positive association with dietary fat, especially saturated fat, although some cohort studies have not supported this relation. It is possible that the timing of fat intakes (e.g., youth, young adulthood), and type of fat may be important. These issues need investigation in prospective cohort studies. Several mechanisms

have been offered for a promotional effect of fat on prostate carcinogenesis, including effects on cell membrane composition, prostaglandin synthesis, and androgen levels in blood or tissue. However these mechanisms are largely speculative, and lack critical testing with observational or experimental data. There is need for more work in this area.

The relation of prostate cancer risk to intakes of various micronutrients is less certain at this time. For example, the role of vitamin A or its precursors, particularly betacarotene, is unclear at present, with some studies showing negative associations and others showing no association or even a positive association. Recent studies have suggested protective effects for intakes of selenium and vitamins D and E.

The relations between androgen production/metabolism and intakes of specific macronutrients and micronutrients (e.g., fat, vitamins D, E, A, lycopene) are not well understood, but potentially important determinants of prostate cancer risk. Moreover, the roles of particular growth regulatory proteins in risk elevation and reduction also deserve further study. For example, recent findings of increased risk associated with elevated serum levels of insulin-like growth factor 1 (IGF-1) need confirmation. These findings implicate non-androgenic growth regulatory pathways as potentially important in determining prostate cancer risk.

Androgen Production and Metabolism

Androgens have some role in the development of prostate cancer. These hormones are required for the growth, maintenance and functional activity of prostate cells. Castration or estrogen therapy can have a palliative effect on prostate cancer. However, the results of epidemiologic studies of serum or plasma androgen levels have been inconsistent. This inconsistency may reflect poor correlation between circulating and intracellular androgen levels. It also may reflect inappropriate timing of androgen measurement. Most measurements are taken in elderly men, while androgen levels may play more important roles in youth, adolescence, or young adulthood.

We need to identify genes that control various aspects of androgen production and metabolism, and more generally, genes that control all aspects of prostate physiology. We need to understand how variations within such genes correlate with risk in different populations. A promising example is the identification of the highly polymorphic polyglutamine tract within the first exon of the androgen receptor (AR) gene, and the finding that shorter, more active alleles of this gene are more common in African Americans, whereas longer, less active alleles tend to be seen in Asian populations. Additional polymorphisms and associations have been found for other genes involved in androgen metabolism (e.g., 5-alpha reductase, various cytochrome P450s), and other regulatory pathways (e.g., the vitamin D receptor).

Other Factors

A wide range of other exogenous exposures and host characteristics has been suggested as having an etiologic role in prostate cancer development, including birthweight, obesity, height, benign prostatic hyperplasia, alcohol consumption, smoking, radiation exposure, infectious agents, vasectomy,

and physical activity levels. At present, however, the evidence supporting an important role for these factors is rather tenuous.

Implications for Prevention

The possibility that there exist modifiable factors suitable for manipulation in prostate cancer prevention is enhanced by the strong variation in risk across populations of different ethnicity, and the increased incidence observed in migrants from low-risk countries to high-risk countries. Although the incidence of clinically manifest disease varies extensively, there is some evidence that the prevalence of histologic or subclinical disease may be less variable. This evidence has been used to implicate prostate cancer progression, rather than its initiation, as the rate-limiting step that determines the magnitude of the prostate cancer problem. This issue illustrates a fundamental difficulty, which resonates throughout any discussion of prostate cancer—what defines clinically important disease? It may not be necessary to prevent prostate cancer initiation, but rather a more effective approach may be to focus on prevention of progression to more aggressive disease. These questions emphasize the need for increased understanding of the molecular differences between progressive and non-progressive prostate cancer.

Potential preventive agents have been identified using mechanistically oriented strategies, and these efforts must be continued. Examples include evaluation of the preventive efficacy of finasteride, which inhibits conversion of testosterone to its active metabolite dihydrotestosterone (DHT), with the idea that DHT promotes prostate cancer development. Another source of potential preventive agents are dietary factors, with epidemiological data suggesting that intakes of various nutrients may either stimulate (e.g., fat) or block (e.g., vitamins D and E, selenium) prostate cancer formation or progression.

Future prevention strategies should be targeted at both the initiation and the progression of prostate cancer. The latter approach is particularly attractive in light of the long natural history of the disease. Indeed, an important step in developing effective prevention strategies consists of validating the evolution of disease from prostate intraepithelial neoplasia (PIN) to localized prostate cancer to metastatic disease.

VISION

An important goal in prostate cancer prevention is to identify men at high risk of developing life-shortening forms of the disease, and to understand how lifestyle characteristics and exogenous exposures influence this risk. This understanding will allow the development of effective prevention strategies.

The ability to identify predisposing factors in a man's DNA and to understand how his lifestyle modifies his risk could be attained with targeted research and exploitation of emerging DNA-based chip technology. For example, it is likely that risk-modifying dietary factors and chemopreventive agents will be more firmly established, and that the magnitude of risk alteration will vary with genotype. It is possible that a man's risk for aggressive prostate

cancer could be estimated using routine screening procedures. For example, one could apply to germline DNA a micro-array-based genotypic analysis of a battery of polymorphic loci previously demonstrated to modify prostate cancer risk. This would allow stratification of men into high-, intermediate-, and low-risk categories. Men at high risk for clinically relevant cancer would be the best candidates for preventive measures, and preventive efforts could be focussed on them.

Increased understanding of prostate cancer etiology provides opportunities for new primary prevention and screening approaches. Based on increased knowledge of the factors implicated in prostate cancer development, new preventive strategies will evolve, which must be tested in rigorous, appropriately controlled trials. Ultimately, men at increased risk of developing prostate cancer may be able to lower this risk by lifestyle modification appropriate for their specific types of risk elevation. For example, if an individual is determined to be deficient in a particular prostate carcinogen-detoxifying enzyme, he could compensate either by avoiding sources of the carcinogen or by incorporating into his diet a specific inducer of other pathways to deal with the carcinogen.

CHALLENGES AND OPPORTUNITIES

Critical to the success of our efforts to prevent prostate cancer will be the design and implementation of randomized intervention trials. We will need trials to evaluate strategies for preventing both the development of clinically important disease in asymptomatic men and the progression of disease in men with localized or regional disease. The current challenge is to expand our knowledge of etiology to the level that such intervention trials are feasible. If we can succeed in doing this, the explosion of new molecular genetic techniques and knowledge will provide unprecedented opportunities for determining subgroups of men who are particularly susceptible to prostate cancer because of their genetic predisposition. These men would be ideal candidates for such intervention trials.

- Better knowledge of etiology also is critical to making progress in elucidating gene-environment interactions in prostate cancer susceptibility. Specifically, we will be able to investigate how the interplay between an individual's genetic makeup and lifestyle characteristics modifies his risk for prostate cancer. As we improve our knowledge of etiology, we will open the doors to new opportunities in evaluating such gene-environment interactions.

The areas most challenging and most promising for future research initiatives in prostate cancer etiology and prevention are:

- Determining the basis for the strong ethnic variation in risk. Does this variation reflect ethnic differences in initiation of malignancy, or differences in disease progression, or both? What are the relative roles of genetic makeup vs. exogenous exposures in determining this variation?
- Elucidating the roles of specific dietary intakes in prostate cancer initiation and progression.

- Understanding the relation between exogenous exposures and disease progression.
- Understanding the roles of specific androgens and their metabolites as contributors to prostate cancer risk.
- Identifying genes responsible for the strong disease clustering seen in some families.
- Identifying polymorphisms of common "low-penetrance" genes whose combined attributable risk may account for most prostate cancer.
- Evaluating genetic determinants of androgen production and metabolism as they influence risk.
- Elucidating gene-environment interactions in prostate cancer susceptibility.
- Developing a sound knowledge base for testing agents for both primary and secondary prevention.

RESEARCH PRIORITIES

Priority One

What genes are important in the etiology of prostate cancer? What fraction of familial prostate cancer is monogenic with Mendelian inheritance of susceptibility alleles? What is the function of such genes? What fraction of all clinically relevant prostate cancer is due to inheritance of rare, highly penetrant alleles of certain genes, and what fraction is due to common, low-penetrance alleles of other genes?

A subset of prostate cancer probably is monogenic, with a Mendelian mode of inheritance of susceptibility alleles. At present, however, we have incomplete knowledge concerning the existence of such genes, and the proportion of all prostate cancer due to them. Identification of such prostate cancer susceptibility genes and the determination of their mechanism of action are important next steps in understanding the molecular genetic basis of prostate cancer.

While the identification of genes with rare, highly penetrant alleles holds the promise to elucidate pathogenesis, it is likely that common polymorphisms of genes involved in metabolic or regulatory pathways will account for a larger fraction of the prostate cancer burden. Accordingly, there is need for further study of genetic factors involved in testosterone biosynthesis, transport to prostate cells, activation to dihydrotestosterone, transport within prostate cells and degradation. Studies showing the functional relevance of any polymorphisms associated with altered prostate cancer risk also are needed. The overall objectives of this type of research are to identify markers which alter risk across multiple loci of specific genes, in order to establish polygenic profiles characterizing men at particularly high and low risk, to determine how exogenous risk factors such as dietary influences modify these genetic risk profiles, and to determine how much of the racial differences in risk can be explained by these markers. Markers associated with prostate cancer risk in

white men have been identified on two genes (the 5-alpha-reductase and androgen receptor genes) in this androgen activation pathway, which culminates in cell division of prostate epithelium. These studies need to be extended to other populations. There exist many other such candidate genes in this androgen activation pathway which, as yet, are unexplored in the context of prostate cancer or are only in the most preliminary stages of investigation.

Recommended Actions:

1. Support the infrastructure for the collection of biospecimens and clinical data from families with multiple cases of prostate cancer for the conduct of gene identification efforts.
2. Establish public databases of clinical information on individuals from families with multiple cases of prostate cancer.
3. Establish repositories of immortalized lymphoblastoid cell lines from individuals in prostate cancer families, with corresponding genotype and phenotype information.
4. Support studies evaluating genetic factors involved in testosterone biosynthesis, transport to prostate cells, activation to dihydrotestosterone, transport within prostate cells and degradation.
5. Support studies evaluating the functional relevance of polymorphisms associated with altered prostate cancer risk.
6. Once genes are identified, support the establishment and availability of transgenic or knockout animal models for mechanistic studies.

Which dietary nutrients affect risk of prostate cancer (e.g., fat, phytoestrogens, micronutrients)? What are the mechanisms by which these nutrients alter risk?

The potential impact of dietary modification on prostate cancer morbidity and mortality is great. Descriptive epidemiological data support a role of diet in this disease. At present, however, we have only rudimentary understanding of which intakes are important, at which stage of the carcinogenic process they are important, and why they are important. Better understanding of these issues is a critically important research priority.

There are preliminary data suggesting that insulin growth factor 1 (IGF1) is positively associated with prostate cancer risk. IGF1 is a strong mitogen with possible effects on hormone biosynthesis/metabolism. Since diet modulates IGF1 levels, IGF1 may provide a clue to the role of specific nutrients or total energy intake in prostate cancer. Limited data also suggest that calcium intake may be positively associated with prostate cancer. Calcium may increase risk by down-regulating the conversion of 25-dihydroxyvitamin D to its active metabolite 125-dihydroxyvitamin D (associated with reduced cancer risk). There is need for better understanding of these and other potential dietary associations. In particular, fatty acids, vitamin E, selenium, lycopene, phytoestrogens and beta-carotene may be important exposures to evaluate. There is also need for studies of genetic factors regulating metabolism and

transport of specific nutrient intakes, such as vitamin D and fatty acids.

Recommended Actions:

1. Support nutritional science and epidemiologic studies that include cohorts with long-term follow-up and repeated dietary assessments over time. These studies should also include the collection of germline DNA and an extensive clinical database.
2. Encourage efforts to attach dietary measurement studies to laboratory nutrition research and ongoing clinical trials.
3. Support studies aimed at better understanding of the roles in androgen production and in prostate physiology of nutrients such as fat, vitamins D and E, selenium, lycopene, phytoestrogens, calcium and beta-carotene.
4. Support studies of genetic factors regulating metabolism and transport of specific nutrient intakes, such as vitamin D and fatty acids.

What other exogenous risk factors are involved in prostate cancer (e.g., viral, exercise, vasectomy, sexual factors)?

A wide range of other exogenous exposures and host characteristics has been suggested as having an etiologic role in prostate cancer development, including birthweight, obesity, height, benign prostatic hyperplasia, alcohol consumption, smoking, radiation exposure, infectious agents, vasectomy, and physical activity levels. At present, however, the evidence supporting an important role for these factors is rather tenuous.

Recommended Actions:

Given the preliminary nature of the findings the PRG has no specific recommendation at this time.

Which genetic and exogenous risk factors account for differences in incidence and mortality between in the high-risk African American population, the moderate-risk Caucasian population, and the lower-risk Hispanic and Asian American populations?

We need better understanding of why different populations have such different prostate cancer risks. Do African Americans have a greater genetic predisposition to the disease, or does some aspect of their lifestyle, such as diet, increase their risk? Are there protective factors that are more prevalent in low-risk Asian populations? Are there ethnic differences in the rate of recurrence, metastasis and death among men with localized or regional disease?

Recommended Actions:

Extend research efforts to include nonwhite ethnic groups. An important priority is the establishment of cohorts of African American, Hispanic and Asian American men to be studied for genetic and lifestyle factors in relation to future prostate cancer occurrence. Further studies of Caucasian men, who overwhelmingly account for the burden

of prostate cancer in this country, are also required.

Are there genetic or exogenous factors associated with prostate cancer progression, as opposed to its incidence?

A major question in relation to prostate cancer etiology is what factors are involved in the progression of indolent prostate cancer to its more aggressive form, which leads to clinical diagnosis and metastasis. A related issue is the need to identify prognostic factors in prostate cancer tissue, which may be used to predict aggressive versus non-aggressive disease. Such information would provide important data to determine which prostate cancers require the most aggressive treatment protocols. In addition, little information is available on patient characteristics that may be associated with prognosis and thereby could be targets for secondary prevention. Establishment of population-based cohorts of prostate cancer patients with tumor tissue banks would be a valuable resource for identifying prognostic factors for progression, metastasis and death.

Recommended Actions:

Support population-based prospective cohort studies of men with prostate cancer to evaluate risk of recurrence, metastasis and death. These studies should include repositories of germline DNA, tumor tissue banks, and clinical and epidemiological data. They also should control for stage and grade of disease and pretreatment PSA. Potential predictors include diet, body size, family history, and physical activity patterns.

Are there interactions between genetic predisposition and exogenous exposures?

When feasible, gene-environmental interactions should be considered in assessing molecular markers at both early and late stages of tumor progression. We need to know whether dietary exposures interact with the genetic determinants of prostate cancer risk. We also need to know what other exogenous exposures interact with the genetic determinants of prostate cancer risk. These studies will require DNA from large samples of men, and their designs will require careful thought.

Recommended Actions:

As we learn more about the genetic and exogenous determinants of prostate cancer risk, support studies with adequate sample sizes to evaluate the possibilities of gene-environment interactions. This goal may require collaboration among multiple centers.

What interventions can alter the underlying etiology of prostate cancer? What are the most promising potential preventive agents and activities?

At present, too little is understood about the mechanisms and timing of intake (e.g., dietary exposures during adolescence, young adulthood) for specific nutrients in prostate carcinogenesis to undertake a dietary intervention trial at this time. We need more data to provide the knowledge infrastructure to support large scale, informative trials.

Recommended Actions:

In order to facilitate future intervention trials, support studies addressing the following questions:

1. What are the likely mechanisms of action of potential chemopreventive interventions?
2. What are appropriate endpoints for chemoprevention trials (e.g., intermediate endpoints, quality of life, decreased mortality)?
3. What are appropriate intermediate endpoints (e.g., high-grade PIN) in designing prevention trials?
4. Can preventive agents be classified by mechanisms and stage of carcinogenesis and inhibition?
5. How can prevention trials be designed with fewer patients and shorter time frames?
6. What characteristics of prostate cancer are most amenable to preventive efforts?
7. What are the criteria for initiating a prevention trial?
8. What is the appropriate target population for a prevention trial?
9. What information should be collected in epidemiologic studies to develop prevention hypotheses?

What is the potential of new animal models for testing of potential chemopreventive agents?

Although the prostate gland is present in all mammalian species, there is enormous variation in its anatomy, biochemistry and physiology. This variation has limited the search for useful animal models for human prostate cancer. There is need for valid, rapid and reproducible mammalian models of prostate carcinogenesis, in order to test potential chemopreventive agents. Transgenic rat models may be useful to overcome the difficulty of testing DHT inhibitors as chemopreventives.

Recommended Actions:

Support the development of mammalian models for prostate cancer initiation and progression that adequately mimic these processes in humans.

Priority Two

- What are the relative contributions of genetic predisposition, host characteristics and exogenous exposures in populations at different risk?
- Why is age such a powerful risk factor in the development of prostate cancer?
- What are the etiological factors that influence prostate cancer risk in young vs. old men?
- Does the progression of prostate cancer in young patients differ from that in older patients?

Priority Three

- How can exposures and outcomes be measured reliably and reproducibly to allow the collection of comparable data across studies?

C. EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Many more prostate cancers exist in men over age 50 than ever become clinically apparent or significant. Consequently, men in the United States face serious dilemmas regarding early detection, diagnosis and treatment for this disease. If prostatic carcinoma goes undetected, a given patient could eventually face a debilitating and frequently lethal disease. On the other hand, if his tumor is one that will remain "quiescent," or clinically insignificant throughout his natural life span, detection could lead to the adverse consequences of over-treatment. Fortunately, the PSA test rarely detects clinically insignificant tumors. Nevertheless, new markers are needed to determine which clinically significant tumors are potentially lethal to a specific patient. Also, the increased morbidity, particularly incontinence and/or impotence, associated with definitive therapies is significant and must be avoided whenever possible.

The challenge to the basic and clinical urologic oncology communities is threefold. First, methods of early detection must be refined to assure that, whenever possible, the carcinomas that are detected are clinically significant and carry the potential to kill their host if not detected and treated. Second, diagnostic methods must be improved to assure that clinically relevant cancers are not missed. Third, improved prognostic "markers" that can guide the therapy of patients in an individualized fashion must be developed. This report summarizes the views of the PRG regarding the current status of research into the three interrelated fields of prostate cancer early detection, diagnosis and prognosis. Also discussed are the areas of research that should be vigorously pursued to bring the clinical management of this disease into focus for the future.

CURRENT STATUS OF THE FIELD

The ability to change our current paradigms of the early detection and diagnosis of prostate cancer depends in large part on the development of refined and clinically significant prognostic markers. This, in turn, depends on a thorough understanding of the basic biology of prostate cancer, as addressed in Section A, *Biology, Progression, and Metastasis of Prostate Cancer.*

EARLY DETECTION

Over the past decade, significant progress has been made in public awareness of prostate cancer in the United States. A decade ago men knew little of the disease and discussed it even less. Now, the Internet has literally thousands of locations for information and discussion about prostate cancer. Also, the health and popular press have routinely run stories on the disease, specifically about the use of the PSA test for detection.

In addition, the number of free detection clinics available at selected institutions has increased each year, resulting in an exponential increase in the number of asymptomatic men who have been screened over the last decade. However, with this rise in screening has also come concern about the relative value of such efforts. Based on autopsy studies it is estimated that as many as 1 in 4 men 30 years of age may harbor a small focus of prostate cancer in their glands. This number stands in stark contrast to the

expected 1 in 9 men who will ever be diagnosed with "clinically significant" disease. No effective retort has been made to Whitmore's dictum that "more men die with the disease than from it." Yet data exist that indicate we can detect prostate cancer relatively early in its course and that the majority of carcinomas detected by serum screening methods are likely to be clinically relevant. Thus, the still missing piece of information is whether early detection of prostate cancer will have a positive impact on the overall morbidity and mortality from the disease itself.

The increasing number of methods used to treat clinically localized disease compounds this problem. Each of these has its own complications and restrictions regarding use. Consequently, to determine whether early detection is desirable, one must define and analyze a broad spectrum of variables that could affect outcome, including race, diet, stage and grade of the disease, and treatment modality. Our knowledge of the specific impacts of each of these variables and their interconnections remains relatively incomplete. We have most of the pieces of the prostate puzzle; we just do not know what the picture is supposed to look like.

DIAGNOSIS

Our ability to diagnose prostate cancer has certainly improved. We are no longer limited to the relatively inaccurate information obtained from digital rectal examination. While digital rectal exams remain a helpful component to diagnosis, we now have available an increasingly sophisticated array of methods, including serum radioimmunoassays and a variety of transrectal ultrasonographic techniques. Despite these tools, however, we still miss carcinomas that could be of clinical consequence. The dimensions of this problem remain unknown. Several new technological advances have been made in body imaging, particularly color flow Doppler and magnetic resonance imaging. The use of reverse transcription polymerase chain reaction (RT-PCR), which detects circulating tumor cells, has also opened new avenues for "molecular" diagnosis and staging. At present, however, the value of such techniques in diagnosing prostate cancer remains relatively unclear.

Nevertheless, the advent of the PSA test has had a profound impact on the diagnosis and treatment, both primary and secondary, of prostate cancer. During the five-year period between 1992 and 1997, the incidence of prostate cancer increased from about 130,000 diagnoses to over 300,000. Current estimates for 1998 incidence are about 185,000, as the "backlog" of undiagnosed, clinically significant prostate cancer has been "culled" out by the screening process. The incidence is declining to a new steady state that will likely be somewhat higher than that prior to the PSA screening era. The use of the PSA test in conjunction with the digital rectal exam has increased the number of patients who are potentially curable at diagnosis from less than one-third to more than two-thirds, and to more than 95 percent for men having three or more serial PSA tests. The basic problem, however, is that while about 11 percent of all men will contract clinically significant prostate cancer in their lifetimes, only 3.6 percent will die of it. The challenge is to determine which of the 7 to 8 percent can safely go untreated. Another problem is that

randomized clinical trial data on the impact of earlier treatment on survival do not exist. Both problems represent significant areas for research, as will be discussed below.

Biopsy remains the "gold standard" against which all other diagnostic tests must be compared. Over the past 20 years we have come to appreciate the fact that prostate cancer is an extremely heterogeneous disease, especially at the morphologic level. We have been able to take this heterogeneity into account, and diagnostic nomenclature has been standardized accordingly. The multifocal nature of prostatic cancer has also been recognized. A few significant questions remain, however, regarding the precursors to prostatic cancer. The presence of one of these precursors, prostatic intraepithelial neoplasia (PIN), in a biopsy specimen has led to a more thorough search for a co-existent carcinoma. However, the question still remains as to whether PIN represents *a* precursor to carcinoma or *the* precursor to carcinoma. Furthermore, it remains unclear what precise morphologic or molecular feature of PIN confirms that a transition has occurred between the premalignant condition of severe dysplasia and true carcinoma *in situ*.

PROGNOSIS

Gleason histologic grading has been consistently recognized to be the best indicator of prognosis available for prostatic cancer. Over the last decade, other modalities have become available and have ushered in a new era of sophistication and exactitude in disease prognosis. While previously limited largely to chance associations between prostate cancer phenotype and clinical behavior, we now have a huge collection of relatively well understood molecules that can be used to determine the biology of prostatic cancer. Most of these have not been adequately evaluated. As a change in paradigm, the term "tumor marker" can now be replaced by the more descriptive term "biologic determinant."

Moreover, we have come to recognize the genetic component of malignancy and have available collections of both tumor-promoting and tumor-suppressing genes. In addition, numerous transcription factors, cell cycle mediators, and signaling molecules have been identified and may be of considerable prognostic utility. What we lack, however, is a complete understanding of the natural history of prostatic cancer within which these factors can be placed: the puzzle template necessary to connect the disparate elements.

Furthermore, while many laboratories across the country and around the world have identified candidate molecules to examine for their prognostic value, comparatively less is known about how to validate these in the clinical setting. While clinical trial mechanisms are in place to test new treatments for prostatic cancer, there are no consortia or trial groups established that specialize in prognostics. It is imperative to validate biologic determinants as well as to discover new and more relevant candidates. Finally, our current approaches depend heavily on human interpretation of histologic preparations. Sophisticated image analysis techniques have been developed for a variety of medical and non-medical needs. The use of such techniques should remove some of the subjectivity that currently results in poor intra-observer

reproducibility. We do not yet have the ability to apply such technology to the problem of prostate cancer in a meaningful fashion.

VISION

The pivotal needs that connect early detection, diagnosis, and prognosis are largely related to issues surrounding the management of clinically localized disease. The primary problem remains our inability to distinguish between "indolent" and "aggressive" carcinomas. In the view of the PRG, the possibilities now look extremely good for progress on this question due to the rapid expansion of our knowledge in tumor biology in other organ sites as well as in the prostate. Opportunities to pursue methods to differentiate between these two types of tumors are described in the section on Research Priorities below.

CHALLENGES AND OPPORTUNITIES

The major gap that exists in our understanding of the natural history of prostatic cancer is our inability to determine with accuracy whether or not a given carcinoma will manifest itself clinically and thereby require treatment within a patient's lifetime. Related to this are ancillary questions of whether early detection actually reduces mortality or improves quality of life. Several factors have contributed to this problem. First, it has taken many years to assemble a list of potential prognostic markers that could provide the needed information. Most of these were derived from studies of other cancers because of the lack of prostatic cancer cell lines and adequate animal models, and the difficulties attendant to the use of human tissue specimens.

Current techniques of molecular analysis offer solutions to these problems. There is a continuing need for animal models to foster the development of new pharmacological treatments (see also Section D, *Laboratory and Clinical Models*). However, the new generation of molecular techniques has increased our ability to define prostate-specific gene expression from benign and malignant cells. Using laser micro-dissection and well-defined human tissue specimens, we can now examine very small numbers of cells and avoid many of the problems associated with tissue heterogeneity.

At the clinical level, however, the problems of heterogeneity still exist. There is little information currently available on the effects that heterogeneous expression of various normal or mutated gene products would have on sampling of the prostate by needle biopsy. Again, the improved degree of detection offered by RT-PCR-based assays provides an opportunity to systematically explore the expression of genes with prognostic potential and correlate that expression with clinical behavior.

Current patterns of clinical practice will present additional research challenges. For example, the transition from histologic diagnosis to diagnosis using molecular assays will be met with skepticism due to the long tradition of confirming a diagnosis with a biopsy. There is also a lack of understanding regarding which of the myriad potential prognostic markers should or can be used in a meaningful way. Validation of any proposed test in large, reliable patient populations will be mandatory to assure its acceptance by the urologic community.

The barriers to progress in this arena are largely those associated with the design of appropriate clinical trials. While the literature is replete with studies of small series of patients, each concluding that the featured marker, gene, or histopathologic characteristic is of value, large-scale validation trials are essentially nonexistent. The challenges that account for this apparent discrepancy are related to several key factors, including:

- Lack of scientific glamour. While it is recognized that translational studies involving the validation of a prognostic marker are necessary, these studies do not attract the same scientific attention as does the discovery of a new marker. Therefore, it is more common for an investigator to discover a new marker than it is to validate an existing one.

- Difficulty with funding. Validation trials of this nature are not as successful at competing for R01 funding through review by conventional study sections as are more basic applications. There is a need for a review mechanism through which the relevance and importance of validation studies in clinically meaningful groups of patients can be taken into account.

- Identification of appropriate patients. Most of the resources within the current clinical trial framework are devoted to testing therapeutic agents. The idea of using clinical trials to validate markers is relatively foreign to this culture. It is probably necessary to create a consortium of selected investigators with an appreciation for the problem who have identified specialized patient populations to assure the success of such efforts.

To address these issues, the PRG recommends that in the future major emphasis is placed on the development, validation, and application of biologic determinants that can provide reliable prognostic information. This is unlikely to occur at the level of individual investigators. The efficient and convincing demonstration of the clinical utility of new markers will almost certainly require large multi-institutional efforts. While cooperative groups exist that can direct clinical trials of new therapies, it is unclear whether they can be readily adapted to these different goals.

The PRG, therefore proposes that a dedicated trial group be convened to address two areas. First, existing markers should be cataloged, and the best candidates identified and then tested in an appropriate setting. Second, an infrastructure should be developed and refined in which new candidate tests could be evaluated in a thorough, cost effective, and timely fashion. These groups should be composed of basic scientists as well as pathologists and urologists to ensure that translational efforts are maximized.

As the expression of markers and their clinical significance and prognostic capabilities are defined, surrogate markers for response to treatment with either chemopreventive or therapeutic substances should emerge. This will set the stage for the facilitation of clinical trials in which chemoprevention strategies can be tested.

In summary, there remains a need for improved diagnostic and prognostic tools. While progress in this area has been relatively slow over the past decade, the advances in molecular and cell biology on a variety of fronts has afforded new opportunities to ensure that changes will come more quickly in the future. The challenge is to create an infrastructure that can capitalize on and assimilate the new data as they become available with an eye toward directly applied clinical tools. The specific steps to accomplish this are outlined as the series of high priority questions identified by the PRG as listed below.

RESEARCH PRIORITIES

There are several fertile areas that should receive increased attention from the research community and support by NCI. In view of this, the PRG recommends that the following initiatives related to prostate cancer be undertaken by NCI.

I. Development and validation of additional biologic determinants with prognostic utility. Although numerous candidates for biologic determinants of prognostic utility already exist, only validation studies will prove their clinical value. Moreover, while we continue to complete this process for known molecules, emphasis should also be placed on identifying additional ones. The search for new markers should reflect new information that has become available about key points in cancer cell biology (i.e., apoptosis, cell cycle control). However, we should also broaden the search to include molecules believed to play key roles in the response to specific forms of systemic therapy. In this way, a panel of determinants can be assembled that not only predict the natural history of the disease, but also its response to therapy.

II. Development and validation of surrogate markers. Surrogate markers for prostate cancer (e.g., nuclear chromatin texture) that can be measured in response to an intervention are sometimes the next best indicator of disease and are useful in the absence of a reliable primary endpoint (e.g., the occurrence of a clinical cancer). The design of clinical trials to test preventive or therapeutic modalities is greatly in need of validated surrogate markers to define response in a timely and cost-effective manner. The need to follow patients until a clinical endpoint is reached increases the numbers of patients required for any given trial and consequently, its cost. In view of the increasing number of agents that are ready for testing in the clinical setting, costs and patient numbers become prohibitive. Localized disease can provide a unique model to study post-prostatectomy specimens. A thorough understanding of the histopathologic and molecular changes associated with prostate cancer progression, which will include such modalities as computer-assisted image analysis, will provide an opportunity to use these tools as surrogate markers of response.

III. Development and validation of molecular assays that can augment or replace tissue-based assays. While conventional biopsy followed by histopathology has remained the mainstay of diagnosis and prognosis, technological advances of the past decade offer new approaches for exploration. Evaluation of limited disease in the prostate is prone to extensive sampling error caused by heterogeneity. The availability of micro-

dissection techniques and/or aspiration biopsy, coupled with molecular analyses (i.e., RT-PCR or array analysis), could provide new approaches to conventional tissue analysis. To do this successfully, however, more extensive knowledge is required regarding the degree of heterogeneity that exists as well as the relevance of any given change that would be detected.

IV. Development of computer and mathematical modeling techniques. Remarkable advances in computer technology have occurred over the past decade which have paved the way for the use of sophisticated methods of modeling various diseases. Such an approach has the advantage of using an individual patient's data for several different purposes. Computer and mathematical modeling technologies, using banked data from clinical trials, could greatly enhance our abilities to diagnose and define prostatic cancer. Likewise, an accurate evaluation of disease heterogeneity and progression could provide a proving ground for the development of future diagnostic techniques without the attendant costs and complications encountered in studies with living patients.

V. Research in improved body imaging techniques. Technical advances continue to be made in body imaging. However, very real needs remain for the detection of small deposits of metastatic disease that would facilitate proper diagnosis and staging. Again, while improved imaging should remain a major goal, existing techniques could be augmented with properly validated molecular staging techniques, leading to a multidisciplinary approach to prostate cancer diagnosis and staging. This is of particular importance in distinguishing patients with local disease from those with locally advanced disease. Thus, by accurately staging the disease and recognizing the early phases of local spread, complications resulting from over-treatment can be avoided.

VI. Refinement of techniques for computer assisted image analysis. The subjective nature of biopsy interpretation is a cause for concern regarding reproducibility and accuracy. The role of quantitative analysis at the tissue level remains to be defined. Newer techniques such as spectral imaging offer the opportunity to measure the expression of several different antigens simultaneously, making it possible to study the coordination of gene regulation.

In addition, the PRG identified the following questions as having the highest priority among all of the topics identified.

Priority One

The five questions listed below were assigned a high priority score by the PRG. This should not be interpreted as meaning that these are the only topics of significant merit that were identified. In general, the questions that received the highest priorities were those that were the most general since they encompassed numerous sub-questions.

What biologic determinants, independent of stage, can provide a better definition of the malignant phenotype, natural history and prognosis with various therapeutic interventions?

The importance of this particular question cannot be over-emphasized. The unifying thread that runs through the topics of early detection, diagnosis, and prognosis is the need for a tool that will allow us to determine whether or not a given carcinoma really requires treatment. Histologic grade, by itself, provides part of this answer. However, the uncertainty that results from tissue heterogeneity, tumor multifocality, and superimposition of phenotypic modulators does not allow us to make these decisions at present with accuracy.

Currently, there is a relatively large amount of NCI funding devoted to the discovery of new determinants that could serve as candidate prognostic markers. However, in view of the fact that this is a major priority for the entire prostate cancer research program, funding is probably still inadequate.

What is disappointing is the minimal amount of effort being directed at translation of these markers into clinical practice. Only one project could be identified that touched on this need. Consequently, the backlog of available markers will grow, since there is little, if any, effort being expended on using the information once it has been made available. This is emphasized by the fact that even at institutions where considerable effort is being expended on marker discovery, these markers are not used in routine practice. In the present environment, studies that are carried out are highly duplicative and there is a tendency to release some forms of analyses into the commercial sector before they have been thoroughly evaluated and clinically proven (e.g., image analysis for DNA ploidy, or p53 mutation analysis).

The major gaps that exist between where we are now and where we want to be are two-fold. First, as stated above, there is a "backlog" of markers in the published literature that should be thoroughly investigated for their prognostic utility. Second, there is a need to identify specific determinants that are likely to regulate the key steps in transformation and progression that discriminate between aggressive and non-aggressive phenotypes.

The barriers to progress in this area are largely those described above. While there are numerous candidate markers available at present, the PRG does not encourage their translational analysis or application in the clinical setting without thorough evaluation. It is often the case that once discovered, a marker never

makes it beyond the walls of the institution from which it came. Even in the largest institutions in the country it is unlikely that adequate patient populations will exist to adequately evaluate clinical utility. Since prostate cancer is already recognized to be heterogeneous with respect to stage and grade, very large numbers of patients are required to stratify groups in a statistically significant fashion. This is compounded by the reality that no single marker is likely to be adequate and that instead, panels of multiple markers will be required. For example, with respect to molecular staging, rather than just detecting circulating prostate cells, it is more desirable to define a panel of markers that could identify a cell as being a prostatic epithelial tumor cell capable of invasion and able to induce angiogenesis.

The specific resource that is clearly needed here is a dedicated trial group that could process and evaluate the prognostic markers available today. In so doing, an infrastructure will be formed that will allow the rapid evaluation of new determinants as they are discovered. This will need to include a centralized resource laboratory for standardization of testing and a biostatistics core for the collection and interpretation of data.

Recommended Actions:

The PRG recommends that NCI sponsor conferences specifically designed to evaluate and standardize the current state of prostate prognostics, including, but not limited to, histopathology, immunohistochemistry, *in situ* hybridization, molecular staging, serum assays, and image analysis. Following this, NCI should convene an interested group of individuals to explore the strategy for future clinical evaluation of prognostic markers. Further design of an approach and necessary infrastructure should be carried out with this group serving as a steering committee.

Second, it is recommended that a peer review group be convened or made available which would be more sensitive to the issues regarding the discovery, development, and validation of these necessary prognostic tools. In a similar vein, it is recognized that physicians and patients may not fully understand the significance of prognostic markers or their limitations. It is recommended that an educational program be considered to remedy this situation.

Third, it is recommended that NCI sponsor a conference or conferences specifically directed toward the issues of surrogate markers. While the importance of prognostic markers is clear, the concept of surrogate markers is a source of some confusion. What these markers are, how they can be defined, whether there are practical methods to implement or study them, and whether they accurately reflect the clinical problem being studied all remain pertinent questions. Although their use could be of great value in clinical trials until the concept is better defined, it is unlikely that they will be adopted. This should be followed by set-aside funds to encourage the development of appropriate examples.

Fourth, the continued discovery of new determinants should be greatly encouraged. It is recommended those future efforts in the area of diagnosis and prognosis are directed at developing less invasive techniques. Research on specific and objective methods of

noninvasive diagnosis and less invasive prognostics should be encouraged with set-aside funding. The use of modeling should also be encouraged. A special emphasis should be placed on the discovery and development of markers that directly pertain to either predicting response to specific forms of therapy, or those that could give objective data regarding the degree of response once therapy has been instituted.

Finally, two other areas of need were identified. Only a few NCI projects could be identified that addressed the relation of PIN to carcinoma. This is a pivotal point in the area of diagnosis since we currently do not know what the probability is that a given PIN lesion will progress to cancer. Identification of markers or determinants that precisely define the stage of progression of PIN lesions should be encouraged. In addition, few projects address directly the issue of prostatic carcinoma heterogeneity. As described above, this is also a key concept that must be fully assessed to permit progress in the development of prognostic tools. Substantial set-aside funding should be established to encourage exploration of these two important areas.

How should prognostic markers be validated?

Again, at present, there are numerous candidate molecules that have been identified by individual laboratories or institutions, each of which is purported to have prognostic power. The lack of use of any of these in clinical practice is obvious. Without a systematic manner in which to proceed, we will be asking the same questions about the same markers for the next decade. The validation process is a particularly important subset of the question listed as the first priority above because markers can only be moved from discovery to implementation if they are properly validated. It was therefore deemed to be of sufficient priority to justify separate consideration. This is a highly complex issue, which has received limited attention in the recent literature but which will require additional efforts for its complete development.

An insufficient number of projects were identified that pertained to the validation of prostatic cancer prognostic markers. These were largely components of other multi-organ efforts and it was difficult to precisely assess what share of the total was prostate related. Even if the entire amounts were directed at prostate cancer, this level of funding would be inadequate.

An Expert Panel on Prognostic Markers was convened in January of 1998 to assess the current state of this field. It was agreed that this is an appropriate time to encourage the active evaluation of prognostic markers in this field. Determinants are available that can assess various aspects of differentiation, invasion, proliferation, cell death, interactions with the microenvironment, induced alterations in phenotype, and angiogenesis, to mention a few.

The PRG focused largely on the issues of predicting survival over the past decade. What are needed now are more precise tools that allow us to ask specific questions about stage subgroups or

therapeutic interventions. For example, markers that are associated with resistance to hormone withdrawal therapy could be directly used to trigger changes to an alternative therapeutic approach before clinical failure becomes apparent.

It was also agreed that the major barrier to progress in this area is the lack of a defined system of evaluation of prognostic markers and the lack of a group that is capable of carrying out such studies. While this concept does not have the glamour associated with basic "bench" research, it is nonetheless important to advance clinical medicine. What is most needed is the creation of a phased system of marker evaluation and the creation of a clinical trial consortium geared toward marker validation.

Recommended Actions:

In 1998 the Expert Panel on Prognostic Markers recommended that a validation consortium be established and that a working group define needs and approaches. In addition, existing markers should be cataloged and existing pre-clinical data evaluated to determine if the markers are ready for clinical testing. Following this, a phased system should be used for evaluation. This includes:

- Phase 1 - Evaluation and assay development in a centralized fashion on a wide range of specimens from diverse origins.
- Phase 2 - Pilot studies to establish sensitivity and specificity in a clinical context, including inter- and intra-laboratory reproducibility.
- Phase 3 - Use within large cohorts in a prospective fashion to evaluate expression versus outcome. Surrogate endpoints such as serum PSA increase or decline could be used instead of hard endpoints such as cancer-specific mortality.
- Phase 4 - Validation trials in multi-institutional, prospective, randomized settings against specific clinical endpoints.

It was felt that Phases 1-3 above would require significant new funding by NCI. Phase 4 testing should be absorbed into the existing cooperative group mechanisms. The statistical analyses of these data need to be robust and will require dedicated biostatistical support. It was also felt that industry support should be sought from companies that might eventually profit from the development of clinical assays.

What biologic determinants characterize the growth rate and/or tumor doubling time during the progression of prostate cancer?

Among the specific variables that could be examined in the field of biologic determinants, one stands out as being particularly relevant: tumor-doubling time. Most of the available treatment algorithms for prostate cancer depend solely on static measurements of features such as grade or pathologic stage. The existing knowledge regarding multifocality of prostate cancer suggests that in a single patient, tumors with different times of origin or different doubling rates must exist. Existing data on tumor doubling times have come from indirect measurements such as rate of increase of serum PSA, which could

be affected by numerous exogenous factors.

A major determinant of whether a given tumor will have an adverse effect on its host is the rate at which it doubles. In essence, this may be the primary factor that determines or indicates whether an individual tumor is aggressive or not. In view of this level of importance, this feature was singled out as being of especially high priority.

No specific projects could be identified that directly addressed this area of research. In view of the potential for such information to modify clinical management, it is highly recommended that support of such research be encouraged and significantly expanded.

Our existing knowledge regarding proliferation of prostatic carcinoma cells is largely based on *in vitro* studies or static measurements, such as determination of S-phase fraction by flow cytometry, Ki-67 immunostaining or BrdU labeling index. Although these give information regarding the fraction of cells in a population that are moving through the cell cycle, they provide no information regarding the rate at which they are replicating. Rate is necessary to determine a potential doubling time. What are needed are dynamic methods for the assessment of prostatic carcinoma growth that could be carried out in a minimally invasive fashion. The barriers to obtaining such information are the need to carry out dynamic measurements on living patients.

Recommended Actions:

In the first priority question listed above, it should be decided whether any of the existing molecules available can provide doubling time data. Interdisciplinary discussions should also be encouraged in the form of a retreat in which potential strategies could be formulated. Set-aside funds should then be designated to encourage investigation into this question using appropriate techniques and patient populations. Such research could be carried out in the format of ancillary studies to existing clinical trials.

Does early detection change mortality from prostate cancer?

As stated above, it is well known that many more men die *with* prostate cancer than *of* prostate cancer. When prostate cancer is detected in relatively young men, the current attitudes regarding this disease in this country dictate that definitive therapy be instituted in the vast majority of patients. In view of this, there is a potential to do more harm through over-treatment than good by appropriate treatment. Because of this quandary it is imperative that we develop accurate information about the risks and benefits of screening. The fundamental question is, do we want to detect all of the clinically significant carcinomas that we can detect? Without a solid answer to this question, it is unclear how to counsel the very large numbers of patients who are presently at risk for this disease.

Several barriers exist to obtaining such information. First, since we are presently limited to using clinical incidence and mortality as endpoints,

studies on the impacts of screening are necessarily very long. Patient adherence, therefore, becomes a major issue, as does cost. With increased prostate cancer awareness we have also seen the emergence of readily available screening tests such as PSA. Because of this, there is a potential for significant outside "contamination" of any randomized clinical trial. Patients who had their PSA determined outside of a clinical trial may seek treatment prior to those men in the trial who are randomized to not be screened (usual medical care). In addition, there are a variety of dietary and homeopathic aspects (alternative treatments) that should be taken into account in study design. However, at present, we do not have accurate information about the influence of these variables on patient characteristics relevant to disease. Ongoing trials, such as the Prostate Intervention Versus Observation (PIVOT) study and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) should provide some answers once completed. In addition, screening studies ongoing in Europe will provide additional important data about the value of screening.

A side issue is the question of how we can develop methods to detect prostatic cancer at an earlier stage. In this case, the lack of data regarding the effect of early detection itself becomes a barrier to further investigative initiatives. Specifically, researchers are hesitant to look for more sensitive assays to detect a disease that many already feel is being over-detected. The question then becomes, "are proximate markers to PSA likely to provide additional benefit or additional harm?" It is likely that because of this dilemma, development of new methods for earlier diagnosis was not viewed as a high priority topic by the PRG.

Recommended Action:

At the present time, there is only one major clinical study, PLCO, ongoing in the United States, only a portion of which is directed toward the specific problems associated with prostate cancer. The Prostate Cancer Prevention Trial may provide data to help refine current screening techniques such as PSA, PSA density, PSA delta, and even free and bound PSA, so as to make early detection assays more sensitive. Considering the importance of early detection, however, it seems that this area is inadequately funded and that considerable additional emphasis should be placed on new clinical trials.

What are the effects of early detection on morbidity and quality of life?

While the clinicians that treat prostate cancer are largely focused on the undeniably important issues of survival, patients frequently indicate that daily issues surrounding quality of life should be of equal concern. It is possible that while a given intervention might not affect survival, it could still improve quality of life. Unfortunately, it is also true that ***even if*** a given intervention does not improve survival, it could cause a ***decrease*** in quality of life. For example, the stress associated with the knowledge that one has a minimally elevated PSA in the face of no definitive diagnosis of cancer can be a source of

substantial anxiety. The emotional aspect of early detection and its sometimes ambiguous interpretations is an understudied area of research.

Priority Two

- What less invasive diagnostic techniques can be developed for the detection of prostate cancer? Can biochemical or molecular assays refine or replace tissue diagnoses?
- What biochemical or molecular techniques can be used to refine diagnosis?
- What methods can be developed to detect prostate cancer earlier?
- What are appropriate surrogate markers for use in clinical trials for early detection? Do surrogate endpoints accurately reflect the clinical problem being studied?
- What imaging methods can better localize cancer within the prostate (e.g. color flow Doppler or radar)?
- What more sensitive biopsy techniques can be developed for the detection of prostate cancer? What model systems can be used to improve biopsy strategies?
- What is the prognostic significance of PIN and does it lead to prostate cancer?
- How can the analysis of tumor heterogeneity and multi-centricity be improved? (The approach to prostate cancer must include the spectrum of malignancy within the entire gland and not simply focal observations.) What innovative technical strategies can be developed to permit analysis of prostate tissue by array technology?

Priority Three

- Do histologic grades progress over time?
- What valid alternatives are there to prospective randomized trials that can determine the efficacy of screening?
- What patient factors, such as age, frequency of testing, or cutoff points, modulate PSA-based detection strategies?
- How can image analysis of tissue sections improve the histological diagnosis of prostate cancer?

D. LABORATORY AND CLINICAL MODELS

CURRENT STATUS OF THE FIELD

Laboratory and clinical models are critical for defining the mechanisms of prostate cancer progression and for testing preventive and therapeutic regimens. Yet only a few laboratory and clinical models have been developed, all of which are encumbered by insufficient biological knowledge of the human cancer they aim to simulate. A better understanding of the basic biology of human prostate cancer will accelerate and refine the process of model development.

A laboratory model ideally simulates all of the properties of prostate cancer in humans, but this is difficult to achieve in practice. A constellation of models (e.g., animal, *in vitro*, and mathematical) must be developed to mimic distinct characteristics of human prostate cancer. Each model then must be validated to permit a predictable level of extrapolation to humans. There are several existing models of prostate cancer, each of which has advantages to exploit and limitations to overcome:

- Xenograft models (in which human prostate tissue is transplanted into an animal, usually an immune-deficient mouse, in order to test aspects of prostate cancer *in vivo*)
- Transgenic mice that express SV40 T-antigen (under the control of a promoter that drives gene expression in prostate tissue)
- Syngraft models, in which urogenital sinus tissue (i.e., precursor prostate tissue) from rodent embryos is isolated, transfected with oncogenes, and then implanted into an adult host
- Hormonally induced rat models that are susceptible to prostate cancer following treatment with androgens, estrogens, and carcinogenic agents, either alone or in combination
- The dog model, which spontaneously develops prostate cancer has a high incidence of prostatic intraepithelial neoplasia (PIN)
- Cell models, which are derived from prostate cancers and which have maintained phenotypic characteristics of the tumor, and
- Computer models, which mimic the proliferation of prostate tumors

A significant resource for evaluating state-of-the-art models in prostate cancer was the First International Workshop on Animal Models of Prostate Cancer. This workshop was organized by Drs. D. Waters, D.G. Bostwick, and G.P. Murphy and held at Purdue University, West Lafayette, Indiana in 1997.

VISION

Currently, we are working in a void when it comes to understanding the etiology, progression, and metastasis of prostate cancer (see Section C, *Early Detection, Prognosis, and Diagnosis*). Because of this lack of fundamental understanding, there are insufficient basic building blocks for model development. It will be critical to define the molecular characteristics of the disease in order to develop more useful models that will mimic the natural progression of prostate cancer.

Additional xenograft models are needed. These models offer the possibility of examining human tumors under a variety of experimental conditions. Thus,

xenograft models should be developed from as many stages and grades of human prostate tumors as is possible. Additional prostate cancer cell lines, which are well defined and which mimic different levels of tumor progression, will contribute to these model systems. The availability of a wide spectrum of human tumors grown in immunodeficient mice will provide an opportunity to define molecular changes associated with progression of the disease. Xenografts grown in castrated mice should provide new insights into the mechanism of hormone-refractory cancer. Moreover, they will offer the opportunity of testing novel treatment modalities *in vivo*.

Transgenic and reconstitution models are needed. These models offer the possibility of testing various oncogenes and tumor suppressor genes for their ability to transform prostate cells *in vivo*. However, before the ideal model can be generated, a better understanding of the biology of prostate cancer will be necessary. Once a gene has been identified that is responsible for initiating human prostate cancer, it can be targeted into mice as a transgene. Such models may more closely mimic the human tumor. These models should elucidate the molecular changes associated with prostate cancer initiation and progression, as well as metastasis to bone. Androgen ablation in this model will allow the study of molecular changes associated with androgen-refractory tumors. In addition to the possibility of testing novel therapeutic regimens, this model can be used to test compounds that might prevent prostate cancer.

Additional models are needed to define the role of hormones in prostate cancer. Rodent models that are susceptible to prostate cancer following treatment with androgens, estrogens, and carcinogenic agents, either alone or in combination, may elucidate the role, if any, that these agents play in the initiation and/or progression of the disease.

In addition, animal models are needed that spontaneously develop prostate cancer at a rate comparable to that in humans. Such a model may help define environmental factors that might be involved in the initiation of prostate cancer. Currently, the dog is the only animal model that appears to fit this criterion.

Prostate cancer cell lines are needed that mimic various stages of the disease. Such cell lines will be useful for defining cell-signaling pathways that are critical for proliferation and apoptosis. Moreover, injection of cells into immunodeficient mice will facilitate the development of new xenograft models that can be used for *in vivo* studies.

The development of computer models of tumor development is in an infant state. However, as computers become more powerful and our understanding of the basic biology of prostate cancer increases, the use of computers should become a powerful tool in defining the complex interaction among cells during tumorigenesis.

The availability of new models will provide the means for testing new modalities of both prevention and progression of prostate cancer. Such models will provide methods of testing both chemopreventive and chemotherapeutic agents. Moreover, novel therapeutic protocols, such as gene

therapy and immunotherapy, can be tested on these models.

CHALLENGES AND OPPORTUNITIES

I. Models that mimic human prostate cancer in initiation, progression and metastasis.

Laboratory models are critical for defining the mechanisms of prostate cancer progression and potential means of treating the disease. There are few models specifically for prostate cancer, and there is insufficient biological knowledge upon which to base them. Currently, there is too little effort in this vital area of research. It is recommended that high priority be given to the development of new models that mimic human prostate cancer initiation, progression, and metastasis. However, before we can design ideal models, we need to understand the basic biology of prostate cancer initiation, progression and metastasis.

High priority should be given to identifying the mutated genes that lead to initiation of prostate cancer. These mutated genes can then be inserted as transgenes into mice via prostate-specific promoters. Only then can the natural progression of the disease be studied in an animal model. Also, genes that are involved in progression and metastasis need to be defined. A potential precursor lesion of prostate cancer is Prostatic Intraepithelial Neoplasia (PIN). Because such lesions cannot be studied chronologically in humans, animal models such as the dog offer the best means of defining the role of PIN in prostate cancer progression. Xenograft tissues and cell lines are needed that represent tumors at different stages of progression. These xenograft models will allow the identification of genes that are involved in tumor progression. These genes offer potential therapeutic targets. Novel treatment regimens can then be tested against target genes in cell and animal models.

II. Use of models in detecting and treating prostate cancer.

Models are needed to screen and test potential chemotherapeutic agents. Moreover, models are needed to test novel therapeutic approaches, such as gene therapy and immunotherapy. Although there are several models available, many more are needed in order to mimic the wide heterogeneity of human prostate cancer.

Androgens are thought to play a major role in tumor development and progression. Hormone-induced rodent models are needed to define potential environmental factors that could influence the development of prostate cancer. Although hormonal therapy is the most widely used treatment against advanced prostate cancer, the majority of tumors return in an androgen-refractory state. Little is known of the mechanisms that lead to androgen-refractory tumors. The development of animal models that mimic the refractory nature of tumors will enhance our ability to treat these tumors.

Animal and cell models are needed to test potential chemopreventive agents. Such agents, which are usually identified by epidemiological studies as part of natural dietary intake, should first be tested as crude extracts. Then, individual purified components of these extracts should be tested in cell lines and animal models. Such natural dietary

components offer the potential for chemoprevention and chemotherapy.

III. Use of current models to understand prostate cancer progression and metastasis.

There are many shortcomings of the models that are available currently. Those that should be developed in the future include xenografts, transgenics, syngrafts, and hormonally induced models. Dog models need to be developed further in order to compare the natural progression of prostate cancer in this species with that of the human. Additional cell lines need to be developed from human prostate cancer tumors. Computer simulation of prostate cancer should be encouraged.

RESEARCH PRIORITIES

Priority One

Can models be designed to display the carcinogenic characteristics of human prostate cancer; namely, its genetic characteristics, host-tumor interactions, micro-environment, angiogenesis, and progression?

This question is important because a model should mimic the human disease as closely as possible. Clearly, additional models are needed to mimic each aspect of prostate cancer. This is all the more important because of the heterogeneity of the disease. Ideally, a model would mimic all of the characteristics of the human disease. However, in practical terms this may not be possible. Thus, it is important to choose a model based upon the question being asked. The PRG believes that this area of research is seriously underfunded, since this represents a translational component that will bridge understanding of the basic biology of prostate cancer to potential therapy protocols. Resources that are needed include: 1) increased efforts to identify mutations that drive the initiation of prostate cancer; and 2) additional cell and animal models that closely mimic the natural course of prostate cancer.

Recommended Actions:

1. Fund projects that focus on genes that drive the initiation process of prostate cancer development.
2. Fund projects to develop new prostate cancer cell lines.
3. Fund projects to develop new animal models.

Can models of human prostate cancer metastases be developed to mimic the affinity of human prostate cancer for bone marrow?

This question is important because prostate metastases are often different from other solid tumors. First, prostate metastases are found predominantly in the bone. Second, the bone metastases are predominantly osteoblastic rather than osteolytic. Thus, animal models that mimic this particular trait of prostate tumor metastasis are needed, if we are to

develop effective treatment regimens for metastatic disease. Although the current level of NCI support for this question appears to be reasonable, to date few advances have been made in this area. Thus, a gap exists and new approaches should be tried. Resources needed to address these questions include an animal model that recapitulates the bony metastasis of prostate cancer, and additional studies of bone factors that influence the growth of prostate cells and prostate factors that influence the growth of bone cells.

Recommended Actions:

1. Fund projects that focus on an animal model that mimics prostate metastasis to bone.
2. Fund projects that focus on the interaction of bone cells and prostate cells.

Can models be designed to display the hormone responsiveness of human prostate cancer and its progression to hormone independence?

This question is important because hormones (both androgens and other hormones such as vitamin D3) play such an important role in prostate cancer development and progression. Moreover, although hormonal therapy of advanced prostate cancer has a profound effect on tumors, in the majority of cases, tumors return in an androgen-refractory state. Thus, we need to understand the basic biology of androgen action in prostate cells and the mechanism by which prostate cells lose their dependency on androgens. Both animal and cell models offer the ideal means of studying these processes. The current level of NCI support for this question is insufficient. Understanding how androgens regulate prostate growth and how prostate cells lose their androgen dependency offers potential therapeutic approaches in addition to the current hormonal therapy. Moreover, such knowledge may challenge the current concepts upon which hormonal therapy is based. Resources should be directed toward defining the mechanism of androgen action in prostate cells and the mechanism by which prostate cancer cells become refractory to the hormone.

Recommended Actions:

1. Fund projects that focus on the mechanism of hormone action in prostate cell lines and animal models.
2. Fund projects that focus on the mechanism by which prostate cancer cells become refractory to androgens.

Can laboratory models be used to screen potential chemotherapeutic agents, clarify dose/response relationships, and understand the development of resistance to chemotherapy, and mechanisms of therapeutic response?

This question is important because novel chemotherapeutic agents can quickly be tested in cell and animal models in order to elucidate their effectiveness on tumor cells. Specificity of these agents is important, and models can be used to test specificity. The current level of NCI support for this question is insufficient,

creating a wide gap in our efforts to identify potential therapeutic agents in model systems. Resources are needed to develop more meaningful models to test these agents. In particular, additional cell lines that maintain the well-differentiated phenotype of prostate cancer cells will be useful for such testing. Also, better means of automated testing of compounds in cells are needed.

Recommended Actions:

1. Fund projects to develop cell lines that mimic the differentiated phenotype of prostate cancer cells.
2. Fund projects that will develop automated methods of testing potential therapeutic agents.

Can models be used to test novel therapeutic approaches, such as cancer vaccines, gene therapy, immunological therapies or other biological therapies?

This question is important because gene therapy and immunotherapy are coming to the forefront as potentially powerful techniques for treating prostate cancer. Animal models will play a critical role in developing such therapies. The current level of support for this question is too low, perhaps because of the newness of the technology. Resources are needed to develop the vectors for gene therapy. Additionally, we need to understand the basic elements of the immune components of prostate cancer cells.

Recommended Actions:

1. Fund projects that will develop vectors for gene therapy.
2. Fund projects that will define the immune components of prostate cancer cells.
3. Fund projects that will test novel therapeutic approaches in animal models.

Priority Two

- Can models be used to test chemopreventive agents?
- Can models be used to test tumor responses to immunotherapies, i.e., therapies that enhance the immune system's ability to recognize and destroy the tumor?
- Using xenograft models: How can xenograft models be used to understand the progression of prostate cancer? How can xenograft models be used to understand the effects of treatment modalities? Can human cell lines with specific prostate cancer phenotypes (e.g., androgen responsivity) be developed for introduction into xenograft models? Can human cell lines be developed to mimic the early stages of prostate cancer for use in xenograft models, where their properties can be investigated *in vivo*?
- Using transgenic models: Can oncogenes commonly expressed in human prostate cancer be identified and used to induce prostate cancer in

transgenic models? (The oncogene currently used in transgenic models, the SV40 T-antigen, is not found in human prostate cancer and has widespread effects on gene utility. Can additional prostate-specific promoters be developed to drive oncogene expression in transgenic models?

- Can imaging/localization techniques be used to study tumor progression in a variety of models?
- Can models be designed to mimic the spontaneous characteristics of human prostate cancer?

Priority Three

- Can the dog model be used to study the expression of oncogenes and tumor suppressor genes in prostate tumors? How does prostate cancer in dogs compare with that in humans in terms of disease progression and other aspects of carcinogenesis? Can the dog model be used to determine the relevance of PIN to prostate cancer?
- Can the hormonally-induced rat model be used to understand the mechanism(s) by which hormones affect tumor induction?
- Can mathematical models be developed to simulate prostate tumor induction and progression?
- Can models be used to develop more effective hormonal therapies?
- Can models be designed to display the long dormancy of human prostate cancer cells?
- Can the syngraft model be used to study the effects of particular oncogenes and tumor suppressor genes on tumor phenotypes?

E. STAGING AND TREATMENT OF LOCALIZED PROSTATE CANCER

CURRENT STATUS OF THE FIELD

When cancer is detected before it spreads beyond the region of the prostate, it can be cured (completely eradicated for the remaining life of the patient) in many patients using treatment techniques that are widely available in the United States today. The increased awareness about prostate cancer among the American public and the widespread use of serum PSA assays to screen for prostate cancer have resulted in the detection of most cancers when they are still localized and can be treated definitively with surgery (radical prostatectomy) or irradiation therapy (external beam, interstitial, or both). In fact, some cancers are discovered so early that they may not require active treatment, especially in men with a limited life expectancy. For some prostate cancers "watchful waiting," or expectant management, is an appropriate strategy.

Although genuine options are available, we do not have sufficiently reliable ways to predict the behavior of an individual cancer or to assess the risk-benefit ratio of active treatment compared to conservative management, nor do we know how to predict whether an individual cancer will respond well to one particular treatment compared to another.

While treatment of localized prostate cancer is usually effective, none of the current treatment techniques are uniformly successful. In some cases treatment fails because malignant cells have already spread to distant areas. Staging tests available today—bone scans and CT scans—are not sufficiently sensitive to detect such cells in most patients. And other more sensitive tests such as the RT-PCR (reverse transcriptase – polymerase chain reaction) assay for prostate cells in the peripheral circulation or bone marrow cannot determine whether such cells have the capacity to become *bona fide* metastases.

Other cancers are not cured because the treatment fails to eradicate the local tumor completely. Surgery, for example, may fail because the cancer extends beyond the margins of resection. And irradiation therapy may fail because some cancer cells within the treated area are not fatally damaged. Better techniques are urgently needed to determine the location, size, and extent of cancer within the prostate and surrounding tissues. Better imaging studies would allow us to monitor changes in the cancer with different treatments. And better indicators (e.g., genetic profiles determined by microarray technology, or key molecular markers of hormone responsiveness or of the cancer's capacity for apoptosis) are needed to predict the response of individual cancers to different forms and intensities of therapy. To achieve this level of prediction will require much more information about the molecular mechanisms that govern progression and metastasis and response to therapy (see Section A, *Biology, Progression, and Metastases).*

Modern medical informatics can play a crucial role here by developing risk profiles for prognosis or the response to treatment. Such profiles can incorporate and quantify multiple variables and correlate them with clinical outcomes

such as pathologic stage and disease recurrence. Tables and nomograms have already been developed which combine standard prognostic factors—clinical stage, tumor grade and PSA levels—to make such predictions. Far more sophisticated analyses, requiring powerful computers, will need to be developed to incorporate the vast information from microchip genetic array technology into risk profiles or response assessments.

A limitation of all current treatment strategies—including conservative management—is the risk of troublesome side effects from treatment and of complications from growth of the cancer. Radical prostatectomy, external beam irradiation, and brachytherapy (interstitial implantation of radioactive seeds) each carry a low but measurable mortality rate, some risk of urinary incontinence or proctitis, and a greater risk of erectile dysfunction. And watchful waiting runs the risk that the cancer will grow and spread, with the chance to cure the cancer lost. For decades specialists have debated the relative merits of these and other forms of therapy for localized prostate cancer. Unfortunately, there are no valid prospective, randomized, controlled clinical trials we can turn to for information about the relative safety or efficacy of therapy for localized prostate cancer. Such studies are expensive to conduct, take many years to complete, and will leave many unanswered questions about the most appropriate treatment for individual cancers in individual patients.

With this understanding of the current status of the field of staging and treatment of localized prostate cancer, the PRG considered research questions and opportunities in the following five major topic areas:

- staging of prostate cancer and indicators (markers) of prognosis or response to therapy in the primary tumor
- efficacy of therapy for localized prostate cancer
- combination therapy for localized cancer
- gene and cellular therapy, and
- new technology for staging and treatment of the primary tumor

Prognostic factors, *per se*—features of a cancer that signify its biologic potential to grow and spread—are addressed in Section C, *Early Detection, Diagnosis and Prognosis*. The staging studies addressed in this section concern ways to determine the size and extent of the primary tumor (such as imaging studies) and the presence and significance of cancer cells outside of the prostate in patients otherwise thought to have a localized tumor. This section also focuses on ways to measure how different primary tumors respond to different types and intensities of therapy (response factors).

With regard to treatment, this section focuses on treatment of the primary tumor, not on therapy for systemic disease (metastases). Thus, systemic adjuvant therapy, whether neoadjuvant (such as, neoadjuvant hormonal therapy) or classic adjuvant therapy (androgen ablation or chemotherapy after definitive local therapy) are addressed here to a limited degree but are primarily dealt with in Section F, *Systemic Therapy*. Systemic therapy is, however,

considered in this section in two contexts: 1) the use of systemic therapy as the sole treatment for the primary tumor (e.g., androgen ablation for locally advanced prostate cancer); and 2) systemic as well as local forms of gene and cellular therapy, since gene therapy is currently being investigated as *in situ* therapy for localized prostate cancer as well as systemic therapy for advanced disease. This section also addresses local adjuvant therapy or combinations of local therapies, such as hyperthermia and radiotherapy, or surgery and adjuvant radiotherapy.

VISION

Today, with systematic screening, we have the ability to detect almost all prostate cancers before they progress to become locally advanced or metastatic. What we do not have is the ability to determine reliably which of these cancers poses so little threat that active treatment can be deferred indefinitely. And we do not have sufficiently safe treatments that can uniformly eradicate the more serious, life-threatening cancers when they are found. We do not know how to judge the response of a given cancer to a particular type of therapy, or how to select the most beneficial, least risky therapy for an individual patient with cancer. Major progress against clinically localized prostate cancer will require new approaches.

There have been major advances in the therapeutic index for external beam irradiation therapy of prostate cancer, especially with the advent of three-dimensional conformal techniques, which have increased the rate of cancer control and decreased the risk of morbidity. In addition, there have been major advances in surgery for prostate cancer, with better selection of cancers suitable for surgical eradication and with less risk of incontinence and erectile dysfunction for patients after the operation. While we would welcome continued improvements in current treatments, the PRG believes that emphasis should be placed on the development of new therapeutic approaches which exploit innovations in engineering (e.g., intensity modulated radiotherapy, particle therapy) or that take advantage of revolutionary discoveries in modern molecular biology (e.g., gene therapy). Prostate cancer, among the solid tumors, seems to be particularly suitable for gene therapy, since the organ is expendable, the primary tumor is accessible for applying treatment and monitoring the response, and a circulating marker of response is readily available.

Another attractive way to increase the effectiveness of local therapy is to combine different modalities—the classic examples are surgery followed by irradiation therapy or interstitial plus external beam irradiation therapy. With improvements in chemotherapy and the development of novel biologic agents, combinations of systemic therapy with definitive local treatment offer promising new opportunities.

CHALLENGES AND OPPORTUNITIES

I. Staging of Prostate Cancer and Indicators (Markers) of Prognosis or Response to Therapy in the Primary Tumor.

Determining the stage (size or local extent) of the primary tumor is particularly challenging in prostate cancer. Palpation is subjective,

insensitive and inexact. In fact, more than half of all cancers detected today are not palpable. Transrectal ultrasonography, in expert hands, adds some additional information about the location, size and extent of the cancer, but has not proven reliable in general clinical practice. With the emergence of PSA screening, prostate cancer is being detected earlier in its natural history. With standard staging studies such as bone scans and CT scans, few patients can be shown to have overt metastases at diagnosis. Yet a third of patients treated with radical prostatectomy, for example, will subsequently recur, largely due to the presence of occult micrometastases. New techniques are urgently needed to detect metastatic cells and to determine their clinical significance. In recent years, molecular techniques have been used to identify prostate cells in the peripheral circulation and bone marrow. While many patients show evidence of having such cells, their clinical significance is not known: prostate cells capable of becoming clinical metastases cannot be distinguished from those that are not capable of surviving.

Treatment may also fail to control an apparently localized cancer because some cells within the local tumor are not destroyed: the cancer may extend beyond the margins of surgical resection or cells within an irradiated field may not be sufficiently damaged. Better methods are needed to determine the size and extent of the local tumor. Better indicators are needed to predict the response of cancers to different forms and intensities of therapy so that therapeutic options can be applied that are appropriate to the characteristics of the cancers being treated.

II. Efficacy of Therapy for Localized Prostate Cancer.

Radical prostatectomy, external beam irradiation therapy, and interstitial seed implantation (brachytherapy) are often used in this country to treat clinically localized prostate cancer. Radical prostatectomy, a major surgical procedure, carries a low but measurable mortality rate, some risk of surgical complications, a small risk of urinary incontinence, and a substantial risk of temporary if not permanent erectile dysfunction. There are rare fatal complications of external beam irradiation as well, a treatment which extends over a long course (7 weeks or more), and risks of permanent bowel dysfunction (diarrhea, hematochezia) and loss of erections over time. Brachytherapy (interstitial implantation of radioactive seeds), which seems to cause less erectile dysfunction, does require anesthesia and may have limited efficacy in the more threatening, potentially lethal cancers. Brachytherapy may lead to urinary incontinence if a transurethral resection of the prostate becomes necessary to relieve urinary obstruction after the procedure. And watchful waiting—a gamble that the cancer will not metastasize and lead to premature death before the patient dies of other causes—runs the risk that the cancer will grow and spread, leading to urinary tract obstruction, bleeding, and painful bony metastases. Moreover, the chance to cure the cancer will have been lost.

For decades now specialists have debated the relative merits of these and other forms of therapy for localized prostate cancer. While each is widely used today, and is reasonably safe and somewhat effective, we have insufficient

evidence to argue that one approach is superior to another. Unfortunately, there are no valid prospective controlled clinical trials we can turn to for information about the relative safety or efficacy of therapy for localized prostate cancer. Currently, NCI (along with the Department of Veterans Affairs) sponsors the PIVOT trial (Prostate Cancer Intervention Versus Observation Trial), which compares radical prostatectomy to watchful waiting. A similar trial is underway in Europe. These long-term, Phase III clinical trials, however, are expensive to conduct, take many years to complete, and still leave unanswered questions about the most appropriate treatment for individual cancers in individual patients.

Nevertheless, there is a need to determine the relative efficacy of the various methods of treating localized prostate cancer. The control arm of the PIVOT trial will be the first prospective trial of conservative management, and the surgical arm will provide important data about treatment-related morbidity. This trial should certainly be completed. Limited additional Phase III trials may be warranted to compare, in selected patients, interventions, such as brachytherapy versus external beam irradiation or versus radical prostatectomy.

At the same time, new treatment strategies are urgently needed, along with better methods to assess the efficacy of new treatments in an expeditious manner (see discussion of clinical trial design in Section F, *Systemic Therapy*).

III. Combination Therapy for Localized Cancer.

Since no single therapeutic modality now available has proven uniformly successful in eradicating the local tumor, investigators have attempted to combine modalities (e.g., radical prostatectomy followed by adjuvant external beam irradiation therapy) to achieve greater success. The efficacy of such combinations has not been established. Systemic therapy (e.g., androgen ablation) has also been combined with local therapy.

Neoadjuvant hormonal therapy markedly reduces serum PSA level and shrinks the local tumor as well as the prostate itself. In combination with radical prostatectomy, neoadjuvant hormonal therapy favorably alters the pathology of the cancer but does not reduce the recurrence rate. In contrast, androgen ablation does appear to reduce the rate of biochemical progression when used in combination with external beam radiotherapy—a benefit demonstrated in several prospective trials. In one study of locally advanced cancers, in fact, long term adjuvant hormonal therapy appeared to significantly improve survival when used for three years after external beam irradiation therapy compared to radiotherapy alone. Much remains to be learned about such combinations.

The indications for using neoadjuvant hormonal therapy before irradiation need to be explored to determine the optimal duration and sequence of treatments tested. The mechanisms of apparent synergy between irradiation and hormonal therapy need to be investigated, which could lead to modifications that would enhance the

effect, whether by improved timing or duration of hormonal therapy or the identification of new systemic (or local) radiation sensitizers. The discovery of molecular markers that predict, for example, hormonal responsiveness or the capacity for apoptosis, may help to better match for different forms and intensities of treatment to the disease in individual patients.

Studies are needed to test new agents, whether traditional cytotoxic drugs or novel biologic agents such as angiogenesis inhibitors, in the adjuvant or neoadjuvant setting, in combination with surgery and with radiotherapy. The effects on the primary tumor of chemotherapeutic agents alone, or in combination with hormonally active drugs, need to be explored in depth.

IV. Gene and Cellular Therapy.

Many features of prostate cancer make the disease a good target for gene therapy. Prostate cancer is slow growing, so that long-term control may be possible even if the cancer is not completely eradicated. The prostate gland is a discrete organ, easily accessible through the rectum, and is dispensable. There is no standard therapy for several phases of the disease (such as local recurrence after radiotherapy or hormonally resistant metastatic cancer). And the response to therapy can be readily monitored with serum PSA levels and repeat biopsies of the prostate, as well as with the more traditional scans.

For localized disease, *in vivo* strategies which aim to revert the tumor phenotype or to provide for the specific killing of tumor cells are promising, but critically depend on gene transfer efficiencies currently not attainable. While bystander killing has been observed in murine tumor models, the mechanism(s) underlying this phenomenon have not been studied in sufficient detail. A better understanding of these mechanisms (particularly immune-related mechanisms) are likely to lead to the development of new, more effective anti-tumor strategies.

For disseminated disease, strategies which depend upon the ability to efficiently transduce tumor cells are unlikely to succeed. Immunotherapeutic approaches which seek to augment the immunogenicity of tumor cells and thereby elicit a systemic anti-tumor immunity are most promising. It is not currently clear whether such immune strategies are best directed toward specific tumor-associated antigens or to the diversity of potential antigens present within tumor cells. The optimal method of presenting tumor antigens to the immune system (e.g., *in vivo* gene transfer with viral vectors or naked DNA, pulsing of dendritic cells (DCs) with antigen, use of genetically modified DCs) has also not yet been established. The identification of new tumor-specific or associated antigens (termed “antigen-hunting”) is very likely to yield important new reagents for both therapy and diagnosis. The pursuit of new antigens in the context of existing clinical studies involving therapeutic vaccination strategies may be particularly useful for establishing correlation between specific immune responses and clinical outcome.

Current pre-clinical studies of gene therapy have employed a number of different tumor models, which significantly differ in their biological characteristics. There is insufficient

evidence of the degree to which the existing tumor models are predictive of efficacy in human studies. Nevertheless, there are a number of characteristics of existing models (e.g., inherent immunogenicity of the tumor, invasive/metastatic, bone-homing potential) which will likely prove to be important components of valid tumor models. While judgements must be made regarding whether results obtained in a particular model warrant movement of a potential therapy into clinical studies, such judgements are very difficult. In some cases, clinical studies may prove to be the primary means of assessing the early promise of a particular cancer gene therapy approach.

Magnetic resonance (MR) spectroscopy may prove to be a valuable diagnostic tool for staging and for monitoring the response of the local tumor to therapeutic interventions. MR spectroscopy has been shown, for example, to be of value when compared to MR imaging (MRI) in distinguishing tumor from hemorrhage in the prostate after needle biopsy and for identifying recurrent tumor in the prostate after irradiation therapy. There is a need for further development of MR spectroscopy, especially its application to the initial diagnosis and characterization of cancer.

New technologies should be sought that will allow safer, more effective treatment of the primary tumor. The development of three-dimensional conformal irradiation therapy has allowed enhanced local tumor control, but further studies are needed to define the benefits of such intense therapy compared to conventionally planned and delivered external beam irradiation.

RESEARCH PRIORITIES

The PRG identified the following investigative questions as having the highest priority. These questions focus on developing better methods to detect micrometastases before treatment, better ways to control the local tumor while reducing the morbidity of treatment, better ways to characterize the biologic potential of a given cancer (that is, better prognostic markers) that would allow treatment to be tailored more accurately to the threat posed by an individual's cancer, and the development of novel therapeutic strategies to control the cancer, such as gene and cellular therapy.

Priority One

What new techniques can be developed to detect clinically significant regional or distant metastases before treatment? What is the clinical significance of the detection by molecular techniques of circulating prostate cells (in the peripheral blood, lymph nodes, or bone marrow)? What is the relationship between these circulating cells and subsequent treatment failure or the development of clinical metastases?

No question was considered more important to progress in the treatment of clinically localized prostate cancer than the development of more sensitive techniques to detect the presence of metastases. When local treatment fails, the cause is most often the presence of undetected metastases before local therapy. If these metastases could be detected, many patients would be spared the side effects of local therapy. Perhaps as important, clinical trials of systemic therapy could be tested in an adjuvant setting in patients with low volume metastases most likely to respond. Despite the importance of this question, the PRG could identify only a few research projects focusing on the detection and characterization of circulating cancer cells. Remarkably little funding was directed at this question.

While preliminary investigations have repeatedly found prostate cells in the peripheral circulation and in the bone marrow, the clinical significance of these cells has not been established. The biological potential of the cells that are found has not been characterized, since there are no adequate tests to distinguish cells which have the capacity to persist and grow from those that will not survive.

Recommended Actions:

The PRG recommends that NCI vigorously support the development of assays to detect prostate cancer cells outside of the region of the prostate gland as well as investigations that will establish better ways to characterize the biologic potential of such cells, especially through the identification of molecular markers of metastatic capacity. NCI should promote standardization of the assays used to detect such cells and should encourage cooperative groups to include studies of the presence of circulating cells during clinical trials so that long-term clinical correlations can be made.

What new technologies can be developed to decrease morbidity and enhance efficacy of therapy for the primary tumor? High dose irradiation therapy? Improved localization techniques?

Currently, there is a modest level of support by NCI for the development of such new technologies for improved treatment techniques or better imaging of the local tumor. Current funding for therapy trials is directly largely at the cooperative clinical trials groups, which focus on Phase II and III studies. The number of funded investigators seeking novel local therapeutic strategies is few.

While there is legitimate debate about the relative merits of the existing forms of treatment for localized cancers (radical prostatectomy, external beam radiotherapy, and brachytherapy), the PRG concluded that each of these forms of therapy control the cancer in some but not all patients, and each places patients at risk for troublesome morbidity. Direct comparisons of each of these therapies in large, randomized prospective controlled trials would be costly and take many years or decades to reach statistically significant end points. With the rapid development of new therapeutic approaches, the results of such trials may be obsolete by the time the trials were completed. Funding should be continued for select Phase III studies within the existing cooperative clinical trials groups, which are poised to address straight-forward questions, such as interstitial brachytherapy versus external beam irradiation, or brachytherapy versus radical prostatectomy in selected patients.

External beam radiotherapy has been improved considerably in recent years through the development of three-dimensional conformal techniques, which have improved the rate of local control without a corresponding increase in the rate of complications. Improved techniques for three-dimensional conformal radiotherapy are currently being supported through program project grants and the efficacy of three-dimensional therapy tested against conventional radiotherapy within the existing clinical trials mechanisms. Further such studies are certainly warranted.

Recommended Actions:

The PRG recommends that resources should be committed to only a few, well-designed clinical trials addressing the relative merits of different techniques for treating the local tumor. The current PIVOT trial should be completed, since it is the only trial in this country addressing the question of whether aggressive therapy is superior to conservative management of clinically localized prostate cancer. Limited additional trials comparing different treatments may help to identify subsets of patients that can be more effectively (or more safely) treated with one modality versus another. Further testing and refinements in three-dimensional conformal therapy, including intensity modulated radiation therapy, should be supported.

The PRG strongly recommends that the greatest emphasis should be placed on the development of novel staging tools (especially imaging studies) and treatment approaches and of more informative techniques that would allow assigning therapeutic options more appropriately to patients based upon the characteristics of their individual cancers.

What critical features of the primary tumor determine the success of treatment? What are the clinical, pathological, and molecular features (markers of virulence) of a prostate cancer indicative of its rate of growth, its ability to invade, and its propensity to metastasize? Which features connote an "indolent" cancer? Which features indicate that a particular cancer cannot be controlled with local therapy alone? Can the results of multiple tests be combined using informatics to determine stage and prognosis more accurately?

While a variety of effective treatment options are available for localized prostate cancer, we do not have sufficiently reliable ways to predict the behavior of these cancers in order to assess the risk-benefit ratio of active treatment compared to conservative management. Nor do we know how to predict whether certain cancers will respond well to one particular treatment compared to another.

Some cancers are not cured because the treatment fails to eradicate the local tumor completely. Better techniques are urgently needed to determine the location, size and extent of cancer within the prostate and surrounding tissues. Better imaging studies would allow us to monitor changes in the cancer with different treatments. And better indicators (e.g., genetic profiles determined by microarray technology, key molecular markers of hormone responsiveness, a cancer's capacity for apoptosis) are needed to predict the response of cancers to different forms and intensities of therapy so that therapeutic options can be tailored to the characteristics of the cancers being treated. To achieve the level of prediction needed will require much more information about the molecular mechanisms that govern progression and metastasis and response to therapy (see Section A, *Biology, Progression, and Metastasis*).

Modern medical informatics can play a crucial role here by developing risk profiles for prognosis or the response to treatment. Such profiles can incorporate and quantify multiple variables, identifying correlations with clinical outcomes such as pathologic stage and local or distant recurrence. Tables and nomograms have already been developed which combine standard prognostic factors—clinical stage, tumor grade and PSA levels—to make such predictions. Far more sophisticated analyses, requiring powerful computers, will need to be developed to incorporate the thousands of bits of information from microchip genetic array technology into risk profiles or response assessments.

The study of the features of prostate cancer that correlate with its response to therapy has been of fundamental interest to investigators. The review of the NCI portfolio identified a moderate number of research projects and funding for research aimed at discovering those features of the primary tumor that can be used to predict the biologic behavior of the cancer. Much of this work, however, was aimed at the development of prognostic markers rather than those that determine the response to treatment.

Recommended Actions:

Studies that correlate the pathological and molecular features of the primary tumor with the natural history of the

disease and the response to therapy require access to large tissue banks that link pathology specimens to accurate clinical and epidemiological information. NCI should establish a national tissue bank for prostate cancer specimens and appropriate clinical and epidemiological information (see also Section H, *Resources Needed*).

New technologies, such as MRI spectroscopy, should be explored to see if they can help to distinguish patients with a high likelihood of having cancer from those with a low likelihood, or those with indolent cancers from those with aggressive tumors.

As the genes that regulate prostate cancer progression and metastasis are discovered, new markers need to be identified that correlate with response to therapy. Informatics may help to combine multiple factors in ways that facilitate predictions of prognosis and of the response to a particular therapy.

Of the different strategies being considered for cancer gene therapy, which appear most suitable for the treatment of prostate cancer? Which treatments are most suitable for localized disease? Which treatments, including immunotherapeutic approaches, are most suitable for systemic disease?

Prostate cancer, among the solid tumors, seems to be particularly suitable for gene therapy, since the organ is expendable, the primary tumor is accessible, and a circulating marker of response is readily available. Gene therapy has thus far been associated with low morbidity and could be applied repeatedly to palliate these slow growing cancers long enough for patients to live out their natural lives even if the cancer is not completely eradicated. In addition, occult micrometastases may be particularly susceptible to gene therapy strategies that augment the immunogenecity of tumor cells. Successful introduction of such novel approaches will require support for a special clinical trials consortium, since gene therapy requires active collaboration of basic and clinical investigators incorporating multiple approaches and should emphasize mechanistic questions rather than simply documentation of response. Even now the opportunities in cancer gene therapy far exceed our capacity to evaluate them. Gene and cellular therapy are complex. Their clinical evaluation will require careful selection of strategies to be investigated as well as refinements in clinical trials methodology. Treatment effects on the tumor and on the host must be identified and measured, valid intermediate endpoints of the immune response and of the antitumor response will have to be defined.

Currently, there are few centers with active programs in gene or cellular therapy for prostate cancer. A review of the NCI portfolio showed relatively few funded projects and very limited funds that could be used to seize upon such promising opportunities to develop a fundamentally new strategy for the treatment of cancer.

Recommended Actions:

NCI should develop programs that support collaborative, inter-institutional studies of different gene therapy approaches in specific, well-defined animal models. While the establishment

of formal standards for evaluating different gene therapy approaches does not appear to be warranted, collaborative studies between investigators in different institutions might provide the ideal setting for comparative testing in similar models and for the establishment of useful informal standards for evaluation.

NCI should facilitate the development of standardized definitions of tumor characteristics (stage, grade, prior therapy), response to therapy, and endpoints so that clinical trials of gene therapy can be compared across time and across institutions (see the section on clinical trials in Section F, *Systemic Therapy*). Pre-clinical animal models have served to gate the entry of new therapies into clinical trials. But early clinical studies, if designed properly, may, in the short term also prove to be a reliable mechanism for the assessment of potential new gene therapies. It is critical to attempt to design clinical studies of gene therapy that will validate the specific characteristics of animal models used for pre-clinical testing.

NCI should develop funding mechanisms devoted specifically to the support of Phase I and II clinical studies involving cancer gene therapy. The current clinical trials groups are not ideal for gene therapy, which requires active collaboration of basic and clinical investigators incorporating multiple approaches and should emphasize mechanistic questions rather than simply documentation of response. Thus far, the initiation of early clinical studies involving potentially important new therapies has depended on piecemeal funding strategies involving conventional RO1 grant support or industrial support. Support from industry for cancer gene therapies has particularly waned in the past few years. Since early studies are critically important for establishing the validity of existing animal tumor models, and may be the only reliable means of sorting through the myriad of potential treatment options, the dedication of funds for early clinical studies in cancer gene therapy is warranted. A standard study section format could be used to review grants which specifically (and solely) focus on clinical studies, but which provide the results of pre-clinical studies as a focal point for the review process. Peer review by experts in the pre-clinical science underlying the clinical studies, in clinical trial design, and in the development of clinical treatment strategies, would be critical. In light of the standardization of analysis inherent in collaborative clinical investigation, the submission of funding requests by therapeutic consortia should be actively encouraged. One goal of this new initiative would be to bring clinical studies further along the clinical development pathway than was possible previously, so as to maximize the chances that industry would become involved in the clinical development process.

Priority Two

- What are the critical features of the tumor that determine response to irradiation therapy? Is there truly radio resistance on a cellular or genetic level, and if so, how can this be overcome? How can we identify which cells die or survive in response to radiation? What are the cellular and molecular mechanisms primarily responsible for cell death with irradiation? What is the role of oxygenation/hypoxia in radiation damage?
- Are there cellular or genetic targets that can be identified which might increase the radiosensitivity of prostate cancer cells? What are the appropriate biomarkers of radiation response?
- What is the relative efficacy of various methods of local treatment (including no treatment and conservative treatment, i.e., delayed hormonal therapy)?
- What models (cells, lines, transgenic animals, xenografts) are most appropriate to study radiation responsiveness?
- What are the intermediate endpoints that predict the efficacy of various local treatments?
- Can local tumor control be improved by combining treatment approaches? Do combinations of local therapies increase local cancer control (e.g., interstitial brachytherapy plus external beam irradiation)? Do combinations of systemic and local therapy increase local control (e.g., neoadjuvant hormonal therapy and radiation)?
- What is the natural history of presumed indolent tumors when observed over long periods? What are the consequences of deferred definitive treatment?
- What are the performance characteristics of tests used to determine the clinical stage of the tumor before treatment (i.e., size and extent of the primary tumor, presence of regional or distant metastases)?

Priority Three

- What is the efficacy of systemic treatment, especially androgen deprivation, for localized prostate cancer?
- What are the criteria for initiating and funding a Phase III clinical trial for a localized therapy? What is the appropriate target population for a clinical trial of localized therapy?
- What is the appropriate definition of treatment failure after local therapy? Does it vary by therapy? What is the relationship between failure defined by biochemical markers (e.g., rising PSA), clinical failure, and cancer-related mortality? What is the definition and clinical significance of local treatment failure? To what degree does local failure result from the biological features of the cancer, as opposed to variations in the

application of each therapy? (Local failure after external beam irradiation relates directly to the dose delivered to the tumor. For example, does the efficacy of brachytherapy or surgery relate to the accurate placement of seeds or the appropriate planes of dissection, respectively?) What host factors (e.g., ethnicity) affect the response to different treatments?

- What is the rate-limiting step in producing vectors for gene therapy trials so that clinical grade vectors are readily available for appropriate prostate cancer clinical trials?
- What is the morbidity of various methods of local treatment?

F. SYSTEMIC THERAPY

CURRENT STATUS OF THE FIELD

Systemic approaches are required for prostate tumors that cannot be cured by local treatment modalities such as surgery or radiation therapy alone. Determining the optimal treatment for a man with prostate cancer requires an understanding of the natural history of the disease and the ability to identify the biologic determinants associated with the development and progression of the disease in that individual. Profiling patients based on clinical and genetic parameters, and, more importantly, using that information to guide therapy, is a high priority. This will not only allow the identification of subpopulations of patients who may respond better to one approach versus another, but because it does not repeat what has proven to be ineffective, will encourage participation in clinical trials. Historically, low enrollment in clinical trials has slowed efforts in these areas.

Hormonal therapy remains a standard of care, but despite the expenditure of considerable resources, there is no definitive answer as to when to initiate treatment, which agents to use, or for how long treatment should be administered. Too much emphasis has been placed on repetitive trials using different forms of the same type of treatment, and too little on definitive trials. Further, based on the net impact of hormonal therapy on survival, most of the trials are statistically under powered and do not produce definitive answers to help guide treatment decisions.

The widespread use of PSA-based detection and monitoring after primary therapy has resulted in the identification of an ever-increasing population of men with a rising PSA value as the sole manifestation of metastatic disease. This creates an ideal situation in which to evaluate immunological approaches because minimal tumor burdens can be monitored with precision, and the patients are healthy, with intact immune systems. The understandable reluctance of men to undergo castration or hormonal ablation, the poor tolerance of androgen deprivation in an asymptomatic population, and the fact that deferring hormone treatments has at best a modest impact on survival create a safe window in which to evaluate immunologic and other non-toxic, non-hormonal approaches.

In most cases of metastatic disease where there are abnormalities visible on imaging studies, the recognition that the tumor is composed of cells that are both sensitive *and* resistant to androgen ablation at the start of treatment provides a rationale for the development of integrated approaches aimed at both cell populations at initial therapy. What remains understudied is the use of novel therapeutic approaches or chemotherapeutic agents in combination with hormones, and when to integrate these therapies. The study of adjuvant and neoadjuvant chemo-hormonal approaches in patients with early disease and a poor prognosis has been initiated recently and should be encouraged. For patients with androgen-independent disease, it is essential that we build on the promising results obtained by several groups with selected contemporary regimens using a post-therapy PSA decline endpoint. But until this level of response is confirmed, and the optimal

duration ascertained, large Phase III trials are premature.

A high priority that should be addressed immediately is the issue of clinical trial design. Urgently needed are standardized criteria for the enrollment of patients with different stages of the disease, validated endpoints that accurately reflect clinically relevant outcomes (e.g., delayed progression, preventing symptoms, palliation of symptoms, and improved prostate cancer specific survival), and standardized methods of reporting. These criteria are essential so that investigators can consider their results in the context of others, thus insuring the rapid development of promising approaches and the discontinuation of those that are ineffective. There are other important trial endpoints, such as the ability to palliate pain, around which trials can be designed and which can have a profound impact on clinical practice.

As our knowledge of the events associated with the development and progression of prostate cancer increases, and in particular the events associated with the lethal androgen-independent variant of the disease, a number of promising mechanism-based approaches worthy of clinical testing have been identified. These include, but are not limited to: inhibiting signal transduction and specific steps in cell cycle; blocking angiogenesis and other specific steps in the metastatic cascade; promoting apoptosis; inducing differentiation; and a variety of immunologic approaches, including vaccines and gene-based therapies. Each is likely to require different endpoints to assess efficacy. How to prioritize these approaches and how to determine which may be most applicable to a given population in the clinical spectrum of prostate cancer will require close interaction with developers of model systems.

VISION

The ultimate goal of treatment is to reduce prostate cancer-specific morbidity and mortality. This goal recognizes that within the prostate cancer population, there is a significant proportion of men for whom elimination of the last cancer cell is not necessary, and for whom modulating the rate of growth of the cancer to the point where a patient remains asymptomatic from his tumor and his treatment, and eventually dies of unrelated cause, is an acceptable therapeutic aim.

The broad research questions to be explored are:

- What are the optimal systemic treatments options for patients with metastatic prostate cancer?
- How do we individualize treatment based on the mechanisms contributing to the growth of the cancer in that individual?
- When should these treatments be initiated?
- How do we assess efficacy?
- Are there intermediate endpoints that can be validated?
- What are the host characteristics that affect response to different approaches?

Urgently needed are definitive trials that address the issues of intermittent androgen ablation, potency-sparing approaches, the net benefit of LHRH agonists, and the optimal use of hormones in patients who have relapsed. Similarly, maximizing the benefits of

currently available traditional cytotoxic agents will require unique trials for discrete patient populations. These trials should include patients with localized disease and a poor prognosis, patients with rising PSA values after hormone treatment or patients with symptomatic hormone-resistant disease. Given the range of agents now currently available for clinical evaluation—angiogenesis inhibitors, signal transduction inhibitors, matrix metalloproteinase inhibitors, modulators of growth factors, differentiating agents, cell cycle inhibitors, apoptosis inducers, immune modulators, immunotoxins, novel cytostatic agents, vaccines, systemic radionucleotide compounds—it is imperative to determine through clinical trials those agents which are active and deserve further study, and how best to integrate them into combination regimens.

It is well recognized that the traditional endpoints used in oncology clinical trials do not apply for metastatic prostate cancer because: 1) bi-dimensionally measurable disease is infrequent (20 percent or less of cases); 2) even when present, bi-dimensionally measurable masses may be biologically different than an osseous lesion; and 3) response or progression is difficult to quantitate using bone scintigraphy or other imaging techniques. This has led to a reliance on changes in tumor markers, such as PSA, as a clinical trial endpoint. Many of the agents undergoing clinical testing modulate the expression of a biomarker, and may actually alter the serum levels of a marker independent of an effect on tumor growth. This has to be considered carefully in protocol design. An additional consideration is how to improve the predictive value of a post-therapy change in a marker by combining it with other parameters that are currently available and/or which may be identified in the future. Equally important is the recognition that different endpoints will be needed for drugs that act via different mechanisms.

Another high priority is to define specific criteria to determine which outcomes in Phase II clinical trials justify the continued development of a given therapeutic approach. In particular, when is a definitive Phase III trial justified? The development of these criteria and justifications requires standardized methods of reporting results for agents with diverse mechanisms of action. Criteria will likely include some index of the proportion of patients who benefit and the duration for which the benefit is maintained, and will vary both as a function of the approach under evaluation and the stage of disease being studied.

The clinical evaluation of agents that target specific biologic mechanisms poses the dilemma of how to dose compounds for which the optimal biologic dose may have no relationship to the maximum tolerated dose (MTD), typically used for Phase I investigations. Trials to study the tumoricidal effects of gene-based approaches via pathologic study of patient tumors, or to measure the effects on expressed genes or signaling pathways, should be encouraged. Factors that can confound the interpretation of results, such as the genetic background of the host, immune competence, diet, and concomitant medications, also need to be considered and identified. It is imperative that we better understand the mechanisms of resistance to a particular form of therapy, whether hormonal or non-

hormonal, and to develop agents to abrogate that resistance.

CHALLENGES AND OPPORTUNITIES

It is likely that different mechanisms contribute to the progression of prostate cancer in different patients. A high priority is to try to characterize these factors more precisely, and to explore treatments that target those mechanisms. One can envision the point where treatment selection will be based more on the biologic determinants of a tumor than on its site of origin. This is a long-range goal. In the interim we have at our disposal the ability to define subsets of patients within each stage of the disease with a range of prognoses. It is essential that we begin to stratify patients based on these factors to address important questions. Obviously, any question that is addressed must focus on clinically relevant outcomes for the patient, including palliation of symptoms, delaying progression of the cancer, or prolonging life. A stand-alone measure of "response" is not an adequate outcome measure without some consideration of the duration for which it is maintained and at what cost in terms of treatment-related morbidity.

Despite the fact that androgen ablation has been available for over five decades, questions remain as to the optimal timing, type, and duration of such an approach. These issues need to be addressed. Strategies that simultaneously treat the androgen-dependent and androgen-independent components of a tumor mass should be encouraged. Important questions to resolve include:

- Are metastatic prostate cancers in different sites equally sensitive to treatment?
- What are the mechanisms associated with resistance to the different therapeutic modalities currently in use, including: hormonal therapy, radiation, chemotherapy, and immunotherapy?
- Are there unique aspects of the bone micro-environment that render prostate cancers resistant to therapy?
- Do we need to simultaneously treat the malignant epithelial component as well as the stromal component in bone to improve outcomes for patients with bony disease?
- What is the role of adjuvant therapies that prevent metastases or block angiogenesis, which in themselves have limited antitumor effects, and how are these best integrated into our treatment programs?
- Are the clinical variants of the disease (e.g., neuroendocrine, PSA-negative tumors, CEA-producing tumors) truly unique, and do they require different therapeutic approaches?

Given the level of benefit observed using selected chemotherapy programs, and our ability to predict the probability of recurrence based on pathologic parameters, it is now appropriate to design adjuvant studies for high-risk patients treated with surgery or radiation. These studies should be initiated immediately.

Alternative agents or non-proven therapies (i.e., saw palmetto, selenium, essiac tea, shark cartilage, antineoplaston) have become quite popular with patients. These agents pose unique challenges because of the lack of

pharmaceutical-grade material manufactured through standard good manufacturing practices and subjected to quality control procedures for clinical testing. Moreover, companies producing these agents are unwilling to have their compounds rigorously tested. Yet many patients continue these treatments while on trials, or begin them at the start of a trial. Do they enhance or inhibit the approaches we are evaluating? Can they confound the interpretation of a trial? Because of the potential to alter the bioavailability, metabolism, distribution, and/or elimination of agents being evaluated, we need to insist that patients discontinue use of these products prior to entering a clinical trial.

Because of the considerable consolidation of pharmaceutical companies in the past few years, there appears to be a decrease in the resources spent on cancer drug development. Some of these companies view prostate cancer (as well as some other types of cancer) as having minimal marketability, thereby limiting clinical testing in the prostate cancer population. Orphan drug status can be obtained by focusing on subpopulations of patients (i.e., androgen-independent, androgen-dependent). In addition, given the cost of developing a compound, it is important to develop a structure so that agents or approaches under study in treating one cancer (e.g., breast) which also show therapeutic potential for prostate cancer receive timely evaluation in prostate cancer. Often, Phase II evaluations do not begin until the pivotal trials in one disease are complete. Small biotechnology companies hold considerable promise for identification of agents with activity in this disease. These companies should be encouraged to evaluate their compounds in NCI's Developmental Therapeutics Program drug screen. Industry/academic/government collaborations should be encouraged.

The current NCI 60-cell-screen has only two prostate cancer cell lines (PC-3 and DU-145), and their predictive ability relative to clinical outcomes is unknown. Urgently needed is the prospective and comparative evaluation of the results from model systems to the results obtained in human trials. The availability of truly predictive models will not only speed preclinical testing, but will allow a more rapid prioritization of approaches for testing in humans (see also Section D, *Laboratory and Clinical Models*).

A comparison of prostate cancer clinical outcomes in Caucasian and African American populations shows that, stage for stage, African American men have equal survival rates in an equal treatment/equal access health care system. Race, however, does correlate with risk of metastatic disease at diagnosis and with risk of high-grade disease at diagnosis. Although African American men have a higher mortality rate than Caucasian men, race is not a significant predictor of outcome once stage and grade of disease are considered. Efforts to accrue African American men and members of other minority groups to clinical trials should continue; however, efforts to recruit sufficient numbers of minorities to statistically analyze that subset in each trial may be unnecessary.

RESEARCH PRIORITIES

The PRG recognized that there have been significant efforts in drug development for prostate cancer, but felt

that closer collaboration is required among individuals with expertise in drug design, understanding mechanisms, pre-clinical testing, and clinical trial design. The gap that remains from the time a compound and its target are identified to its approval for use in humans remains large. This is due in part to the tacit assumption that clinical trials in prostate cancer are similar to those in other tumor types. In the clinic, the path from Phase I to Phase III testing is arduous at best. The PRG believes that disease-specific trial groups that include clinical investigators with unique expertise in the disease and its management, and who have a large patient base, would be in a better position to address the Phase II questions that are critical in determining the level of efficacy of an approach.

Many of the barriers to progress appear to be related to insufficient attention to the fundamental components of a clinical trial, which are: 1) ask relevant questions; 2) carefully define the population in whom to address the question; 3) use a specific intervention with a high probability of success; and 4) report the outcomes in a meaningful way that can be interpreted by others, and that address the critical question of whether drug development should proceed.

Priority One

What are the mechanisms associated with resistance to hormone therapy, immunotherapy, radiation and chemotherapy?

A number of approaches are available which produce antitumor effects in a proportion of patients. In the majority of cases the responses are incomplete and are not durable. A better understanding of the mechanisms of resistance will allow more effective combinations to be developed, and to improve both the proportion who respond and the duration for which it is maintained.

What is the role of gene and cellular therapy for prostate cancer?

A unique aspect of prostate cancer progression is the ability to monitor the disease at low tumor burdens. The areas of gene and cellular therapy are complex, and their evaluation in the clinic requires careful selection of the agents to be studied as well as refining the ability to assess treatment effects, both on the tumor and the host. Currently, the number of approaches far exceeds our ability to evaluate them, and because many cannot be evaluated preclinically in immunocompromised animals, new preclinical models will be essential to optimize the selection of agents and to assess their effects.

Determining which patients have an intact immune system and which do not is a priority in treatment selection. Further, new intermediate endpoints of the immunologic response and of the antitumor response will be needed, and their significance will need to be validated. Currently, there are an insufficient number of projects

addressing this question in the NCI portfolio.

Recommended Actions:

NCI should facilitate real-time biology. Data from pre-clinical and clinical trials show that tumors that survive or resist a given therapy are different than those that have not been exposed to that therapy, suggesting some effect of therapy. This phenomenon applies to both chemotherapeutic agents as well as hormonal treatments. How do we monitor these effects *in vivo*? How do we determine what mechanisms are contributing to the growth and progression of the disease in the individual? A more balanced understanding of disease-specific versus mechanism-specific therapeutic approaches is needed, requiring the direct characterization of patient tumors. Only then will we be better able to characterize the targets unique to prostate cancers in different individuals, and to optimize treatment selection.

What are the relevant endpoints for clinical trials of systemic therapies (e.g., changes in PSA, time to progression, quality of life, survival)? How can these endpoints be validated? What is the impact of treatment on survival?

Only a few projects address this issue, but more important is that few focus on the degree of benefit required in the Phase II setting to justify the expenditure on large Phase III trials. Further, although many consider Phase III trials to be the "last word" in clinical trials, enrollment in these trials is highly selective, raising questions as to the relevance of the study population to the disease population as a whole. In a recent trial of suramin and hydrocortisone, it took 76 centers close to 3 years to enroll 456 patients, the equivalent of 2 patients/center/year. This raises the question of whether novel Phase II designs focusing on patients with a defined prognosis can be used for registration studies. Such designs are encouraged.

Recommended Actions:

Encourage novel trial designs that focus on clinically relevant endpoints. In a tumor for which the classical endpoints of tumor regression do not apply, novel designs are needed to show whether a treatment is beneficial. An Advisory Committee to CTEP should be appointed which includes investigators with established expertise in prostate cancer clinical trials. The complexity of designing and interpreting the results of trials in this disease is grossly underestimated, and too often decisions regarding drug development rest with individuals with little understanding of the disease. Recently, the Food and Drug Administration approved the combination of mitoxantrone plus prednisone based on a palliative endpoint although no survival benefit was demonstrated. Unknown at this point is whether a statistically significant difference in a palliative endpoint is clinically meaningful to a patient. Finally, access to clinical trials must be improved. This can be accomplished by several means, including direct subsidies to patients, and encouraging the participation of third-party payers in the

support of definitive trials that address important clinical questions, whether Phase I, II or III. This points to a high priority area identified by the PRG, which is currently underfunded by NCI.

How can new targets be identified and what is the role of novel therapeutic agents directed at these targets?

Although four studies address this question to some degree, none focus exclusively on this question.

Recommended Action:

NCI should convene a consensus conference every three years, with industry participation, to discuss the newest molecular targets and drug development in prostate cancer.

What is the optimal treatment for androgen-independent disease?

Androgen-independent disease includes tumors with and without sensitivity to further hormonal manipulation. It also includes the more lethal variant of truly hormone-independent tumors. How to identify which tumors are actually resistant to hormones and which will still respond to a change in hormones is a high priority. For tumors that are in fact hormone-independent, several approaches are under study, but many are being studied in small, stand-alone trials that do not allow us to understand better the reasons for success or failure of treatment. Currently, there are numerous projects in the NCI portfolio addressing this issue, and several novel agents or combinations of proven agents are being clinically examined.

Recommended Actions:

Develop risk-stratified clinical trials: The search for new and different prognostic indicators is essential. Frequently neglected is the fact that few research groups use indicators that are already available. For example, combining the results of the digital rectal examination, the Gleason score on biopsy, and the baseline PSA allows the identification of patients who may have a high rate of disease progression despite local treatment. Similarly, the question of when and how a rising PSA should be treated is a high priority. Few groups have focused on determining the probability that a patient with a rising PSA will develop: 1) clinical metastases that can be detected radiographically or clinically, 2) symptoms of the disease, or 3) risk of prostate cancer mortality. These estimates are essential both as a guide to management and to clinical trial design. Focusing the evaluation of new compounds or approaches on patients with a high probability of failure will allow us to have a more rapid understanding of which approaches have an impact on the disease. This knowledge will help answer the following question:

At what point in the progression of prostate cancer should novel therapeutic agents be initiated (e.g., anti-angiogenic, anti-metastatic agents)?

Currently, there are an insufficient number of NCI-funded projects addressing this question, and little emphasis on the issues of tumor burden or host-tumor interactions on outcomes.

Recommended Actions:

The PRG felt that disease-specific initiatives that integrate the validation of preclinical models (*in vitro* and/or *in vivo*), and screening for drug effects on specific biologic determinants such as PSA, would offer a better understanding of which model, if any, may be more relevant for questions related to a given stage of the disease. These efforts would optimize the selection of compounds or approaches for clinical testing. Although it is recognized that a drug development infrastructure is in place, establishing central facilities where new drugs or targets could be evaluated on a confidential basis would obviate the need for individuals to commit already sparse resources to set up different model systems on their own. Any such facility would have to recognize the academic and legal interests associated with scientific discovery.

When should a patient with a rising PSA be treated?

Although a few projects in the NCI portfolio address this issue, few appear to be focused on stratifying risk. This ever-increasing subset of the population has the potential to be simultaneously under- and over-treated, based on our lack of understanding of the natural history of the disease.

How can new targets be identified?

Although a handful of NCI-supported trials address this question to some degree, none focus exclusively on this question. The PRG recommends that a consensus conference be held every three years to discuss the newest molecular targets and drug development in prostate cancer, with industry participation.

Priority Two

- Is there a role for non-radioactive agents that target bone stroma in delaying progression of preventing the development of metastases?
- How can tumor regression and progression in the setting of no measurable disease be quantitated?
- How do we better define the patient population for a clinical trial to limit heterogeneity and to increase the chance of a successful outcome (co-morbid conditions; genetic factors, medications, diet, immune competence)?

- Should novel therapeutic agents be used in conjunction with hormonal therapies?
- What is the optimal use of hormonal therapy?
- Which non-hormonal systemic agents have anti-tumor activity?
- What patient (host) characteristics affect the response to treatment?
- What factors determine a patient's response to hormonal therapy?
- What is the optimal time to integrate non-hormonal systemic therapy in relation to hormonal therapy?
- What agents can be used to palliate symptoms of the disease and how can palliation be quantitated reliably?
- Are there reliable surrogates on which to base preliminary Phase II screening investigations that will allow us to identify treatment approaches rapidly and at the same time discard those not worthy of further testing?
- How can the development of agents that target specific mechanisms be prioritized?

Priority Three

- What are the criteria for initiating a clinical trial of a systemic therapy?
- Does a change in the primary tumor reflect changes in a metastatic lesion?
- What are the relevant endpoints for a time to progression trial? (A rising PSA, new bone metastases, new soft tissue disease, disease-related symptoms?)
- How do we determine that an approach is worthy of a Phase III trial?
- What trade-offs in quality versus quantity of life will a patient accept or consider in selecting treatment?
- What is the role for systemic radionuclides?
- Are there specific clinical variants of the disease, e.g., neuroendocrine or soft-tissue only, that should be treated in a different manner?
- Does a response in measurable disease reliably predict for changes in bone metastases?
- How can the optimal dose of a compound which is in itself not toxic and for which the maximal tolerated dose is not the appropriate measure of safety be defined?
- How should agents that are not anticipated to have direct antitumor activity per se be tested?

G. OUTCOMES RESEARCH

CURRENT STATUS OF THE FIELD

"Outcomes" include a spectrum of end points which, in the context of this chapter, describe the results (both patient-focused and disease-specific) of therapeutic interventions in the management of prostate cancer. Disease-specific outcomes include such characteristics as disease-free survival and overall survival. These are well-described endpoints of clinical cancer treatment and have been widely applied in clinical trials research. In contrast, patient-focused outcomes have had less widespread inclusion in clinical trials despite their importance in prostate cancer treatment and research. The patient-focused outcomes that were the subject of this review include quality of life, treatment-related morbidity, economic outcomes, and quality of and access to care.

Quantitative and comparative assessments of a variety of measures of immediate or long-term morbidity and of quality of life are currently integrated into almost all large-scale trials in prostate cancer. There are, however, few projects that directly address morbidity, late complications, or supportive care. In addition, disease-focused outcomes, such as disease-free survival and overall survival, are being studied to a limited degree through the clinical trials mechanism as well as through NCI's Surveillance, Epidemiology and End Results (SEER) program.

It is only within the last few years that the technology has become available to quantitatively evaluate these outcomes in a systematic way. In the past, the technology of outcomes research has largely been separate from the traditional health care research mechanisms. Reasons for this separation include the application of different scientific principles such as psychology, economics, and survey research, as well as the need for resources to collect this additional information. There should be a coordinated development of a structure within NCI to advance this type of scientific inquiry and facilitate cooperation among researchers.

VISION

New approaches to early detection, as well as improvements in treatment, have resulted in a dramatic rise in the long-term survival rate of prostate cancer patients. Most patients can now expect to live more than 10 years after their diagnosis. However, the same treatments that have enabled long-term survival can also cause potentially disabling effects, ranging from minor alterations in day-to-day activities to major functional loss involving critical organs. While the physical effects of cancer treatment have been documented, the impact of these sequelae on quality of life and economic consequence is less well understood.

There is considerable diversity in the methods being employed to measure outcomes, including both qualitative and quantitative studies. Given the differences between study methodology, it is not surprising that reported quality of life varies. This makes it difficult to draw firm conclusions about the magnitude and nature of the long-term consequences of prostate cancer for survivors. Clearly, more data about all

aspects of quality of life are needed to provide a more comprehensive and complete perspective on the needs of the long-term cancer survivor.

To accomplish this, the scientific community should address the methodological issues in long-term survivorship research. In addition, we need to understand the long-term impact of different treatments on quality of life. We also need to understand the impact of different treatments in more diverse populations. We need to assess, from the patient's perspective, what they need and want. Although curing prostate cancer is one criterion of successful cancer therapy, understanding the long-term impact on quality of life will ultimately determine the effectiveness of new and existing treatments.

CHALLENGES AND OPPORTUNITIES

Prostate cancer is the most commonly diagnosed cancer among men in the United States. Thus, it exerts an enormous financial impact, with an estimated $5 billion spent annually in direct medical care costs. NCI research is focused on the long-term costs of cancer care in the Medicare population, according to clinical and sociodemographic characteristics. However, the Medicare-based studies do not include patients under 65 years old. In addition, these studies do not include the out-of-pocket burden faced by patients, including prescription drugs, lost earnings, or other family burdens. Current efforts are focused on describing the cancer-attributed portion of Medicare payments for prostate and other cancer sites. However, more studies are needed that directly address the issue of the cost of treatment and the cost/benefit ratio of treatment for prostate cancer. There remain important opportunities to increase understanding of the costs of prostate cancer.

In addition, there has been limited research on how financial concerns affect treatment choice or the quality-of-life issues following treatment. A recent area of investigation supported by NCI has focused on the patient costs of NCI-sponsored research trials. Studies have been initiated to examine this question in support of the NCI's efforts to extend third-party payer coverage for routine care costs for patients involved in NCI-sponsored studies. We have few data on the determinants of treatment choice. Population-based studies have demonstrated that there are distinctly different patterns of prostate cancer care among African Americans and Caucasians and the reasons for this should be studied. How patient decisions are made, including the role of insurance coverage, is unclear. In summary, there is a need to develop and test the factors that determine treatment choice.

Hypothesis-driven research focused on differences among interventions provides an opportunity to develop new knowledge that may improve patient-focused outcomes after prostate cancer. Among the many important questions to be answered is whether interventions aimed at enhancing quality of life may also affect survival, in addition to their likely impact on outcomes important to patients, such as alleviation of pain or retention of continence. Although a small number of studies have evaluated quality-of-life issues in patients with metastatic disease, these efforts have been insufficient.

There is insufficient research in the development of new quality-of-life

measurement instruments. The main barrier may be a lack of resources within the clinical trials and cooperative groups to answer these questions. The NCI portfolio, through the Community Clinical Oncology Program, focuses to a large extent on doctor/patient communication. However, there is insufficient examination of how this communication affects treatment choice or outcome. There is a need to develop ways to explain the prognostic variables in a simplified way in order to help providers develop methods to incorporate this into patient preferences and treatment decisions. Furthermore, there are few tools available to explain the complex statistics and risk-to-benefit ratios necessary to make these decisions.

Finally, efforts must be made to educate the biomedical research community about outcomes research. It is clear that consumers and purchasers of health care find these endpoints important. Furthermore, communication to patients about the impact of treatment on patient-focused outcomes has been limited, and a broader discussion of these endpoints should enhance participation in outcomes research. Another important obstacle to increasing the collection of quality-of-life data within the existing clinical trial mechanism is economic: there have been few additional resources available to add quality of life and outcomes research to this mechanism. The resources required for this type of patient-focused research are greater than standard clinical trials because of the length of follow up necessary, as well as the fact that these are typically not endpoints collected as part of clinical care.

RESEARCH PRIORITIES

During the initial Roundtable meeting for the outcomes group a number of questions were proposed for examining outcomes in prostate cancer during the next five years. After reviewing the questions and comparing them to the current NCI portfolio, several general recommendations emerged, which are summarized below the Priority One research questions.

Priority One

What is the impact of treatment on outcomes? How do the benefits differ in subsets of patients by age, morbidity, race, etc? What are the outcomes in the community setting compared with those from clinical trials or centers of excellence? How do provider characteristics (e.g., volume, expertise) affect outcomes? How do patients value tradeoffs between length of survival and quality of life?

The NCI portfolio sponsors a number of research programs addressing the questions listed above. However, specific age-related questions are an important aspect of completing these analyses. Because prostate cancer is largely a disease of older men and will be increasingly so as the population ages, we need additional data on the efficacy of various treatments in older men. Many older men have been excluded from clinical trials because of co-morbid conditions; they may not have been encouraged to participate in clinical trials, thereby impeding research that aims to determine which conditions are

important when considering treatment and outcomes in this group of patients.

The NCI portfolio currently does not support the development of instruments to assess quality of life. Nor does it support interventions to increase health-related quality of life for prostate cancer patients, such as pain management, and enhancing cancer control and screening in Hispanic and African American men. In addition, there are gaps related to the impact of different approaches to prostate cancer screening and different options on quality of life and other manifestations of stress. The question of how patients value tradeoffs between survival and quality of life has not been adequately addressed.

There have been relatively few studies evaluating differences in outcomes between the clinical trial mechanism, centers of excellence, and community centers, and there are few data on how provider characteristics affect outcome.

How are different types of outcomes defined? What are the standardized measures of outcomes, e.g., quality of life, morbidity, and patient satisfaction?

Both the prostate cancer outcome studies (PCOS) and the SEER program evaluate treatment practice patterns and the long-term prevalence of urinary, bowel, and sexual complications subsequent to initial treatment for prostate cancer. These studies include thousands of men treated in a general community setting. Results from these studies will complement ongoing randomized trials of treatment efficacy, providing prostate cancer patients and their physicians with information about likely outcomes of differing treatments. Researchers should also strive to determine which co-morbid conditions are important when considering treatment and outcomes.

In the NCI portfolio, there are many studies collecting data on morbidity and quality of life. NCI has several existing research mechanisms that can facilitate these outcomes studies, including clinical trials groups and SEER. The clinical trials groups can study patient-focused outcomes within the setting of randomized control trials. In contrast,

the SEER program tracks incidence of mortality rates for cancer in the U.S. population, thereby focusing primarily on disease-focused outcomes. These two mechanisms are not necessarily linked.

What is the impact of early detection and screening on outcomes?

The NCI research portfolio is conducting ongoing research into early detection with the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. However, few of these studies will result in relevant information on how screening and early detection effect patient-focused, quality-of-life issues, or more specifically, cost. In summary, there is a need to include aspects of patient-focused outcomes in clinical trials of early detection and screening.

Recommended Actions:

- Use NCI clinical trials groups to foster outcomes research
- Expand and support the scientific committees within clinical trials groups to focus on outcomes
- Invest resources in the existing NCI clinical trials infrastructure and SEER mechanism so that the overall cost of outcomes research will be minimized
- Convene a working group to identify the key patient-focused variables and make recommendations for how to include them in the clinical trials databases
- Increase interactions among funders of health care to determine the optimum strategies for long-term management of prostate cancer patients
- Train more researchers in outcomes research
- Develop mechanisms to disseminate to patients outcomes information
- Promote cooperation with health researchers and health economists through targeted workshops and conferences
- Encourage the development of common mechanisms for reporting patient outcomes in prostate cancer studies

Priority Two

- What are the determinants of treatment choice?
- What are the important system/insurance/access factors?
- What is the cost effectiveness of treatment?
- What is the impact of treatment on quality of life relative to the benefit gained in life years?
- What is the benefit or cost of treatment in dollars per life years saved?
- What interventions can effectively enhance health related quality of life?
- What types of new quality of life instruments can be developed and tested?

Priority Three

- How does the source and type of patient information (e.g., patient-physician communication) affect treatment choice and outcomes?
- How can quality of life information be collected in more clinical studies?

H. RESOURCES NEEDED

Throughout this report the PRG has made a number of recommendations regarding research initiatives that should be addressed in order to accelerate the pace of research in prostate cancer. In this section, we describe those resources that the PRG considers most essential and common to many of the high-priority research initiatives. These resources will provide the essential infrastructure to facilitate a multidisciplinary research agenda in prostate cancer. The major recommendations to enhance progress in prostate cancer research include: 1) long-term, sustained investment in talented clinical and basic research investigators; 2) the development of a national informatics network linking clinical and epidemiological databases, and tissue and specimen repositories; 3) an emphasis on better preclinical models of prostate cancer; 4) the development and application of novel technologies such as genetic arrays; and 5) the implementation of a focused clinical trials mechanism.

I. EDUCATION AND TRAINING OF PROSTATE CANCER INVESTIGATORS

The PRG unanimously agreed that the education and training of investigators who will pursue research in prostate cancer should receive top priority. Training of young investigators will provide the foundation on which to build new research initiatives in the future. This cadre of young scientists will provide the seed for novel ideas and new technological advances, which will enhance the fight against prostate cancer. Young clinicians who have the necessary clinical background and desire to devote their careers to prostate cancer research should be given the means to pursue these goals. However, NCI support should not stop with training; it should assure sustained funding for investigators of proven productivity. Thus, future progress in the areas of research described in this report is dependent on a highly trained and adequately sized scientific workforce dedicated to prostate cancer research.

Recommended Actions:

To ensure the future supply of investigators focused on prostate cancer research, NCI should:

1. provide funds for training of outstanding graduate students, post-doctoral fellows, and residents in prostate cancer biology, pathology, and treatment
2. allocate adequate research funds to qualified young investigators for the initiation of independent research programs
3. diversify the workforce engaged in prostate cancer research by recruiting minorities and women to these efforts, and
4. provide sustained funding for prostate cancer investigators of proven productivity.

II. INFORMATICS NETWORK OF DATABASES AND SPECIMEN REPOSITORIES

Prostate cancer research is hampered by an inadequate infrastructure for tissue acquisition, storage, and use. The limited tissue repositories available are not closely linked with appropriate clinical, pathological and epidemiological information. And there is a lack of databases serving the burgeoning needs of basic, clinical, and epidemiological researchers. An informatics network, through computer interfaces, can bring together pathological and genetic information with clinical, epidemiological, and demographic information. Thus, a national informatics network forms an essential link between the repositories and the databases that are recommended below.

A. Databases

The creation of new databases is essential to tackle interdisciplinary research opportunities. Databases must be inter-linked and must form part of a broader informatics network (described below).

More specifically, the Human Genome Project has rapidly accelerated the identification and characterization of genes, even if these genes had no known name or function. Short segments of DNA, termed "Expressed Sequence Tags" or ESTs, when entered into a database that is widely accessible, have allowed multiple investigators to compare their sequences of special interest with those of other investigators around the world.

With the enormous explosion of computer technology has come the ability to handle much larger amounts of information more quickly and efficiently. This has been especially applicable to very complex systems such as that exhibited in biology. Thus, a new discipline (bioinformatics) has emerged to manage, compare and compute the mega-bytes of information being collected on biological and clinical specimens.

Recommended Actions:

1. NCI should support the development of new prostate cancer databases and of bioinformatics to ensure that the vast amount of information that becomes available can be assimilated and exploited. NCI should also play a leading role in facilitating the appropriate communication of information about prostate cancer-related genes among academia, industry, and government.

2. Prostate cancer-related databases should be developed and expanded, especially:

- genetic databases to facilitate gene discovery;
- clinical databases that include demographic factors, clinical information, and outcomes for patients with localized and metastatic disease;
- human prostate cancer Expressed-Sequence Tags (ESTs) should be catalogued and disseminated;
- new family registries; and
- new epidemiologic databases.

3. A national inventory of databases of populations under study would greatly facilitate epidemiological research.

B. Repositories

There is a need to collect selected specimens that are well characterized, with comprehensive clinical, demographic, and epidemiologic information included. Standardized methods for tissue procurement and banking are not only indispensable for current studies, but also for emerging technologies which require validation. Laser microdissection is a new technology that has enabled researchers to dissect tissue down to the cellular level. This technology permits the precise excision of highly enriched, homogeneous tissue samples, which is vital given the heterogeneity of prostate tumors. Researchers using biological measurements require access to a stable supply of well-characterized tissue samples complete with epidemiological clinical profiles.

Recommended Actions:

Specifically, NCI should undertake or encourage the following efforts:

1. Establish a National Prostate Cancer Repository to procure and distribute well- characterized tissue from prostate cancer patients, including samples obtained from autopsies and from patients in clinical trials.
2. Support repositories that selectively emphasize the collection of uncommon specimens, such as well-characterized, microdissected, matched pairs of normal and malignant tissues and of primary and metastatic tissues from the same patient, along with serum, and DNA and RNA samples.
3. Support repositories to collect, or be linked to, clinical and epidemiological information and clinical outcomes from patients who provide specimens.
4. Establish guidelines for the high-quality collection, handling, and storage of tissue samples.
5. Develop standards for the acquisition of RNA from human tissues in order to facilitate intra-laboratory comparisons of gene expression profiles. Given the lability of RNA, cooperation between surgeons, pathologists, and researchers is needed to ensure proper handling and preservation of samples.
6. Develop a peer-reviewed mechanism for distribution of tissue specimens and corresponding patient information to appropriately qualified researchers.

C. Patient Consent

Researchers are thwarted by the absence of broad patient consent for multiple and unforeseen uses of donated specimens and clinical information. Researchers currently are compelled to return to the Institutional Review Board for re-approval and patient re-consent before initiating many new studies, and patients may no longer be available to provide consent. New policies for patient consent are vitally needed to expand and expedite the use of tissues and clinical and epidemiological information in research. NCI should bring together the ethics, legal, medical, and scientific

communities to develop standards to facilitate improved collection and broad utilization of specimens and information.

Recommended Actions:

To promote enhanced collection and utilization of tissue samples and patient/subject information while still protecting patient confidentiality and patients' rights:

1. NCI should lead an effort to encourage Institutional Review Boards (IRBs) to develop patient consent policies that facilitate the broader use of tissue and clinical information for research. Consent requirements should be appropriate to the scope of the research. For example, research investigating highly prevalent and highly penetrant genes should have different requirements from those for low prevalence, low penetrant genes.

2. NCI should forge consensus among investigators for developing standardized patient consent forms which will allow multiple research applications for human biological specimens and clinical information used in analytical, clinical, or outcomes research.

III. PRE-CLINICAL MODELS

Researchers in prostate cancer are fortunate to have several excellent pre-clinical models available with which to study the disease. These include xenograft, transgenic, reconstitution, spontaneous tumor, and hormonally induced models. However, each of these models has specific drawbacks, which makes it less than ideal. Moreover, within each of these classes of models few specific examples are available, thus providing only a small portion of the potential information needed.

Transgenic and reconstitution models have been valuable in studying the initiation, progression, and metastasis of a rodent prostate tumor. The development of some of these models has been facilitated by the identification and characterization of promoter regions on prostate-specific genes. Limitations of these models include the androgen-dependent nature of these promoters and the artificial nature of the oncogenes used as initiators. With a clearer understanding of the basic biology of initiation and progression of human prostate cancer, better transgenic models can be developed in a manner that more truly recapitulates the human disease.

Xenograft models offer the potential of studying human tissues in a well-controlled *in vivo* environment of the immune-deficient mouse. Researchers have the ability to manipulate these models to test compounds for therapeutic and chemoprevention potential. The disadvantages of these models are the abnormal host environment (i.e., immunodeficient) and the limited ability to grow human prostate cancer consistently in xenographic hosts.

Cell lines from human prostate cancer are crucial for understanding the molecular and cell biology of the disease, for the development of xenographic models, and for testing

therapeutic interventions. Indeed, for other cancers, cell lines have greatly facilitated investigators' study of the biology and pathology of cancer. Yet it has been difficult to establish cell lines from human prostate cancer and few established cell lines are available. Therefore, a major goal should be the development of additional cell lines, which reflect the heterogeneity of human prostate cancer.

In summary, although some excellent models of prostate cancer have been developed, too few are available. Additional models are urgently needed that more faithfully recapitulate the human disease. Research is needed to identify additional prostate specific promoters, as well as to characterize those genes that are crucial for human prostate cancer initiation, progression, and metastasis. Such information is essential for developing more effective models that more accurately mimic human prostate cancer.

Recommended Actions:

Existing laboratory and clinical models have been useful, but have significant disadvantages that need to be overcome in the design of future models. A major barrier is the paucity of cell lines from human prostate cancers.

1. New cell lines from human prostate cancer should be developed and made available.
2. New animal models should be developed and made widely available.
3. Additional prostate-specific promoters need to be identified and characterized to stimulate the further development of *in vivo* animal models.
4. Greater knowledge about those genes that are critical for human prostate cancer initiation, progression and metastasis will lead to the development of models that better mimic the human disease.
5. Greater emphasis should be placed on models that metastasize.

IV. NEW TECHNOLOGIES

This decade has witnessed a remarkable surge in the development of new biomedical technologies. However, the dissemination of new technologies for research in prostate cancer has been inhibited by costs, limited availability and rapid technological change.

Microarray/chip technology is a rapidly evolving tool in which samples of nucleic acids are hybridized onto an array or matrix, allowing for a faster, more automated approach to genetic analysis. The advent of this technique has revolutionized the way we study gene expression. Rather than examining the expression of one gene at a time, this technology allows one to examine thousands of genes at once, thus revealing interactions and synergism among entire families of genes. Applications in cancer research include assays of numerical chromosomal alterations, high throughput sequencing, and differential gene expression, with the latter of greatest interest to prostate cancer research at this point. This technology should be applied and refined in conjunction with advances in laser microdissection and development

of animal and cellular models of the disease.

Recommended Actions:

Microchip/array technology involves substantial costs, is accessible to few investigators, and is rapidly changing. NCI should develop mechanisms to make this technology more readily available as a resource to highly committed and qualified investigators with well-defined hypotheses. Specifically,

1. NCI should facilitate the development and dissemination of technologies, reagents and data related to gene expression patterns (microarrays).
2. NCI should support regional centers that provide access to microarray/ chip technology. Such centers will be helpful only if implemented quickly, as the technology is advancing so rapidly.
3. Genetic arrays should be standardized for general use, allowing for reliability and reproducibility.
4. NIH should facilitate technology development by making maximal use of all available technology transfer mechanisms to promote the optimal development and dissemination of microarray/chip technologies.
5. A web-based program should be developed to update the research community on progress in the development of this technology.

V. CLINICAL TRIALS

Clinical trials are pivotal to validate prognostic markers in prostate cancer and to develop new preventive agents and novel therapeutics for prostate cancer. Trials have been less effective because of the absence of standardized methodology and the low accrual of patients. New, directed, more efficient mechanisms are needed to test novel hypotheses in prostate cancer in a timely manner in the areas of prevention, early detection, marker validation, treatment of local and advanced cancer, and outcomes.

Recommended Actions:

1. NCI should play a leadership role in the design of clinical trials, establishing standardized systems for assessing prognostic markers, determining appropriate endpoints, and identifying response criteria.
2. NCI should develop a special prostate cancer trials consortium. This consortium should include major medical centers engaged in prostate cancer treatment and research.
3. NCI should appoint a prostate cancer clinical trials coordinator.
4. New funding mechanisms and/or review processes should be developed to promote the rapid initiation of carefully designed trials of prostate cancer human gene therapies.
5. Clinical trials should be designed to ensure adequate representation of minorities.

VI. OTHER RESOURCE PRIORITIES

The previous section presents those resources that were considered by the PRG to be of the highest priority in accelerating the pace of research in prostate cancer. The following resources, which are germane to many of the high priority research initiatives recommended in this report, were also considered important, though less urgent or of more narrow scope, and are listed in order of priority.

Priority Two

- Funding should be directed at clinical trials, especially in:
  - Etiology,
  - prevention,
  - treatment of localized disease,
  - methods to assess treatment efficacy more quickly,
  - the role of adjuvant therapy,
  - quality of life instruments, and
  - behavior.

- Referral and study design of clinical trials:
  - Incentives should be developed for physicians to refer patients to clinical trials, especially patients from minority populations.
  - Incentives should be developed for patients to participate in clinical trials.
  - Incentives must overcome patients' social/cultural barriers and/or improve their reimbursement.
  - Clinical trial design should incorporate uniform assays and reagents in order to facilitate the translation of one study to another.
  - Eligibility criteria for Phase II clinical trials should not necessarily exclude patients who have failed prior therapies.
  - Clinical trials groups should work more effectively together to expedite progress of large-scale trials.
  - Given the current minimum of 3-5 years to evaluate a single drug by one institution, trials should be performed in multi-institutional settings and should proceed more quickly.
  - NIH reviewers should be more willing to take risks in the review of clinical trial applications.
  - Consensus needs to be forged on how to interpret PSA changes in the context of a hormone refractory clinical trial.
- Better image analysis software will allow better quantification and discrimination of tissue gene expression patterns.
- New technologies should be developed to decrease morbidity and enhance cancer control in radiation therapy.
- More prostate cancer family registries are needed for genetic analysis and counseling; develop repositories of germline and cancer tissue samples (e.g., cell lines) from these subjects.
- Dedicated research groups, such as SPOREs, should be expanded and

coordinated to promote translational research.

- Laser microdissection should be made available as a shared resource at centralized facilities.
- Education of patients from a variety of population groups would facilitate progress in prostate cancer research.

Priority Three

- Cultural and socioeconomic barriers should be overcome to guarantee that high-risk populations are informed about the extent of, and known risk factors for, prostate cancer and the impact of diagnosis and treatment.
- Patients should be educated about the importance of research and the value of their personal participation in research.
- Existing databases (e.g., SEER and PLCO) should be supplemented with information about co-morbidity, cancer descriptors, sociodemographic information, treatments, quality of life and morbidity outcomes, population-based treatment data on patients under 65, and costs.
- Patients and providers should be educated about recent scientific discoveries and their impact.
- Existing cooperative group mechanisms should cultivate translational research.
- Novel technology should be developed and applied to patient education.

APPENDICES

APPENDIX 1
MEMBERSHIP ROSTER
NATIONAL CANCER INSTITUTE
PROSTATE CANCER PROGRESS REVIEW GROUP

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APPENDIX 2

AGENDA
NATIONAL CANCER INSTITUTE
PROSTATE CANCER PROGRESS REVIEW GROUP
ROUNDTABLE MEETING

June 29 - July 1, 1997
Westfields International Conference Center
Chantilly, Virginia

Sunday, June 29

4:30 p.m. - 5:30 p.m.	Reception	
7:00 p.m.	Introduction and Opening Remarks Charge to the Roundtable	Dr. Klausner
	Progress Review Group (PRG)	Dr. Scardino Dr. Tindall
	Meeting Process	Dr. Chiarodo
7:30 p.m.	Meeting of the PRG co-chairs and breakout session co-leaders, scribes, and Office of Science Policy staff	Dr. Scardino Dr. Tindall Dr. Chiarodo
8:00 p.m.	Meetings of co-leaders, scribes, and OSP staff for individual breakout sessions	

Monday, June 30

8:00 a.m. - 12:30 p.m.	Morning Breakout Sessions Etiology Early Detection, Diagnosis, and Prognosis Therapy: Localized Disease Biology Clinical and Laboratory Models
2:00 p.m. - 6:30 p.m.	Afternoon Breakout Sessions Prevention Cancer Control Outcomes Research Therapy: Systemic Disease Progression and Metastasis
8:00 p.m. -10:00 p.m.	Co-leader preparation for Tuesday presentations: co-leaders, scribes, and OSP staff

Tuesday, July 1

6:30 a.m.		Registration and Message Center	
7:00 a.m. - 8:00 a.m.		Breakfast meeting for PRG members	
8:00 a.m. - 12:15 p.m.		Breakout Group Presentations	
	8:00 a.m.	Moderators: Dr. Scardino and Dr. Tindall	
	8:05 a.m.	Etiology	
	8:30 a.m.	Early Detection, Diagnosis, and Prognosis	
	8:55 a.m.	Therapy: Localized Disease	
	9:20 a.m.	Biology	
	9:45 a.m.	Clinical and Laboratory Models	
	10:10 a.m.	Prevention	
	10:35 a.m.	Cancer Control	
	11:00 a.m.	Outcomes Research	
	11:25 a.m.	Therapy: Systemic Disease	
	11:50 a.m.	Progression and Metastasis	
12:15 p.m. - 12:30 p.m.		Concluding Remarks	Dr. Klausner Dr. Scardino Dr. Tindall
12:30 p.m. - 2:00 p.m.		Co-leaders, scribes, and OSP staff work to revise final breakout group reports based on morning discussion	
2:00 p.m.		A D J O U R N	

APPENDIX 3
NATIONAL CANCER INSTITUTE
PROSTATE CANCER PROGRESS REVIEW GROUP
ROUNDTABLE MEETINGS

JUNE 29 - JULY 1, 1997

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Pat Brown
Michael Emmert-Buck
David Krizman
David Lockhart
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Gene Therapy and Vaccines

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Tyler Jacks
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