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NURA

National Urology Research Agenda

*A roadmap for priorities in
urologic disease research.*



AUA FOUNDATION

*The Official Foundation of the
American Urological Association*



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Executive Summary

The American Urological Association (AUA) Foundation launched an ambitious initiative to define national research priorities for the field of urology. This major effort was commissioned by the AUA Foundation Board of Directors to 1) define research priorities in urology by the urology research community, 2) reverse the decline in urology research funding and progress, and 3) promote an increase in funding and research activity. The endpoint is the creation of this document, the “**AUA Foundation National Urology Research Agenda: 2010 (NURA)**,” which will serve as a roadmap for articulating the basic and clinical research, and research infrastructure priorities in urology, thereby promoting substantial improvements in patient care. There is a tremendous need for such an initiative and we have much to gain from this effort.

Table 1: Major Goals of the National Urology Research Agenda

- Articulate and quantify the national burden of urological diseases
- Inform Congress, funding entities and researchers about high priority areas in urological research
- Identify areas of scientific opportunity
- Stimulate progress
- Identify and prioritize the most fertile areas of current research progress
- Foster translational activities to ensure that basic research is translated into clinical practice and that clinical practice findings are translated back to the bench for examination
- Foster transdisciplinary activities to ensure interactions between MDs and PhDs, and among individuals from diverse areas of science and medicine within and outside of urology
- Set priorities for research infrastructure needs to facilitate all areas of urology research
- Periodically reevaluate NURA to ensure that it continues to meet the needs of the urology community

Most basic research focusing on human health in the United States is funded by the National Institutes of Health (NIH). The NIH budget has been essentially flat for the last nine years and, when inflation is considered, the budget has actually declined significantly in real terms since 2003. This is a large contraction that has negatively impacted most academic fields that rely on NIH funding.

Although all health-related biomedical research in the United States has been adversely affected by the funding climate, urology has been particularly hard hit, as the field has historically been underfunded in comparison to many others. The disparity is particularly evident in light of the immense burden of urological disease on the nation, which is increasing dramatically as the U.S. population ages.

The major goals of this effort include articulating and quantifying this burden (Table 1). Taken together, these goals provide a framework

to advance progress by stimulating new funding or allocations of existing funds to urology, and increasing activity in this field.

NURA seeks not only to identify areas of scientific priority and opportunity, but also to emphasize the importance of multidisciplinary activities and to define areas of multidisciplinary potential.

This is critical to “growing” the field and to increasing competitiveness for funding.

Table 2: NURA Priority Areas of Research and Research Infrastructure

- Benign Prostatic Hyperplasia (BPH)
- Bladder Cancer
- Chronic Pelvic Pain/Prostatitis/Interstitial Cystitis/ Bladder Pain Syndrome
- Developmental Anomalies
- Kidney Cancer
- Male Reproduction and Infertility
- Nephrolithiasis
- Prostate Cancer
- Research Infrastructure
- Sexual Dysfunction
- Urinary Incontinence/Overactive Bladder (OAB)/Neurogenic Bladder(NGB)
- Urinary Tract Infections (UTIs)

NURA is organized into 11 distinct disease-focused research priority areas and one research infrastructure area (Table 2). Major priorities and approaches are delineated which must be addressed to advance progress in each of these areas. Also described are multidisciplinary opportunities that may exist in each area.

Common themes that span multiple research and research infrastructure areas have emerged. Among these are the needs for:

- Validated biomarkers across all urological areas, including cancer and non-malignant urological diseases
- Comparative effectiveness research (CER) to provide concrete guidelines on the most appropriate and cost-effective therapeutic interventions
- Basic exploratory research to increase understanding of the cellular and molecular basis of normal and abnormal structure and function of lower urinary tract tissue
- Understanding the parameters that underlie ethnic disparities
- Biospecimen repositories of well-documented diseased and normal tissue
- Animal and cellular models that effectively model the human condition

- Understanding the relationship between urological diseases and a host of co-morbidities including diabetes, metabolic syndrome, and obesity
- Attracting new individuals into the field
- Identifying and nurturing the careers of rising star MD and non-MD scientists early in their careers
- Developing and enhancing urology centers of excellence
- Developing urology research repositories and databases
- Increasing financial support from government, industry and philanthropy

From the start of this initiative, a concerted effort was made to ensure that NURA was developed with representation from basic, translational and clinical science across the spectrum of urologic diseases and conditions. Also essential to the success and validity of this effort is the requirement that the priority areas developed for NURA align with major focus areas of the NIH and other major federal agencies, as well as with those of other major stakeholders.

To achieve this alignment, a summit meeting was held in September 2009 that brought together 75 leading clinicians, academic researchers, patient advocates and industry representatives to discuss NURA, and provide input and concurrence. The Summit and post-summit meeting activities focused on articulating critical next steps to accomplish the goals of NURA (Table 1). The three levels of discussion solicited at the summit meeting were 1) priority topics within each research priority area, 2) priority themes that bridge two or more research areas, and 3) priority “super themes” that span multiple research areas and disciplines.

This was a pivotal point in the development of the document.

The future of urological research lies not only in identifying critical priorities, but also in delineating how those priorities intersect with the broader research and clinical communities. When taken together, the individual priorities provide the necessary background that will inform decisions on how to develop multidisciplinary collaborations. Thus, the major recurring emphasis throughout NURA is the development and fostering of multidisciplinary research. This emphasis will allow the urology research community to capitalize on synergies that arise when individuals from diverse disciplines work together.

By its nature, urology is a diverse and multidisciplinary field. As such, it opens up tremendous opportunities to bring together scientists and clinicians from diverse backgrounds to forge new collaborations to leapfrog progress. To emphasize the extent and potential for multidisciplinary efforts in urology, a matrix was created which demonstrates some of the multidisciplinary possibilities and opportunities that exist when each NURA priority area is linked with one or several thematic areas (Table 3). While this does not show the total extent of multidisciplinary opportunities, it does provide an at-a-glance picture of the potential.

At the summit meeting, opportunities to open up multidisciplinary collaboration within and between each priority area were discussed. Several post-summit meetings were held to define overarching areas that would stimulate development of transformative multidisciplinary urology research efforts or super-themes that would jumpstart progress in curing or controlling multiple urological diseases and conditions and stimulate allocation of resources.

The focus would be on processes or pathways that underlie multiple urological and non-urological disease states for the purpose of leveraging scientific progress to fill fundamental knowledge gaps in urology, and to increase potential funding opportunities for urological researchers by broadening the pool of collaborators and funding sources.

Seven super-themes spanning multiple urological and non-urological disease states, and multiple scientific disciplines were developed.

1. **Regulatory networks of growth and differentiation, and their role in cancerous and non-cancerous states of the urinary tract.** This super-theme encompasses genetic and epigenetic processes, the dynamics of protein interactions, and the role of metabolites in the context of cellular pathways and networks that are relevant to many of the NURA research priority areas, in particular: benign prostatic hyperplasia, various cancers, developmental anomalies, reproduction, and male infertility. They also connect with many non-urology disciplines.
2. **Inflammation and immune function and their causal influence in cancerous and other abnormal urinary tract states.** This super-theme is also relevant to most of the NURA priority areas, in particular nephrolithiasis, urinary tract infections, and various cancers, and connects to a multitude of other conditions, including other types of inflammatory disorders, e.g., inflammatory bowel disease, infections in other organ systems, and non-urological cancers.
3. **Pain, and its etiology and management in urinary tract disorders.** This super theme is common to many of the NURA priority areas, including chronic pelvic pain syndromes, urinary tract infections, sequelae of various cancers and procedures, and is relevant to non-urological disorders characterized by pain. New and innovative measures, methods and technologies are required that integrate human social and behavioral science with urological research.
4. **Coexisting conditions and their role in the etiology, progression, prevention and treatment of urinary tract disorders and dysfunction.** This super theme focuses on the relationship between urological diseases and conditions, and the influence of highly prevalent metabolic syndrome conditions such as obesity, diabetes, cardiovascular disease and hypertension that are known or hypothesized to impact the health of the urinary tract. Many of the NURA areas potentially fall into this category, – e.g., erectile dysfunction (ED) as a marker of occult cardiovascular disease or the role of obesity in nephrolithiasis. This super theme connects to research in all of the aforementioned areas as well as potentially into broader

Table 3: Orthogonal Matrix of Multidisciplinary Areas

Disease or Condition	Regenerative Medicine	Inflammation/ Infection	Neurobiology	Rehabilitation/ Pharmacology/ Smooth Muscle	Developmental Biology/ Pediatrics	Aging	Epigenetics	Men's Reproductive Health	Nano-technology
BPH		X	X		X	X	X		X
Bladder Cancer	X			X		X	X		X
Chronic Pelvic Pain Syndromes			X			X			
Developmental Anomalies	X	X	X		X	X	X	X	
Male Reproduction and Infertility	X	X			X	X	X	X	
Nephrolithiasis		X		X		X	X		X
Prostate Cancer		X	X		X	X	X	X	X
Renal Cell Carcinoma	X			X			X		X
Sexual Dysfunction				X	X	X		X	
Urinary Incontinence/ OAB/NGB	X		X	X	X	X	X		
Urinary Tract Infections		X			X				

treatment and prevention topics such as smoking cessation (relevant to many cancers and ED) and weight loss (relevant to cancer etiology, cancer recurrence prevention, cardiovascular health, etc.).

- Neoplasia.** This super theme entails a broad spectrum of basic, translational and applied research activities seeking to deliver new scientific knowledge in the etiology, prevention, diagnosis, and treatment of urological malignancies. Specific emphasis is placed on investigations exploring the biological, genetic and molecular underpinnings of urological malignancy; the development of biomarkers; and novel targeted therapies against cancer. This super theme highlights NURA's commitment to cancer research through innovation and the seamless collaboration between basic science and clinical investigators.
- Health Services Research.** This super theme subsumes research that examines how individuals and groups access health care, ascertains the quality of that care determines which elements of care are utilized, measures the costs of that, and assesses patient-centered outcomes of care. It is a multidisciplinary field of inquiry, both basic and applied, that includes the use, costs, quality, accessibility, delivery, organization,

financing and outcomes of health care services. Research comparing the effectiveness of different treatments, surgical and pharmacological, and the outcomes of varying approaches to specific urological disorders will identify the most effective ways to organize, manage, finance and deliver high-quality care, reduce medical errors and improve patient safety. Investigations span the individual patient to the population level, from fundamental epidemiology to the translational population sciences, and collaborations with researchers in many fields, will be required to fulfill these goals.

- Research Infrastructure.** This super-theme encompasses issues that touch virtually every aspect of urology research and are critical for advancing urological research priorities. Fragmentation of effort into disciplinary silos must be addressed by removal of structural barriers to interdisciplinary research by, e.g., changing the academic culture to foster collaboration. Important gaps in urologic training and research resources must be addressed. A major need is to attract and nurture young investigators via rigorous research training and effective mentoring. Among the research resources that are critical for progress are availability of well-documented tissue for study, animal models, accessible databases (e.g., drawn from electronic

medical records and genetic/genealogical data) and real-time networking capabilities.

Since its inception, NURA has been considered a “living” document. It will be subjected to an annual review and revision process to ensure that it remains current and responsive to progress and evolving trends. NURA will be implemented through a series of clear, concise and compelling messages intended to be used as targeted tools that will allow the research, clinical and advocacy communities to realize the goal of increasing awareness, research activity and funding in urology research.

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Introduction

The **National Urology Research Agenda** was developed under the guidance of the AUA Foundation Board of Directors. Through a series of initiatives from October 2006 to August 2007, the Board, AUA Foundation Research Council, and members of the urology research and clinical communities initiated this important undertaking. Michael Freeman, PhD was designated as the Chair of the NURA work group.

He and Anthony Schaeffer, MD, Chair of the AUA Foundation Research Council, were charged with carrying out this directive. At the Research Council Strategic Planning Meeting, in August 2007 members of the work group developed the strategy for initiating this important endeavor. The charge to the group was to decrease the public health burden of urological diseases by substantially advancing progress in the treatment of urological diseases, and enriching and expanding the investigative urology field.

The NURA process began in earnest in the fall of 2007. Input on the top priorities identified by the research community was solicited from 16 research-focused AUA affiliated specialty societies. The initial list, created in early 2008, contained 43 research priority areas. This list was substantially revised and condensed during the ensuing 12 months using a prioritization matrix that was developed specifically for this purpose. Each disease or condition and its related research priorities were evaluated according to nine criteria:

1. economic impact
2. morbidity/mortality
3. prevalence
4. alignment with urology research resources
5. alignment with NIH strategic plans
6. alignment with AUA Strategic and Tactical Plan
7. alignment with industry related research
8. overlap with other fields
9. needs of the public.

By using that matrix, the initial 43 research priorities were condensed to a total of nine. Following extensive discussion among work group members, that list was later modified to include the 11 research priorities and one infrastructure priority chapter that make up the current document.

In February 2009, work group members, who created 1 to 2–page narratives that described the priorities most closely related to their areas of expertise, developed a first draft of NURA. After the Board approved this draft in April 2009, the next phase was initiated. The primary focus was to have NURA critically evaluated, reviewed, and refined by external stakeholders who had interests in urological disease research. This evaluation was accomplished through an iterative sequential process where the initial draft was reviewed and commented on by successively larger and more inclusive groups of individuals. The goal was to solicit input and concurrence from all urology stakeholder communities, and to have NURA undergo a critical and rigorous evaluation to ensure that this list of priorities was consistent with the goals and strategies of their organizations. Stakeholders include key individuals from federal funding and regulatory agencies, the academic research community, patient advocate and industry.

Early in the process, it became evident that a major driver for progress in urological disease research would be to capitalize on the inherently multidisciplinary nature of urological diseases as a means to attract talented individuals from other areas of research to enter the field. This is a major emphasis of NURA and a consistent theme throughout.

NURA is divided into Research Priorities and Infrastructure Priorities. Within each **Research** area the chapters are divided into three sections of 1) **Background**, which characterizes each disease, and discusses its economic and social burdens; 2) **Priorities and Approaches**, which outlines the major priorities and provides a brief discussion of promising approaches; and 3) **Multidisciplinary Opportunities**, which provides suggestions for potential synergy. Within the **Infrastructure Priority** area, the chapter is divided into, two sections of **Training** and **Core Resources**.

It is important to emphasize that NURA is a living document with the intent to review and revise it annually to ensure that it remains current and responsive to the needs of the urology research and patient communities.

The AUA Foundation is tremendously grateful to all who participated in this major effort and we thank you for your contributions.

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Priority Research Areas

Chapter I - Benign Prostatic Hyperplasia

Background

BPH is a non-cancerous proliferation of glandular epithelium and connective tissue stroma within the periurethral prostate gland that results in bladder outlet obstruction. Irritative symptoms attributed to detrusor muscle overactivity are often reported as the most bothersome and are sometimes classified as overactive bladder symptoms. The cause of the BPH, which is variable in location and extent within the gland, is unknown¹. Taken together, the obstructive and irritative effects are referred to as lower urinary tract symptoms (LUTS), and can dramatically decrease quality of life. Treatment currently consists of medication for milder cases and surgical techniques for more advanced obstruction.

BPH is a prevalent urological condition. In 2009 almost 7 million men over the age of 65 were estimated to have BPH.² In 2000, the last year for which data are available, there were more than 12 million outpatient visits to physicians for BPH, many of which resulted in hospitalizations for men 65 years old or older.^{2,3} In the same year 87,000 men underwent transurethral or laser resection of the prostate for refractory LUTS. An approximate 13 percent increase in the over 65 male population since 2000 predicts almost 100,000 such procedures in 2009.⁴ The economic burden of BPH is considerable with the minimum 2009 cost of around \$1.55 billion.⁵ Expenditures for ineffective herbal medications (used by more than 2 million men in 2002) are not available.⁶ BPH disproportionately affects racial and ethnic groups. In 2000, although many more Hispanic and Caucasian men had outpatient visits, African-American men were hospitalized almost 30 percent more often than the former groups.⁷ Whether these disparities represent genetic or environmental and socioeconomic influences is unknown.

Research Priorities and Approaches

Understanding the basic biology, physiology and pathogenesis of BPH is of critical importance to making progress. These types of studies would provide the background to understand fundamental issues, including: how to distinguish between LUTS caused by processes in the bladder from that in the prostate, why LUTS develops in some men with BPH but not in others, why some men have rapid growth of the prostate and some men don't, which individuals may be at risk for moderate to severe symptoms, what the risk factors might be and how prostate growth relates to bladder function even in the absence of obstruction. The persistence of LUTS in some men, even after obstruction has demonstrably been surgically removed, cannot be addressed without a better understanding of the pathogenesis of this condition.⁸

The sites of action of current medications are unclear. For example, alpha-blockers may work at sites other than the prostate. Exploration of alternate sites of action of BPH medications could prove critical

for better understanding their true mechanism of action and to reveal alternate pathways that may be exploited for better effect.⁹ Information is lacking regarding genetic and epigenetic changes that influence BPH, as well as the molecular events and regulatory pathways involved. Definition of these parameters will aid in the discovery of yet unexploited drug targets.

The relationship between BPH and comorbidities needs to be understood at a molecular, cellular and tissue level. LUTS has been linked to erectile dysfunction.¹⁰ It is not known if this is a causal relationship (i.e., does LUTS due to BPH influence erectile function or abnormal sexual function, or do diminished erections influence LUTS). Recent data have also linked LUTS and the metabolic syndrome. The relationship between LUTS and other potential comorbidities, such as diabetes and vascular pathology, should be examined

Current methods of diagnosing BPH are symptom based. More objective means of diagnosing this condition need to be developed. Molecular biomarkers or related diagnostic tests will permit more precise definitions (e.g., distinguishing LUTS due to abnormal bladder function from LUTS due to prostate pathology).

To make progress in prevention and treatment of BPH, it is essential to understand how genetic predispositions to BPH can be modified by lifestyle or dietary changes and whether new, less invasive treatments can reverse the underlying disorder rather than merely mask symptoms.

Clinical trials involving multidisciplinary groups are required to examine the impacts of diet and lifestyle factors, such as lack of exercise and weight changes, on LUTS. It will be necessary to involve urologists, endocrinologists, endothelial cell biologists, neuro-biologists and others to form a consortium to investigate them, perhaps using the Urinary Incontinence Treatment Network as a model. In addition, CER with all LUTS phenotypes should be undertaken to identify who will respond to which class of drug, e.g., an alpha-blocker; a phosphodiesterase type 5 (PDE5) inhibitor; a 5 α -reductase inhibitor or a combination thereof.

In the Medical Therapy of Prostatic Symptoms (MTOPS) trial men in the placebo arm who had inflammatory infiltrates on baseline transrectal ultrasound (TRUS) biopsies, were the same patients who were predestined for acute urinary retention. Although preliminary, this suggests potential merit in performing studies that examine inflammation of the prostate as a predictor of an adverse outcome.^{11,12}

Clinical epidemiological studies that focus on the effects of sociodemographic factors such as race/ethnicity and access to health care on BPH prevalence, and the relationship between LUTS and other conditions such as diabetes and sexual dysfunction have the potential to increase our understanding and improve care. Whether the similarity between gradients of severity are related to common mechanisms in BPH and that of other conditions, like

diabetes and the metabolic syndrome which are more prevalent and expressed at a younger age in minority populations, should be investigated.

Application of advanced imaging techniques, such as targeted nanoparticles, fluorescent in situ hybridization (FISH) and fluorescent antibody markers of surface molecules must be implemented to unravel the complex transcriptional changes that cause changes in the growth patterns of urothelial and mesenchymal cells. Epigenetic manipulations, such as the use of small interfering RNAs, could result from an understanding of these changes. The existence of populations of epithelial and mesenchymal stem-like cells in the murine prostate indicates a promising area of translational research that may have implications for BPH and prostate cancer.¹³ While existing animal and in vitro models of BPH have served to advance our understanding, new generation models that more closely recapitulate the human condition must be developed to stimulate future progress. An increased understanding of the genetics of BPH would facilitate the development of such models.

Data mining is a technology that should be applied to the study of BPH. A large amount of data exists from large clinical trials in this area which include serum, plasma, DNA, biopsy data and more. However, much of this information has yet to be analyzed. Data mining of current databases (from studies like the MTOPS trial), coupled with exploration of histology and other aspects to determine if there is actually a predictive response, could be most productive. A database containing a master list of such resources, including key contacts, should be established at a central site and made available online. Additionally, using those data to design a prospective trial of a non-alpha blocker should be considered.

Multidisciplinary Opportunities

The processes and mechanisms that lead to BPH and LUTS include cell proliferation, aberrant intracellular and intercellular signaling, and neurological and neuromuscular abnormalities. It is likely that molecular, genetic and epigenetic aspects of these processes and mechanisms are shared with other conditions, including urinary incontinence/OAB/NGB, prostate cancer and urinary tract infections. These commonalities offer opportunities for urological disease investigators to develop multidisciplinary collaborations with investigators from a variety of areas including neurobiology, endocrinology, vascular biology, genomics, proteomics and epigenetics.

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Chapter 2 - Bladder Cancer

Background

Cancer of the bladder is most commonly transitional cell carcinoma derived from the lining epithelium (around 90 percent), with the rest composed of squamous cell carcinomas and adenocarcinomas. At presentation, 70 percent of patients with bladder cancer are diagnosed with non-muscle invasive tumors that are successfully treated with local endoscopic resection.¹ While these tumors are not often life threatening, their management requires intense follow-up to monitor for recurrence, which happens often. Of the cases of recurrence 10 percent progress to the muscle invasive form of the disease with an associated worsening of the prognosis.

The remaining 30 percent of patients with bladder cancer initially present with muscle invasive disease, which is a much more serious condition. More than 50 percent of these patients eventually have metastatic disease, which is essentially incurable.^{2,3} Presently, this form of the disease is commonly treated by removal of the entire bladder (radical cystectomy). Recent data have suggested that neoadjuvant chemotherapy can improve survival by 6 to 8 percent in some patients by reducing metastatic recurrence following cystectomy.⁴ However, only 2 percent of appropriate patients in the U.S. receive neoadjuvant chemotherapy for bladder cancer.

There is an important gap between the impact of bladder cancer and the level of research support it attracts.⁵ In the United States approximately 71,000 individuals are diagnosed with bladder cancer yearly.⁶ Among them, approximately four times as many men will be diagnosed than women.⁷ This incidence is associated with tobacco use and exposure to industrial chemicals, indicating that chemical carcinogenesis is a critical inducer of this cancer.⁸ As of January 1, 2007 approximately 388,965 men and 138,531 women were living with bladder cancer in the U.S., making it the 3rd most prevalent cancer in men and the 10th most prevalent in women.⁶ On average, 4.3 individuals per 100,000 die yearly.

The risk of bladder cancer is strongly age-related, increasing nearly 16-fold from age 40 to 80 years, with a median age at diagnosis of 73 years and median age at death of 78 years. The risk of bladder cancer varies by race and ethnicity, with Caucasian subjects being affected almost twice as often as African American and Hispanic subjects, while Asians, Pacific Islanders and Native Americans are least likely to suffer from this disorder.⁶ In every racial group women are 25 percent to 50 percent as likely as men to be affected. Whether these differences are due to genetic, environmental or socioeconomic influences is unknown.

Because of long-term survival, and the need for lifelong routine monitoring and treatment, the per patient cost of bladder cancer from diagnosis to death is the highest of all cancers, ranging from \$96,000 to \$187,000 (2001 values) in the U.S. Overall, bladder cancer is the fifth most expensive cancer in terms of total health care expenditures, accounting for almost \$3.7 billion (2001 values) in direct costs in the United States.⁹

Research Priorities and Approaches

There is a need for molecular and cellular characterization of non-muscle invasive tumors that are likely to progress so that appropriate follow-up can be instituted and effective tools for detection of recurrence can be developed. For patients with muscle invasive bladder cancer we must also develop tools that will permit the classification of the risk of metastasis, and the development and use of personalized therapeutic selection strategies based on host and tumor characteristics. Such characterization would provide significant advances in bladder cancer therapy by targeting the use of novel and established agents only for patients who would benefit, while sparing others unnecessary toxicity.

There are many treatment options for bladder cancer, including behavioral, chemical, surgical and radiological approaches, but there are few data about them to provide informed good choices. It would be helpful to be able to use risk classification tools effectively in either the neoadjuvant and/or adjuvant setting to select which patients should receive such treatments. Development of new agents and novel treatments, and determining optimal therapy for both of the disease phenotypes is a top priority. The need for effective new agents is especially acute for patients with metastatic disease who have a nearly universal fatal outcome with current regimens.

Use of genetic and cell surface markers has the potential to permit identification of the biological characteristics of cancers and the tailoring of chemotherapies for individual patients. Trial designs based on knowing the differences in individual cancers will be more effective, and such individualized approaches will spare patients from ineffective treatments. The urological community should build upon infrastructure developed through the bladder cancer Specialized Program of Research Excellence (SPORE) program for these efforts.

Community urologists should become involved in tissue acquisition, and should explore avenues for depositing samples at SPORE sites. Another important resource is the Cancer Genome Atlas program. Working with that program and similar efforts would provide avenues to investigate additional genetic mutations and epigenetic changes.

Development of clinical trials consortia focused on bladder cancer could unify and accelerate efforts to fill these needs. Efforts should be made to develop a centralized database for tissue microarrays (TMAs) for dissemination to researchers. Trials of the comparative effectiveness of different approaches are needed. For example, when should surveillance cystoscopies be performed after treatment for non-invasive disease, or how often should prophylactic treatments be applied to prevent recurrences. Untreated and treated tissues from the same bladder cancer patient are available, and their use would make pretreatment and post-treatment tissue acquisition for marker analysis highly achievable.

Identification of changes in cell surface markers and receptors would be greatly facilitated by using techniques such as direct fluorescent

antibody staining with monoclonal antibodies along with cancerous and non-cancerous tissues from the same patient.

Use of these markers could augment urine cytology as an effective screening tool for early detection of new and recurrent cancers. Genome-wide association studies and FISH to detect changes in DNA and RNA transcripts would permit investigation of changes that lead from normal to cancerous cells, and differentiate metastatic from invasive and non-invasive phenotypes. This information would also provide the information needed to devise effective therapeutics based on the changes in cellular signaling mechanisms.

Multidisciplinary Opportunities

Research in bladder cancer should be linked to efforts in prostate and renal cancer. Since urinary tract infection and inflammation seem to be capable of inducing neoplastic changes, connections should be made to these areas as well. Quality of life issues must be addressed for bladder cancer survivors. They are often significant, especially in patients with muscle invasive disease and urinary diversion.

Collaborations with social and behavioral scientists can be effective in devising the necessary research approaches to address these issues. Development of processes to manage the physical and psychosocial impairments that bladder cancer survivors endure as a result of the natural history of the disease or its treatments is imperative. Since the general public is not strongly aware that bladder cancer is closely linked to environmental factors (including smoking), collaboration with social and behavioral scientists can help develop methods to build awareness of bladder cancer symptoms and alert people to these risks.¹⁰

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Chapter 3: Chronic Pelvic Pain / Prostatitis/ Interstitial Cystitis / Bladder Pain Syndrome

Background

Pelvic pain and voiding dysfunction are enigmatic and debilitating syndromes associated with a constellation of symptoms that affect men and women. These syndromes develop through unknown mechanisms and may occur in the absence of detectable inflammation or infection. Interstitial cystitis, also called painful bladder syndrome or bladder pain syndrome, is designated as interstitial cystitis/bladder pain syndrome (IC/BPS) in this document. IC/BPS predominantly affects women, and has been associated with elevated mast cell counts in the bladder lamina propria and abnormalities of the mucosal lining.^{1,2}

The disease typically fluctuates in severity and rarely resolves completely. Patients suffer considerable morbidity over the course of their lives, especially during the most productive years of work and family life.³ Chronic prostatitis/chronic pelvic pain syndrome (CPPS) is a similar condition that occurs in men and may or may not be associated with leukocytes in expressed prostatic secretion.⁴ A feature common to IC/BPS and CPPS is that symptoms tend to fluctuate and may go into remission. The factors that influence symptom fluctuations, however, are not well understood.

Inflammation has not been shown to be a cause of CPPS and IC/BPS, and no infectious agent has been implicated in either condition. Comorbid conditions are common in IC/BPS patients, and include panic disorder, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and immune conditions such as Sjögren's syndrome. Although little is known of genetic influences, CPPS patients also suffer comorbid diseases that overlap with those of IC/BPS. Thus, given the regional and comorbid similarities, it is uncertain whether CPPS and IC/BPS represent distinct clinical entities. As a result, these conditions are best viewed as regional pain syndromes for which multiple underlying conditions may elicit similar symptoms in men and women.

The most recent U.S. data suggest that 2.7 percent of women have symptoms highly suggestive of IC/BPS, yielding a prevalence of greater than 3 million women.⁵ CPPS in men accounts for approximately 2 million annual cases in the United States.⁶ The average onset for IC/BPS is after age 30 years but varies over a wide age range. The mean patient age at CPPS diagnosis is 43 years. Racial distribution is highly skewed, with 74.8 percent of IC/BPS occurring in Caucasians, 13.3 percent in Hispanics and 11.9 percent in African American patients.³ Supporting a genetic component, there is a strong familial association in IC/BPS as first-degree relatives of IC/BPS patients are 17 times more likely to also have the disease.³

Genomic and epidemiological studies indicate a close connection with panic disorder and implicate several neurotransmitter mechanisms in the etiology.⁷ End-stage bladder disease due to IC/BPS is a measurable adverse outcome but psychological and

social morbidity, and work time losses are highly prevalent as well. Sustained chronic pain and sleep disturbances associated with frequent nighttime voiding may result in secondary effects such as depression. Indeed, some women become so desperate as a result of their severely compromised quality of life from IC/BPS that they elect bladder removal or even commit suicide.¹ The economic burden is approximately \$84 million annually for prostatitis and \$90 million for IC/BPS based on 1997 estimates and after adjusting for inflation.⁸

Research Priorities and Approaches

Understanding the mechanisms and etiology of pelvic pain and inflammation is critical. In contrast to other mucosal sites, inflammation and immunity in the genitourinary tract are poorly understood. Little is known about mucosal immunity in the bladder, despite the high prevalence of bladder infections and the potential association of IC/BPS onset with UTI.⁹ Mechanistic studies on the pathogenesis of prostatitis are also limited. As a result, the lack of understanding the disease mechanisms in the genitourinary tract precludes the development of targeted therapies.

Current treatments for IC/BPS and CPPS address symptoms. Future treatments must be directed at causal mechanisms within appropriately identified patient groups. Understanding the involvement of specific pain processing pathways, and inflammatory and neural crosstalk between other organ systems is critical for defining disease mechanisms and developing targeted therapies.¹⁰ Further studies of gender specific inflammation and pain are clearly needed to elucidate genitourinary disease mechanisms and develop effective therapies. Genome-wide association studies will also inform us of the genetic and molecular disease mechanisms, and enhance efforts to develop novel diagnostic and therapeutic interventions.

Although cystoscopic examination is sometimes useful in the diagnosis and management of IC/BPS, it is invasive and costly, and there is a need for non-invasive methods to diagnose patients and enhance stratification of patient subsets within IC/BPS and CPPS. Developing drugs directed toward novel therapeutic targets identified in mechanistic studies is essential. Also critical are comparative effectiveness and cost-effectiveness studies of generic medications, non-medical therapies and other treatments to determine optimal approaches for delivering the best care to the greatest number of patients in a cost efficient manner. As in other areas of urology research, tissue banks for mechanistic and clinical studies of pelvic pain are currently lacking and should be developed.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Multidisciplinary Approach to the study of Chronic Pelvic Pain (MAPP) Network is an important advance in the field, and will generate essential information over the next several years to guide future basic and clinical research. However, there is still much to be done. Development of patient registries is essential for long-term analyses of pelvic pain disease trends. The aim of these long-term longitudinal studies is to prospectively obtain critical data over time on disease progression, remission and risk factors for development of associated syndromes.

Development of animal models of IC/BPS and CPPS is essential to continued mechanistic studies. For example, feline interstitial cystitis is a spontaneous disorder with promise for investigating molecular, cellular and neural mechanisms in IC/BPS.¹¹⁻¹³ Murine IC/BPS models can be induced with a variety of agents to study specific elements of the human disease, including inflammatory cascades and neuro-immune interactions.^{14,15} Murine models also offer a wealth of convenient immune and genetic tools that facilitate mechanistic and genome-wide studies. Together, these complementary systems enable studies otherwise impossible in IC/BPS patients. They will facilitate mechanistic characterization of potential clinical biomarkers, such as a recently identified peptide inhibitor of cell proliferation derived from the frizzled-8 gene that appears specifically secreted by bladder epithelial cells from IC/BPS patients.¹⁶ Development of additional animal models of inflammation and pain is crucial to understanding disease mechanisms of CPPS.¹⁷

Multidisciplinary Opportunities

The relationship between pelvic pain and other conditions requires additional clinical, epidemiological and mechanistic scrutiny. Strong similarities exist among IC, CPPS and irritable bowel syndrome. Further overlap is shared with other regional or systemic pain conditions, such as fibromyalgia, chronic fatigue and migraine. These commonalities must be exploited in a multidisciplinary manner to accelerate research and treatment of pelvic pain.

Antecedent UTI is potentially associated with IC, suggesting an infectious basis of chronic pelvic pain that bears further research. Finally, tissue engineering studies are also required to develop viable bladder replacement tissue suitable for bladder replacement to restore bladder function in patients with bladder cancer or end-stage IC/BPS.¹⁸

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Chapter 4 - Developmental Anomalies

Background

Embryonic and fetal development of the urinary tract involves proliferation, differentiation and migration of cells that form the kidneys and their collecting system, ureters, bladder, urethra and external genitalia (including the testes). Genetic and epigenetic programming, cell differentiation, hormonal signaling, enzyme activity and tissue remodeling are involved. Intercellular and intracellular signaling processes that guide these changes may go awry, leading to structural anomalies and defects of function at birth.

Developmental anomalies of the urogenital tract include a wide range of conditions, all having a spectrum of severity that ranges from causing early death or renal failure to the social burden of incontinence.^{1,2} These conditions include vesicoureteral reflux (VUR) in which an abnormal attachment of the ureter to the bladder causes retrograde flow of urine into the ureter and kidney; mechanical obstruction of the bladder outlet due to posterior urethral valves (PUV) or bladder neck dysfunction; cloacal anomalies in females when the urinary, genital and gastrointestinal tracts exit the body through a single opening; and anomalies of the external genitalia such as epispadias and hypospadias, cryptorchidism, and ambiguous genitalia.³⁻⁵ Many of these conditions, such as the intersex conditions and other congenital anomalies of the genitalia, may have severe psychosocial impact as well as direct health impact.

An increased risk of infection is the most significant complication of VUR and PUV.^{6,7} However, the long-term side effects of the antibiotics used to treat them are unknown, and there is serious concern about the resulting emergence of resistant bacterial strains. The severity of VUR and its complications vary from cases with renal scarring present at birth (which account for most cases of subsequent renal failure) to the more prevalent mild and moderate cases when kidney damage is not present at birth and reflux is likely to resolve spontaneously. For both VUR and PUV, surgical correction can be undertaken but results are often less than optimal. A major challenge of VUR is to determine in which cases a surgical procedure is recommended instead of medical therapy. Surgery can be performed for PUV in the neonatal period but these children remain at long-term risk for renal failure and urinary incontinence.

Cloacal anomalies are a group of malformations in the female when the urinary, genital and gastrointestinal tracts exit the body as a single opening. These rare conditions require extensive surgical intervention to achieve normal function. These patients usually have permanent issues with urinary and fecal incontinence as well as impaired sexual function.

Cryptorchidism is the most common birth defect of male genitalia. Undescended testes may lead to future infertility and have been associated with an increased risk of testicular cancer, yet bringing the testis into the scrotum surgically does not reverse the higher incidence of testicular cancer.⁸ Hypospadias is the second most

common birth defect, and occurs when the urethra opens on the underside of the penis. The etiology of hypospadias remains largely unknown, although exposure to environmental factors may explain its increased incidence. Surgical repair is usually performed in the first year of life but complications from the repair can be as high as 30 percent, requiring reoperation. Some patients require multiple operations but never obtain full functional ability.⁹ The extrophy-epispadias complex involves the urinary and genital tracts, as well as the musculoskeletal system. These patients may have to deal with a lifetime of urinary incontinence and inadequate genitalia, which can impair sexual function and fertility.¹⁰

Ambiguous genitalia and malformations of the external sex organs can result in sex assignment along with appropriate surgical reconstruction. Sex assignment decisions when optimal gender is based on factors such as potential for sexual function and reproductive capabilities have been highly contested. Affected individuals may object to the gender assigned, resent the effects of genital surgery and feel a sense of stigmatization. Despite the best treatments available today, surgical outcomes are not optimal and repeat operations are often needed. Many patients require a lifetime of hormonal replacement which, due to its unmodulated dosing, is not physiologically ideal.^{11,12}

Abnormal development of the urinary tract occurs in as many as 15 percent of all pregnancies (approximately 675,000 newborns every year).¹³ Vesicoureteral reflux affects up to 10 percent of newborns (approximately 450,000 babies annually). VUR occurs in 17.2 percent of children without prior urinary tract infection, 40 percent to 70 percent with a history of urinary tract infection and up to 37 percent with prenatally detected hydronephrosis. Among children younger than 18 years, the annual reflux-related inpatient hospitalization rate was stable between 1994 and 2000 at 6.4 to 7 per 100,000 children.

This trend was true for females and males, with the female/male ratio remaining relatively constant at 3:1. Cryptorchidism occurs in about 3 percent of full-term and 30 percent of premature male infants being born with at least one undescended testis. However, most testes descend by the first year of life (the majority within three months), making the true incidence of cryptorchidism around 1 percent overall. Hypospadias is present in about one of every 150 male births but its incidence is increasing according to the Centers for Disease Control and Prevention. In 2000 the incidence of in-patient stays for hypospadias was 3.7/100,000 children¹⁴ and in 2000 expenditures on hypospadias alone amounted to \$8 million.

Research Priorities and Approaches

Understanding the molecular mechanisms of normal development is critical if we are to be successful in elucidating the causes of abnormalities of the internal and external genitalia. Characterization of the signaling cascades critical to morphogenesis is needed, and research must center on applying corrections prenatally. For ambiguous genitalia, prospective studies of gender identity, reproductive function and quality of life are needed to guide

clinicians and families in making decisions about gender assignment and surgical reconstruction.

Increasing evidence suggests that epigenetic changes may affect later development. This is critical, because as genetic bases of urological diseases are investigated, we want to make sure that we can control, or facilitate when we can, the normal genetic changes that occur and try to moderate, or control, the epigenetic changes that occur in the environment. Understanding and controlling or moderating epigenetic effects may lead to novel prevention strategies and treatment strategies for long range urological disease.¹⁵ Improved methods for prenatal diagnosis and predicting risk for later complications are needed. The genetic correlates of urological congenital anomalies must be examined. More research is needed to understand how ischemia and increased pressure attributed to obstruction cause long-term decline in neuromuscular control of the bladder.

The establishment of bio-repositories for urological developmental anomaly associated biological materials with an emphasis on appropriate phenotyping of materials and individuals is needed for the advancement of the field. The bio-repositories should allow for the integration of clinical and specimen data. A catalogue of information and materials from the bio-repositories should be made available to the scientific community. A registry of available congenital anomalies would be of extreme importance as the genetics of the diseases are correlated to the cell and molecular biology findings, the tissue effects, associated morbidity and long-term outcome of patients. To properly evaluate treatments, long-term clinical trials assessing outcomes such as bladder and kidney function, and quality of life are needed. Establishment of a patient registry is a vital prerequisite for adequate clinical trials.

Organ culture of developing urinary tract components will permit exposure to growth modulators and analysis of their genomic effects.¹⁶ Genome-wide association studies will allow detection of genetic loci associated with anomalies.¹⁷ Technologies that are ever more selective will permit tissue specific detection of genetic¹⁸ and epigenetic processes, including RNA interference and histone methylation.¹⁹ Cell therapy applications may have profound implications in managing tissue and organ abnormalities. Stem cell homing and small molecule regenerative strategies may be useful for therapy of congenital anomalies. Tissue engineering and regenerative medicine techniques need to be developed as strategies that may be useful for urological developmental anomalies prenatally, postnatally and into adulthood.

Understanding the cellular and molecular basis of normal and abnormal urinary tract development in humans will be advanced by the use of animal models. Discovery of a rat mutation causing unilateral urinary tract anomalies offers the possibility of comparing normal to abnormal development in individuals.²⁰ Knockout mice lacking the *Shh* gene have persistent cloacae and hypospadias and presumably are relevant to the conditions in humans.²¹ Systems such as stem cell tracking and stem cell populations (like induced pluripotent stem cells) should be used to determine how to translate findings in these animal models to humans. It is necessary to investigate stem cells, stem cell progeny, and their differentiation

to determine not only how they affect and promote normal development, but also to define their role in abnormal development and as targets for intervention.

For ureteral obstruction, clinical trials will be required to assess the value of therapeutic approaches such as upper urinary tract diversion, intermittent catheterization and pharmacologic interventions. For bladder outlet obstruction clinical trials are needed to assess current therapeutic approaches and how these effects can lead to chronic diseases. Long-term follow-up studies would provide vital information regarding the natural history of the diseases, disease progression, and the environmental and public health implications. Integration of epigenetic studies with developmental studies will lay a mechanistic framework for understanding immediate and long-term affects of maternal nutrition, and will facilitate studies in tissue regeneration.

Multidisciplinary Potential

Embryonic and fetal development is under genetic and environmental control, and elucidating the contributions of numerous factors will be necessary to understand, manage and possibly prevent congenital anomalies. Cross-disciplinary collaborations among urologists, geneticists, embryologists and obstetricians should prove fruitful in untangling the determinants of abnormal tissue and organ morphogenesis.

Discovery of genetic determinants can make possible genetic counseling to avoid affected pregnancies. Investigators who build stem cell-based replacement organs will contribute, as will behavioral and social scientists, who will develop new strategies to cope with lifelong difficulties that cannot be repaired.

The collaborative efforts of cell and developmental biologists, clinicians, computational scientists and biomaterial experts will enable investigators to examine molecular and cellular mechanisms underlying the formation of individual genitourinary tract structures, their patterning, the fates of different cells in the genitourinary tract, and the way in which epithelial and mesenchymal cells interact in normal and disease states.

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Chapter 5 – Male Reproduction and Infertility

Background

Compromised male reproduction may be the consequence of external or internal genital phenotypic defects, endocrine defects, blockage or aplasia of the sperm transport system, varicocele, testicular failure, erection and ejaculatory failure, poorly understood immunological factors, deficient sperm production, abnormal sperm function (motility, morphology, fertilization), surgery and exposure to toxic agents (including chemotherapy, radiotherapy and occupational chemicals).

Exposure to environmental or occupational chemicals may be detrimental to male reproduction.¹ It is hypothesized that household products and commonly uncounted substances such as pesticides, herbicides, detergents and plastics may harbor compounds that mimic natural hormones that affect men's health.^{2,3} The causes of male infertility, while not clearly understood, are numerous and likely multifactorial.

It is noteworthy that many diagnoses of male factor infertility are descriptive and provide no insight into the molecular or biological etiology. Indeed, the cause of one quarter or more of male infertility is unknown. Although many believe, at present, that most male infertility has an underlying genetic basis, the cause of only a small percentage of genetic defects of male infertility is actually known.⁴ These include, but are not limited to, some of the endocrine causes of male infertility, the association of congenital bilateral absence of the vas deferens with mutations in the cystic fibrosis transmembrane regulator gene and the association of numerical or structural chromosomal defects, such as Y chromosome microdeletions, with sperm production deficiency.⁵ Investigators are only now beginning to dissect the defective molecular deficiencies in spermatogenesis and sperm function that result in human male infertility.

About one in five couples seek treatment for infertility and in about 40 percent of cases a male factor is the sole identifiable cause. For another 20 percent of couples, male and female factors exist. In a study by the Centers for Disease Control and Prevention analysis of data from the 2002 National Survey of Family Growth, revealed that 7.5 percent of all sexually experienced men reported a visit for help with having a child at some time during their lifetime. This equates to 3.3 to 4.7 million men. Of men who sought help 18.1 percent were diagnosed with male related infertility, including anomalies of sperm or semen (13.7 percent), or varicocele (5.9 percent).⁶

Infertility disrupts the life plan of individuals afflicted and makes the couple's vision of becoming parents unattainable, which results in significant emotional distress. The advanced infertility treatment needed to circumvent these cases is extremely expensive, thereby adding to the total health care expenditure. Since insurance coverage is rarely available, this may financially stretch some couples to their fiscal limit or close the door on many who simply cannot afford it.

A technique called intracytoplasmic sperm injection (ICSI), the micro-injection of a single sperm into an egg to achieve fertilization and embryo development, is being used more frequently as an alternative to correcting sperm deficiencies. In 2007, 142,415 cycles were performed at an average cost of \$12,400 per cycle and a total expenditure of more than \$1.76 billion.^{7,8} ICSI was introduced as a treatment before it was subjected to rigorous analysis and risk assessment, and long-term outcomes are still unforeseeable.⁹⁻¹¹ As our ability to study individual genes and perform genome-wide analyses improves, scientists suspect that achieving normal male fertility will require the proper functioning of more than 50 percent of all genes in the cell. New molecular techniques have identified specific but relatively rare gene defects in infertile men. This is an emerging field with the promise of defining many new advances.

Conversely, contraceptive challenges exist for couples throughout the world. There is a need for the development of a male contraceptive that is safe, reversible and effective with few if any side effects.¹² Although vasectomy remains a commonly used approach to male contraception, vasectomy reversal is costly and not always successful, again leading couples toward costly advanced assisted reproductive technologies. In addition to endocrine modulation of the hypothalamic-pituitary-gonadal axis, new drugs that disrupt spermatogenesis are under development.

Research Priorities and Approaches

Although methods to diagnose and treat some forms of infertility have been developed, the causes of reproductive failure in many couples cannot be identified prior to therapy. This is due to our limited understanding of several processes including mechanisms controlling sperm production by the testis, maturation and transit of sperm through the male and female genital tract, and events required for fertilization and early embryonic development. Defects in cellular processes involved in spermatogenesis may cause male infertility. These may include DNA replication and repair defects; intracellular and extracellular signaling defects in nuclear receptor pathways; and defects in mitosis, meiosis and spermiogenesis. Growth factor and cytokine signaling are key aspects of normal testis functioning and may be compromised by defective signal transduction.

Sperm function, beginning with the acquisition of motility in the epididymis, capacitation and binding to the zona pellucida followed by egg penetration and fertilization, may be compromised. There is a significant need for epidemiological/epigenetic studies (ideally coupled with molecular analyses) to define the safety and efficacy of ICSI for couples with severe male factor infertility.

For patients who would otherwise be rendered sterile after chemotherapy or other cancer treatment (e.g., children who are too young to bank sperm prior to treatment), isolation and storage of testicular stem cells offer the hope that these cells can be transplanted after the patient is cured of the cancer to rejuvenate spermatogenesis and restore fertility. Of note, spermatogonial stem cells seem to exhibit plasticity and pluripotency, suggesting wide reaching applications for these cells and offering the promise

of regeneration of tissues derived from all three embryonic cell lineages.

Studies in mouse models demonstrate the promise of this technology. The finding of rare foci of spermatogenesis upon testis biopsy, together with mixed pathologies throughout the testis, offers the possibility of comparing non-functioning and functioning cell populations. Techniques including proteomics, high resolution imaging with fluorescent markers and direct fluorescent antibody detection of surface molecules can be brought to bear in this environment. Germ line therapy to reverse male infertility also remains a future goal.

For more than 50 years, researchers have sought to achieve complete spermatogenesis in vitro. This field of research remains a topic of considerable interest and translational potential. The use of spermatogonial stem cells, which can be both pluripotential for tissue regeneration and unipotential for fertility regeneration, may be helpful in this effort.

Multidisciplinary Opportunities

Birth defects involving the genitourinary system that are associated with infertility are common, and research on the underlying mechanisms of developmental anomalies will provide information in this area. Shared common processes or elements exist among infertility and a variety of fields including developmental biology, inflammation, infection, endocrinology, sexual medicine and carcinogenesis. There are also likely to be common pathways among these areas that use many of the nuclear, protein and growth factor receptors that link development and male reproductive function.

Normal weight, metabolism and body homeostasis are also required for normal reproductive function. Moreover, genetic defects that cause reproductive compromise may be associated with other unrecognized systemic diseases that result in illness in addition to infertility, such as testis cancer associated with impaired spermatogenesis. Longitudinal epidemiological studies of infertile male patients are essential to uncover these associations.

Exploring and elucidating these issues will require extensive collaborative efforts among individuals from many disciplines, including clinical and laboratory experts in male reproductive medicine and surgery, endocrinologists, mathematical and computational experts, psychologists and neuroscientists, regenerative medicine experts, and geneticists and molecular biologists.

For the field to advance there is a need to understand factors and processes that lead to deficiencies in a variety of areas. These include normal development; genital tract function; sperm number, morphology and function that precipitate reproductive failure; gene therapy; methods to preserve male fertility; the use of in vitro spermatogenesis to restore fertility; and how knowledge of

spermatogonial stem cell biology could be used in regenerative medicine.

Contraception in the male remains a critical need for all societies. Finally, the monitoring of the offspring conceived using assisted reproductive technologies with observational and genetic/epigenetic follow-up should be a high priority undertaking.

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Chapter 6 - Nephrolithiasis

Background

Kidney stones are solid concretions of minerals and other substances that form in the kidney. Such stones may travel from the kidney to the ureter, a process that frequently results in severe pain. They may also grow to a large size and obstruct the kidney, which may cause permanent damage and renal insufficiency.¹ In addition, stone formation may result in end stage renal disease, particularly in patients with primary hyperoxaluria who are at highest risk.² A small number of individuals, fewer than 1 percent, may die of complications (such as sepsis) associated with kidney stones. Genetic factors play a role in kidney stone formation in the majority of patients.

A small number of individuals develop stones due to monogenic disorders such as cystinuria, the primary hyperoxalurias, chloride channel disorders, hypoxanthine-guanine phosphoribosyl transferase deficiency and adenine phosphoribosyl transferase deficiency. The responsible genes for these entities have been well characterized. However, the majority of stone formers have idiopathic calcium oxalate nephrolithiasis. This is a polygenic disorder and the responsible genes have not yet been identified.³

Kidney stone formation should be considered a systemic disease due to its association with many other disease processes, including diabetes mellitus, hypertension, obesity, certain gastrointestinal disorders, renal tubular acidosis, gout, primary hyperparathyroidism and bone disease. There are also strong associations with nutrition.⁴ While effective non-invasive treatments for eradicating stones, such as shock wave lithotripsy (SWL), have been developed, there are potential downstream complications of this procedure, such as diabetes mellitus and hypertension.⁵

The prevalence of kidney stones in the United States is increasing and is estimated to be 5 percent greater than the last decade.⁶ Kidney stones most commonly develop in white males during the third to sixth decades of life, although infants and geriatric patients may also form stones. The male/female ratio for the development of kidney stones has changed from 1.7:1 to 1.3:1, perhaps due to environmental stresses.⁷ Nephrolithiasis exerts significant economic stress on the United States, as the estimated cost of providing care for individuals of working age with kidney stones in this country was \$5.3 billion dollars (direct and indirect costs) in 2000.⁸

Research Priorities and Approaches

There are advances that need to be made in stone basic science research, including integration of physical chemistry (crystal generation and retention), anatomical changes (Randall's plaque and other histological changes) and physiological responses.⁹ Factors that regulate urinary excretion of calcium, oxalate and citrate, major metabolic risk factors for stone formation, as well as the properties of inhibitors of crystallization and their participation in these processes need to be further defined, including at a molecular level.¹⁰

Identifying susceptibility genes is paramount, as this should facilitate a better understanding of the aforementioned events and the development of more targeted preventive medical therapy. The role that certain colonic bacteria play such as *Oxalobacter formigenes* in calcium oxalate kidney stone prevention needs to be determined.¹¹ Research on cystinuria should be a priority, as this is the most common of the monogenic stone forming disorders. These patients tend to form stones earlier in life, are prone to recurrence and may have renal damage.¹²

Struvite stones, which form in some individuals whose urinary tract is infected with urease-producing organisms, can reduce renal function and lead to death. Yet not all such infections lead to struvite stone formation, and investigation of the interactions of the urothelium, infecting organisms and collecting system dynamics that differentiate these outcomes may lead to strategies to prevent this condition.

A better understanding of the physiology and dynamics of the collecting system could lead to pharmacologic prevention or relief of ureteral obstruction due to spasm or edema, which would promote spontaneous passage of stones as well as improve the passage of fragments after lithotripsy or ureteroscopic fragmentation.

Epidemiological research is required to better define the scope and extent of this problem (incidence, prevalence, recurrence), populations at risk, associated comorbidities and economic impact. This will, in turn, facilitate the design of clinical trials and comparative effectiveness studies to determine the optimal methods for diagnosis, stone removal and prevention, as well as compare outcomes of SWL and ureteroscopy. An SWL registry should be supported to help determine the subsequent risk of developing systemic diseases, such as diabetes mellitus and hypertension, and associated risk factors.

There must be increased attention to pediatric stone disease and the long-term sequelae it produces. It is important to develop optimal metabolic evaluation and medical treatment regimens for children, as well as guidelines on how best to treat children with stones, from a surgical as well as a medical and metabolic standpoint. It is time to evaluate drug regimens similar to those applied to the adult population for potential use in the pediatric population.

Utilization of new technologies will advance stone research. Proteomics will help identify proteins associated with stone formation in stones, urine and tissues. Genome-wide association studies will permit the identification of susceptibility genes and can also be linked to proteomics.

These novel technologies should permit a better understanding of the association of kidney stone formation with a number of associated diseases. Genetic data will permit the development of animal models to better approximate the disease process in humans and facilitate studies of pathophysiology, as well as the development of preventive and therapeutic strategies.

Multidisciplinary Opportunities

Collaboration with members of the UTI research community will accelerate identification of common mechanisms that will permit advances in the management of patients with struvite stones. Such collaborations may provide more insight into the fecal microbiome and its influence on stone formation or prevention.

Patients with the metabolic syndrome are at risk for the development of kidney stones as well as a number of other urological disorders including erectile dysfunction, benign prostatic hyperplasia and lower urinary tract symptoms, incontinence, infertility and prostate cancer.¹³ Common mechanisms may be involved in these processes providing an avenue for synergistic research.

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Chapter 7 - Prostate Cancer

Background

Adenocarcinoma, the most common form of prostate cancer, is an uncontrolled proliferation of glandular type cells. Prostate cancer can grow and invade surrounding structures, obstruct the bladder outlet and metastasize widely often to bone where it causes painful lesions and pathological fractures. Obstruction can cause urinary retention which, if not relieved, can result in kidney damage. Although rare in men younger than 40 years, prostate cancer incidence increases with each subsequent decade and is present in virtually every man who reaches the ninth decade.

The prostate is under the control of androgens, and prostate cancer is generally androgen sensitive in its early stages. Thus, one of the effective ways to control metastatic prostate cancer is with androgen deprivation, either by surgical castration, or by pharmacologically blocking androgen release or its binding to cancer cells. Progression of prostate cancer following androgen deprivation therapy is, however, typical and therapeutic options thereafter are limited and largely ineffective in the long term.¹

Prostate cancer is the second leading cause of cancer death and third of all causes of death in American men. In 2009 more than 190,000 new cases occurred, more than 27,000 men died of prostate cancer, and another roughly 2 million lived with prostate cancer and its consequences. The economic burden of prostate cancer is considerable, with figures published in 2007 estimating overall expenditure to be approximately \$1.3 billion.²

There is a large and yet unexplained disparity in the racial distribution of prostate cancer. The incidence in black men is about 1.6 times that for white men, even when access to healthcare is equivalent.^{3,4} The mortality rate for black men is about 2.4 times that for white men.²

Research Priorities and Approaches

Many prostate cancers are indolent, (i.e., they grow slowly and metastasize infrequently, and as such may not require aggressive treatment. However, a significant number of prostate cancer cases behave aggressively, which can lead to clinical symptoms, metastatic disease and death. Presently there is no effective treatment for metastatic prostate cancer beyond palliation of its effects. Understanding the underlying biology and pathophysiology of aggressive prostate cancer is essential to the development of directed pharmaceutical treatments.

Currently it is not possible to differentiate between the indolent and aggressive phenotypes of prostate cancer at an early stage, which in turn leads to overtreatment, generating adverse effects and unnecessary costs. To decrease the burden of treatment, new methods must be devised to stratify patients according to likelihood of disease progression but this will require the discovery and validation of reliable biomarkers of aggressiveness.

To improve treatment of men with prostate cancer, it is necessary to identify new targets, pathways and therapeutic modalities that are more discriminating than those used today. Thus, there is an urgent need to understand the biological characteristics that define aggressive disease and develop biomarkers that will allow identification of truly indolent disease.⁵ Understanding the genetic and epigenetic features, as well as the intercellular and intracellular signaling pathways that determine susceptibility, disease progression and treatment outcomes for clinically significant prostate cancer requires investigation of the genomes, transcriptomes and proteomes of the neoplastic cells, and the microenvironment that supports them.⁶

Central to progress in these areas is continued development of relevant cellular and animal models of prostate cancer that mimic the human disease, creating opportunities to explore cellular characteristics in a manner impossible in humans which can be translated to the human condition.⁷ These models can also be used to evaluate the potential effectiveness of novel treatment strategies without the need, initially, for expensive clinical trials.

For instance, it has been shown that stem-like progenitor cells in mouse prostate can generate carcinoma after deletion of the tumor suppressor gene Pten.^{8,9} Such basic discoveries must be pursued and may lead to clinical interventions. Identification of proteins and other molecular species capable of serving as indicators of biological behavior, or as targets for “smart” directed strategies, will facilitate movement toward improvement of methods of detection, prognosis and inhibiting progression of prostate cancer.

The two million men who currently live with prostate cancer may experience complications of the disease and its treatments. These are numerous and include incontinence, impotence and the sequelae of androgen ablation such as osteoporosis, gynecomastia and loss of muscle mass. Better strategies to manage these problems are required and need to be applied uniformly to improve quality of life.

We know little about the impact of treatment, nutrition, metabolism and exercise on the well-being of prostate cancer patients and their families. Prevention of prostate cancer is also a high priority. Research aimed at exploring lifestyle factors that may prevent the emergence of progressive disease is essential. This includes dietary modifications that can reduce the risk of prostate cancer.¹⁰

Our present inability to significantly affect the long-term outcome for patients demands that comparative effectiveness studies be urgently performed. Large randomized trials comparing surgery vs. radiation therapy vs. chemotherapy and immunotherapy will provide the data required to make rational choices among treatments.

Tissue collections and registries with openly available databases can facilitate sharing and dissemination of the information required to design effective trials. Application of advanced technologies, including intravital and magnetic resonance imaging, high throughput screens, large-scale automated DNA sequencing, computation and mass spectrometry-based proteomics, may provide new information

about the basic biology of prostate cancer as well as new and unanticipated avenues for therapeutic intervention.¹¹

Multidisciplinary Opportunities

Prostate cancer shares molecular and cellular features with breast cancer and certain other malignancies. These shared characteristics should be exploited when possible and findings from other fields should be brought to bear on prostate cancer. Collaboration with social and behavioral scientists and specialists in rehabilitation can address issues of lifestyle, both in prevention and survivor quality of life. Training of urologists in methods of basic and translational research is also necessary to facilitate the application of research findings to the clinical setting.

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Chapter 8 - Renal Cell Carcinoma

Background

Cancers of the kidney and renal pelvis represent a constellation of types but the most common are renal cell carcinoma (RCC) in the kidney and transitional cell carcinoma in the renal pelvis and ureter. Identification in 1993 of the von Hippel-Lindau (VHL) gene on chromosome 3p25-26 began a trend to greater understanding of the molecular mechanisms of renal tumors.¹

An inherited mutation of one gene copy defines the disease, and somatic mutation or epigenetic silencing of the remaining allele leads to the disease phenotype. The VHL mutation results in loss of the E3 ubiquitin ligase complex degradation of hypoxia-inducible factor- α (HIF- α).² This permits buildup of HIF- α with increased downstream signaling that promotes cell survival and angiogenesis. It is now appreciated that in addition to inherited cases, 60 percent of sporadic renal cell cancers demonstrate mutations or hypermethylation of one or both copies of the VHL gene.³

Invasive tumors demonstrating loss of VHL consistently demonstrate additional genetic changes, which appear also to be essential for tumor progression.⁴ These altered events now provide targets for new therapies that have improved the progression-free and overall survival of patients with this disease.⁵ Although systemic therapies exist, metastatic disease is still virtually incurable.

In 2008, 54,390 cases were estimated to occur in the United States with a male predominance, and RCC has risen to become the seventh most common cancer in men and the eighth most common cancer in women in the United States.⁶ This year 58,000 new cases of RCC are expected in the United States, reflecting a continued increase in incidence.⁷ Of these cases 50 percent will progress to advanced renal cancer.

A total of 13,010 persons is estimated to have died of this disease in 2009. While there has been an increase in the detection of localized renal cancers due to imaging performed for other indications, metastatic disease at presentation has also slightly increased. Mortality from renal cancers has not decreased significantly and may even be rising, suggesting that other factors may be involved.^{8,9}

Known risk factors, in addition to genetic mutations, are smoking, obesity and diet. The greatest risk factor is end stage renal disease with a prevalence of 4.2 to 5.8 percent, nearly 100 times that of the general population.^{10,11}

The associated annual economic burden of RCC was approximately \$4.8 billion (\$43,749 per patient) in 2005. Health care costs and lost productivity accounted for 84.9 percent (\$4.1 billion) and 15.1 percent (\$726 million) of the total, respectively. Focusing only on newly diagnosed RCC cases (approximately 25,000 per year), the annual burden was estimated at \$1.5 billion, with a per patient cost of \$62,340.¹²

Research Priorities and Approaches

The etiology of kidney cancer is imperfectly understood. The cellular and molecular basis must be elucidated so that effective treatments may be designed. Infection and inflammation appear to be significant in prostate cancer and may be in kidney cancer as well. Environmental factors clearly play a role. Some are similar to bladder cancer associated factors (tobacco, occupational exposure), while others are more specific to carcinogenesis of the upper urinary tract, including phenacetin, Balkan endemic nephropathy, Chinese herb nephropathy, Blackfoot disease (chronic arsenic poisoning) and possibly aristolochic acid.¹³

Early detection is critical, and the ease of obtaining urine dictates the development of cell or protein based screening tools for which genomic, proteomic or metabolomic markers must be sought, and detection methods developed and validated.

There is a need for kidney cancer clinical trials, particularly those with an emphasis on tissue acquisition and molecular correlative science. A clinical trial to extrapolate cytoreductive nephrectomy data from immunotherapy to multi-kinase therapy is needed. Additionally, trials of neoadjuvant agents are also needed. Programs that promote research in kidney disorders, such as the SPORE Program at NCI and the Cancer Genome Atlas program, and similar efforts should be searching for genomic alterations, both genetic and epigenetic.

Focusing on tissue acquisition is critical to making progress in the field. In neoadjuvant trials, tissue should be obtained prior to therapy and compared with tissue from subsequent nephrectomy for target validation as well as for identification of markers that predict response to therapy. Tissue bio-repositories linked to microarray analyses or clinical trials should be established.

Studies into the mechanisms of renal carcinogenesis have begun to reveal some stages in the development of this cancer. Overexpression of vascular endothelial growth factor receptor tyrosine kinase is one such stage, and inhibitors are being investigated in the adjuvant setting.¹⁴ High density gene expression microarrays have been used in a functional epigenetic study of 11 human RCC cell lines. Eight of 28 selected genes showed frequent (>30 percent of RCC tested) tumor specific promoter region methylation. Hypermethylation was associated with transcriptional silencing of these putative tumor suppressor genes, suggesting that demethylation may be a promising therapy.¹⁵

Development and use of animal models are high priorities, and will expand our ability to conduct detailed mechanistic studies. For example, in one mouse model, gene expression profiling on a set of urothelial carcinomas of the renal pelvis has identified a phosphatidylinositol 3-kinase (PI3K/AKT) activation expression signature in 76.9 percent of the samples. Mice containing biallelic inactivation of Pten in the urogenital epithelia developed typical renal pelvic urothelial carcinomas at a high rate. This finding indicates

an important role for the PI3K/AKT pathway in the development of urothelial carcinoma and suggests that inhibitors of this pathway (e.g., an mTOR inhibitor) may serve as effective therapeutic agents.¹⁶ Continued development of transgenic models, including those suitable for investigating risk factors like smoking and dietary influences, should be vigorously pursued.

Multidisciplinary Opportunities

Commonalities among renal, prostate and bladder cancer indicate a need to coordinate efforts in all three areas. Because urinary tract infection and inflammation seem to be capable of inciting cancerous changes, connections should be made to these areas as well. Since the public is not aware that renal cancer is closely linked to environmental factors, collaboration with social and behavioral scientists can result in development of methods to build public understanding of renal cancer symptoms and disseminate to the public the message that smoking is a strong risk factor for kidney cancer, as are obesity and physical inactivity.¹⁷

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Chapter 9 - Sexual Dysfunction

Background

Sexual dysfunction refers to difficulties engaging in sexual intercourse, and comprises a set of sexual disorders affecting men and women, which have general health and disease implications. These include ED, ejaculation disorders and Peyronie's disease in men; failure of arousal and painful intercourse in women; and anorgasmia in both sexes. Intact sexual health infers overall physical and mental wellness.

Sexual dysfunction, particularly ED in men, is believed to serve as a barometer of a number of disease states including diabetes, obesity, cardiovascular disease, hypertension, dyslipidemia and depression.

ED is defined as "the inability to attain and maintain erections of sufficient quality to permit satisfactory sexual intercourse," and emerging evidence suggests that this sexual dysfunction serves as a harbinger for subsequent cardiovascular morbidity and mortality.¹ Such data for other sexual dysfunction conditions may also be illuminating. ED is recognized to adversely affect quality of life, decrease occupational productivity and increase health care resource utilization.^{2,3}

The prevalence of ED is estimated to be 10 to 20 percent of U.S. adult males, with most studies closer to 20%.⁴ This amounted to approximately 152 million men in 1995, a number projected to increase to 322 million in 2025.⁵ Current data indicate that the prevalence of ED increases with increasing age and the presence of comorbid medical conditions that include diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia and depression.⁶⁻¹⁰ Other risk factors for the development of ED include lower level of education, cigarette smoking, cigar smoking, passive exposure to cigarette smoke and overweight status.¹¹⁻¹³

Total expenditures in the United States in 2000 for outpatient clinical management of ED (exclusive of pharmaceutical costs) approximated \$330 million, ranking as the ninth most costly among most frequent urological diagnoses.¹⁴ National sales of drugs to treat ED were reported to be \$2.7 billion in 2005.¹⁵

Female sexual dysfunction often results from problems of the urogenital tract, particularly those related to defects in the structures of the pelvic floor: Conditions such as uterine prolapse, cystocele and rectocele, which involve protrusion of surrounding organs into the vagina, as well as urinary incontinence, have a profound negative effect on sexuality and are managed by urologists who specialize in urogynecology.¹⁶

Other causes of female sexual dysfunction, such as failure of vaginal lubrication and the impact of estrogens, as well as factors such as cardiovascular disease, smoking and obesity that also affect males, fall within the scope of this discipline.^{17,18}

Research Priorities and Approaches

Specific priority areas that must be addressed to make progress include smooth muscle biology, neurobiology and endothelial mechanisms involved in both male and female dysfunction. Details of the neural control of vascular smooth muscle, including the nature of neurotransmitters and target membrane receptors, need to be elucidated, as well as how these are related to endothelial mechanisms such as nitric oxide pathways.

It is presumed that common pathophysiological mechanisms for dysfunction of the genital organs may also apply elsewhere in the genitourinary tract. In addition, advances in reconstructive capabilities, such as tissue and organ engineering must be harnessed to address anatomical defects. Better tools are also required to detect and characterize the aberrant mechanisms that underlie sexual dysfunctions. Genetic and molecular techniques should be developed for diagnostic use.

Development of novel therapeutics is a high priority. In sexual medicine treatments still need to be developed that fully address the biological basis of dysfunctions and achieve such goals of ideal therapy as long-term functional and structural preservation of sexual organs. Discovery of new therapies that range from novel pharmacotherapies and technologies to futuristic therapies, such as gene therapy, stem cell therapies and tissue engineering, must be pursued.

The study of the impact of treatments administered by clinicians that result in sexual dysfunction represents another research direction of high priority in sexual medicine. Emphasis should be given to understanding and addressing iatrogenic sexual dysfunction. This focus underscores that sexual dysfunctions result from numerous medical and surgical treatments that are performed in urology as well as in other clinical disciplines. This area includes consideration of the withdrawal and replacement of sex steroids such as androgens that may affect not only sexual function, but also prostate health and other systemic health concerns

Epidemiological studies that will provide insights into the natural history and disease progression of sexual dysfunctions in men and women in relation to comorbidities and aging need to be performed. This applies to ED, female sexual dysfunction, hypogonadism and Peyronie's disease. More research is critically needed to define incidence data for sexual dysfunctions and establish their disease state risk factors.

Human genital tissues (benign and diseased) are not easily retrieved for research purposes. Thus, development of an infrastructure for tissue repositories for urological tissues, and an associated database with information about the source and characteristics, including genotypes and epigenotypes, of the samples is particularly relevant in sexual medicine research.

Such a resource would facilitate programs of a national urologic research agenda which are multidisciplinary and include both basic scientific and clinical research aspects of sexual medicine.

Multidisciplinary Opportunities

Sexual dysfunction is a complex mix of physiological, anatomical and psychological/social factors that are sometimes difficult to disentangle.

Collaboration with researchers in areas such as voiding dysfunction, pelvic pain syndrome, developmental biology, vascular function, psychology and cancer rehabilitation will produce discoveries that can lead to a more complete understanding of sexual dysfunction and facilitate progress in its treatment.

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Chapter 10 - Urinary Incontinence/Overactive Bladder/Neurogenic Bladder

Background

Both the autonomic and voluntary nervous systems normally control storage of urine in the bladder and its subsequent excretion by voiding. Nerves originating locally in the spinal cord control the muscles that keep the exit sphincters closed, sense the buildup of urine and then deactivate the sphincters while stimulating the detrusor muscle in the bladder wall to expel the contents.

This local neural circuit is sufficient to regulate cyclic filling and emptying of the bladder. After infancy, the local circuit is itself subject to voluntary control by higher levels of the central nervous system which modulate the rhythm in keeping with other activities and social norms.

Urinary incontinence, the involuntary loss of urine, results from failure of these mechanisms. Overactive bladder, also called urge incontinence, results from inappropriate contraction of the detrusor muscle that forces urine past the sphincters. Insufficient closure of the sphincters, a condition called stress incontinence, permits urine flow upon modest increase of the pressure on the exterior of the bladder, such as occurs with coughing or sneezing.

In overflow incontinence obstruction of the bladder outflow leads to greatly excessive filling of the bladder, which results in such high pressure that urine leaks past the obstruction. Finally, any condition that interrupts the control of the local neural circuit from the higher central nervous system (e.g., multiple sclerosis, Parkinson's disease and spinal cord injury) restores the infantile state of automatic voiding upon filling with no voluntary control, a disorder known as neurogenic bladder.

From 1999 to 2000 urinary incontinence affected an estimated 38 percent of women, of whom one-third had urinary incontinence after vaginal delivery, and an estimated 17 percent of men 60 years old or older.¹⁻⁴ In those same years the estimated annual number of hospital admissions among adults 18 years old or older with urinary incontinence was 47,802 (1,332 men, 46,470 women), and the estimated number of doctor visits and outpatient hospital visits by patients 20 years old or older with urinary incontinence reached 207,595 for men and 1.16 million for women.

Direct care in 2000 cost \$463.1 million (\$10.3 million for men, \$452.8 million for women) in hospital stays and visits to office-based physicians, hospital outpatient clinics and emergency rooms by adults.⁵ In addition, more than \$1 billion per year is spent for management products and devices, including adult absorbent undergarments.⁶

The social impact of urinary incontinence can be severe, and includes isolation/depression, early institutionalization (urinary incontinence is the leading cause of nursing home admission), financial burden

for purchasing management products and devices, fear of urinary incontinence and odor in public; and withdrawal from normal social interactions due to being "tethered" to the toilet.

Other quality of life domains impacted by urinary incontinence include sexual function, travel and participation in physical activities (walking, sports, etc.). Neurogenic bladder predisposes to frequent UTIs that can lead to deterioration of kidney function.⁴

Diabetes, obesity, neurodegenerative/neurological disorders and pelvic organ prolapse are highly associated with urinary incontinence. The best surgical management for leakage due to coughing, straining or exercise is effective less than half the time. For leakage associated with urgency, only one class of drugs, anticholinergics, is approved for use and the efficacy of these drugs is only 13 percent to 25 percent greater than placebo.⁷ Moreover, nearly two-thirds of patients discontinue use of these drugs because of intolerable side effects.

Research Priorities and Approaches

Normal physiological mechanisms of bladder storage and emptying are poorly characterized at the cellular and molecular levels. These include pharmacology, neurophysiology, smooth muscle physiology, striated muscle physiology and urothelial biology. Identifying and characterizing pathophysiological derangements of these mechanisms that produce specific phenotypes may lead to biomarker discovery and a more objective mechanistic basis for diagnosis and descriptions.

Medications that more specifically target neuromuscular pathways of the bladder mechanism with fewer systemic side effects are urgently needed. Whether genetic and epigenetic phenomena are involved in urinary incontinence/OAB is completely unexplored territory, and a search for pathophysiological parameters or measurable biomarkers must be pursued. There is a need for human biospecimen repositories, requiring both normal and urinary incontinence diseased samples, to understand the pathophysiology of urinary incontinence. Development of a national consortium for banking normal bladders should be pursued. Specimens could be obtained through organ donation programs.

Several levels of interaction merit investigation. At the cellular and tissue level, stromal-epithelial and epithelial-immunologic interactions involving various mediators and cytokines should be explored. At the organ level, relationships between the bladder and other pelvic viscera should be examined.

Development of animal models of urinary incontinence is critical, as the needed basic physiological data cannot be obtained from normal healthy humans. Dogs and cats spontaneously develop urinary incontinence, and may be suitable for physiological investigation and genetic profiling.⁸ Species amenable to genetic manipulation must also be assessed for suitability as vehicles for urinary incontinence research.

Multidisciplinary Opportunities

Neurological, neuromuscular; inflammatory and neoplastic conditions are among the causes of urinary incontinence, and investigators in all of these fields should be involved in understanding its pathogenesis. Neurophysiological investigation of both central and peripheral nervous mechanisms will be central to our understanding and the deployment of synaptically acting pharmaceuticals.

Other urological conditions, especially benign prostatic hyperplasia and chronic pelvic pain syndromes, undoubtedly impinge on bladder control, and collaborations with practitioners in these areas must be encouraged and supported. Involvement of biomedical engineers should be explored with an eye toward development of implantable devices to control sphincter and detrusor muscles.

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Chapter 11 - Urinary Tract Infections

Background

Urinary tract infections are a heterogeneous group of bacterial and fungal infections of the upper or lower urinary tract that are typically classified by anatomic location.

Cystitis is typically classified as uncomplicated or complicated. Uncomplicated cystitis occurs in an otherwise apparently normal urinary tract and is primarily (approximately 90 percent) caused by uropathogenic *E. coli* (UPEC). Complicated cystitis refers to infections in the presence of anatomical abnormalities, foreign bodies such as stones or catheters, or conditions that impair host defenses and often involve other pathogens in addition to UPEC. Recurrent UTIs in healthy women who have recovered from an acute infection is a major problem.

Between 25 percent and 44 percent of women experience a recurrent infection annually, and 3 percent experience three or more episodes within six months of their initial infection.¹ Recurrence often develops within 30 to 90 days of an initial UTI, despite standard three 10-day antibiotic treatment and clearance of bacteriuria.¹ In fact, over 900,000 women and men in the United States experience three or more UTI episodes per year. Thus, antibiotics do not stop recurrence in this population. Recurrent UTI is even more common in men and women with abnormal urinary tracts, such as those with catheter associated UTI or neurogenic bladder.

In pediatric patients younger than three years UTI is the leading cause of fever without localizing signs and the leading etiology of fever presentation in the emergency room setting. Additional serious sequelae in children include renal scarring, premature hypertension and early end stage renal failure.² In children younger than three months UTI poses a serious risk as the precipitator of sepsis and meningitis.

Although *E. coli* remains the major pathogen causing UTI in children, preterm infants and adolescents also experience UTI due to unique pathogens, including coagulase negative Staphylococci. The interaction between the developing urinary tract and urinary tract pathogens also remains poorly understood, as does the microbial ecology of the developing genitourinary system and its impact on reservoirs of uropathogens.

Acute or chronic bacterial prostatitis causes significant pain in the pelvic/anogenital region.³ Acute prostatitis can be due to a variety of bacterial species, including *E. coli*, *Klebsiella* and *Pseudomonas*, and is usually treated with a two to three-week course of antimicrobials.

Chronic bacterial prostatitis represents approximately 7 percent of prostatitis cases and is usually associated with *E. coli* (80 percent of cases) and recurrent UTI. Current treatment is a four to eight-

week course of antibiotics, yet, similar to cystitis, relapse occurs in approximately a third of patients within three months.³

The treatment of UTIs, as with other microbial infections, is further complicated by increasing antimicrobial resistance both in the institutional setting and the community.⁴ In women with uncomplicated cystitis and pyelonephritis the rates of resistance to current regimens are rapidly rising.⁵⁻⁷

Men and women with frequent UTI recurrences often are infected with uropathogens that are resistant to available oral agents, necessitating use of parenteral agents for many non-severely ill patients.^{8,9} With the prevalence of resistance to trimethoprim-sulfamethoxazole empirical therapy has increasingly been switched to fluoroquinolones, leading in turn to reported increases in resistance to this class and perhaps an associated rise in multi-drug resistance.^{5,9-11}

It is estimated that 7 to 11 million cases of UTI occur in the United States each year, primarily in women. The annual cost of caring for women with UTIs is estimated to approach \$2.5 billion.^{12,13} There are around 2 million cases of prostatitis with costs estimated at \$84 million. In addition, UTI is one of the most common infections of childhood with a pooled prevalence of febrile illness at 7 percent for children younger than 19 years.¹⁴

Pediatric UTIs account for about 1.1 million annual physician visits with an estimated annual cost of hospitalization of \$180 million.¹⁵ Finally, catheter use is associated with UTI. In the United States 15 percent to 20 percent of short-term hospitalized patients are given an indwelling urinary catheter, which results in more than 1 million cases of catheter associated UTIs reported in hospitals and nursing homes annually.¹⁶ This accounts for over 40 percent of all nosocomial infections, and approximately \$424 to \$451 million in overall medical costs in the United States each year.¹⁷ Bacterial spread from UTI can progress to major morbidities, such as perinephric abscesses, sepsis, meningitis and death.

Research Priorities and Approaches

UTIs are more complex than previously appreciated in terms of microbiology, immunology, etiology and natural history. Previous clinical definitions, such as uncomplicated and complicated, do not capture these relevant diagnostic complexities and are no longer adequate for organizing treatment options.

A mechanistic classification of UTIs that captures relevant parameters for an etiological agent, host response, natural history and treatment response should be a primary goal. More discriminating diagnostic criteria, matched to an improved UTI classification framework, will better organize treatment recommendations, clinical trials and epidemiological studies.

Delays in diagnosis result in a vicious cycle of inappropriate and escalating antibiotic use, leading to increasing resistance. Furthermore, risk stratification of patients more prone to morbid

sequelae is essentially nonexistent. Progress in evaluation and treatment of UTI mandates that research be done to better elucidate *E. coli* virulence factors, including investigating mechanisms of colonization, invasion and biofilm formation on urothelial tissues. Also, investigation of diagnostic molecular biomarkers is an essential step to improve evaluation and treatment.

This research will improve rapid point-of-care diagnosis, and permit the development of calibrated therapy to bacterial resistance, virulence and host susceptibility for serious sequelae. It will also allow for translation of basic science findings into the identification of targets and virulence mechanisms for development of novel therapeutics.

Basic research in UTI model systems is critical for ongoing improvement of clinical diagnosis and therapy. More refined animal models of UTI are needed to clarify these issues. The molecular pathogenesis of acute, chronic and recurrent UTIs must be better understood, including the role of persistent undetected infection. Progress in evaluation and treatment of UTI mandates research into better elucidating *E. coli* virulence factors, including researching mechanisms of colonization, invasion and biofilm formation on/in urothelial tissues.

Biofilm formation, referring to poorly defined bacterial communities that form on or in human tissue or abiotic surfaces such as catheters, is a particularly troublesome aspect of bacterial infections. Within a biofilm, otherwise sensitive bacteria become resistant to antibiotics and host immune responses.¹⁸ For example, in cystitis the presence of intracellular bacterial communities (IBCs), which are essentially biofilms inside urothelial cells, results in bacterial persistence within the bladder epithelium,^{19,20} and possibly causes chronic and recurrent infections.

Currently, empirical antibiotic suppressive therapy is the only treatment option and relapse frequently occurs upon cessation of therapy. Unfortunately, laboratory models for biofilms are still in their infancy and, therefore, thus basic research focusing on discovery of basic biofilm biology, elucidation of mechanisms of biofilm formation and novel anti-biofilm therapeutics is needed to impact this recalcitrant pathogen state, particularly for chronically infected patients and the high risk catheterized patient population.

The vaginal microflora has long been recognized as a major reservoir for uropathogens where they gain niche dominance preceding ascending UTI.²¹ Application of recent advances in molecular ecology tools is necessary to understand the dynamic changes in the vaginal microbiome, and its impact on and therapeutic potential for UTI.

New therapeutic development should focus on vaccines and drugs that target virulence properties of bacteria but avoid processes essential to bacterial survival. By targeting functions essential for infection, such as adhesion or immune evasion, this alternative approach may disarm pathogens within the host without killing them, thereby potentially minimizing the selective pressure on bacteria to evolve resistance.

Multidisciplinary Opportunities

Answering major questions about the mechanisms and etiology of UTI and prostatitis, and translating new scientific discoveries into practical applications will require multidisciplinary and interdisciplinary research involving investigators in basic and clinical sciences, pharmacology and medicinal chemistry, epidemiology and health services. The urinary tract's clinical accessibility, along with recent multidisciplinary research models, presents a unique opportunity to better understand how alterations in host and flora lead to disease.

To effectively address the myriad issues involved in UTI, a nationwide consortium or network of multidisciplinary centers and laboratories, which would attract individuals with talents and interests in a variety of disciplines, should be developed. Importantly, it would also support young basic and clinical investigators in these areas, and stimulate collaborations around developing better ways to evaluate and treat urological infections.

Strong support for collaborations devoted to better understanding UTI pathogenesis, molecular epidemiology focusing on antimicrobial resistance patterns and pathogen evolution (using specific virulence factor studies, antibiotic marker studies, polymorphism analyses and genomics) must be sustained.

Other urological infections of stones, prostheses and operative sites share attributes with UTI, and collaborations with infectious disease specialists will be fruitful for urologists. The role of bacterial biofilms in creating or colonizing renal stones is a potentially synergistic area of study. Also, UPEC infection of the bladder activates exfoliation of the terminally differentiated umbrella cells and subsequent tissue regeneration networks, a phenomenon which is of interest to developmental biologists.²²⁻²⁴ In this same model it was discovered that UPEC are able to access transitional cells in the deeper tissue and form quiescent reservoirs that can seed recurrent infection.²⁵

The continuing use of bacillus Calmette-Guérin (BCG) as adjuvant bladder cancer treatment is another potentially important area that could stimulate interdisciplinary collaborations with urological oncology, particularly since a side effect of BCG is an increase in urinary tract infections. In addition, UPEC infections induce complex inflammatory responses in the bladder that dictate the fate of disease. These inflammatory responses promise to shed light on the disease as well as attract immunologists to this field of study. Including more microbiologists, urologists and clinicians in translational studies of UTI/prostatitis will aid in the identification of pathogen virulence and host factors that can be targeted in the future.

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Research Infrastructure

The highest priorities for research infrastructure are training and developing core resources, both of which are critical to the future of urological disease research. Training encompasses recruitment and mentoring of new scientists and clinicians, and support for mid career researchers to ensure the development and maintenance of

Training

Chairs and Chiefs. Urology Department Chairs and Senior Leaders play critical roles in the success of Research Programs, and recruitment and retention of faculty into research careers. Creating practical guidelines and milestones that can be adapted by interested Chairs, and put into place to modify the environment and institution to establish and expand research programs is essential.

Clinician-Scientists. Central to progress in urological disease research is the career path of physicians who play leading roles as academic urologists. Progress in the field requires that training, professional opportunities and financial incentives become available to urologists to allow them to develop and sustain productive academic careers in clinical, translational and/or basic research.

Needs assessments and long-range strategic planning should be developed to determine how many surgeon scientists can be supported in our academic urology programs with existing resources, and how many would be needed to meet current and future needs.

Basic and translational scientists. Academic Urology Program Chairs have attempted to deal with the decline in trained and/or committed urologist clinician-scientists by recruiting into their programs basic scientists with translational interests. This approach has potential but so far has met with limited success.

There are some notable exceptions but, in general, non-MD scientists at well funded and productive urology centers face significant hurdles, including isolation from their basic science peers, skepticism from funding agencies and committees about their qualifications or research priorities, and insufficient interaction and collaboration with clinical faculty in their own departments.

Because it is becoming increasingly difficult to recruit urologists as principal investigators, non-MD scientist faculty members are becoming even more of a critical element in the development of the urology research field. Strategies to overcome these barriers must be developed and adopted at urology centers.

Training programs. Clinical urology programs have historically borne the expense of research training during residencies and fellowships. The T32 National Institutes of Health mechanism, as it is currently

an effectively sized and trained cadre of researchers for the future. Core resources include developing innovative ways to stimulate collaboration and communication among members of the urology research community, and tools such as tissue banks and animal models that have the potential to leapfrog progress.

configured, is not suitable for training urology residents because of its requirement for a two-year commitment. Post-residency fellowship programs have been successful in competing for T32 grants.

Other training mechanisms also exist, including the K12 mechanism for recruitment of junior faculty. The K12 is one of the most promising, relatively new funding strategies for launching new research faculty in the field of urology and is especially appropriate for the recruitment of faculty outside urology into the field. In addition to enhancing the field by recruiting promising new investigators, the K12 mechanism confers the indirect benefit of providing clinical urology faculty with investigative interests to partner with full-time scientists on funded projects.

If residency training could be restructured so that a two-year research fellowship (“time-out”) were possible, the T32 mechanism would then become applicable, allowing research-oriented urology programs to successfully compete for these grants.

Support of new investigators. The transition from mentored scientist to independent, principal investigator is a tremendously challenging career stage. About one independent, tenure-track position typically exists for every 100 qualified applicants. Increased availability of career transition type awards targeted to the field of urology, whether from federal or private sources, would substantially alleviate this bottleneck by enhancing the ability of urology departments to recruit and retain new faculty.

Transition awards (as distinct from start-up funds) will also help to provide junior faculty with sufficient time to ramp up their programs, recruit colleagues, and become competitive for R01 grants and similar funding.

Mid-career transition/support awards. Retention of clinician-scientists who have established independent research programs or who work within larger research groups is becoming increasingly difficult due to increasing clinical responsibilities. K-type awards that support mid-career clinicians to keep them active in research are an important means of retaining these individuals and must be increased.

Research Resources

Development and enhancement of Urology Centers of Excellence. The NIH supports a variety of center/multi-investigator grants through the P01, P50 and U01 mechanisms. These serve to integrate basic, clinical and translational investigators, accumulate and distribute valued clinical resources, and provide a structured platform to facilitate disease related studies and move basic findings more rapidly into the clinical setting.

SPORE grants support major multi-investigator studies in genitourinary cancers. These programs have become major nucleating centers of research activity in the field, influencing in a variety of ways a larger community than is actually funded directly through this mechanism.

Currently, the George O'Brien Urology Research Centers, funded by the NIDDK, are focused on non-cancer urological diseases. While the O'Brien Centers are a good start, they are few in number and limited in scope. Additional centers or consortia are necessary to bring urology research to the forefront and nucleate research progress.

The non-cancer urology field is in need of greater organization. Scientists and clinicians who share research interests are, in large part, scattered among centers that have no formal, or even informal, relationship with each other. Successful competition for center grants requires a high level of integration, expertise and disease or area focus.

Consequently, developing these complex proposals stimulates new interactions and dissolves the walls of isolation among investigators that can inhibit progress in the field. It is apparent that just as the SPORE program was successful at building up core groups of sites/investigators working on individual cancer types, such centers or consortia are critical to building a critical mass of individuals working on benign urological diseases.

Such national centers would result in increased training and collaborations, and would attract the best scientists to the field. These centers could also serve as a clearinghouse for clinical trials in this area as well as a mechanism by which clinical trials in the field could be more easily implemented.

Development of urology research repositories and databases. In the field of urology research there is a critical need to develop core resources that can serve as the foundation of our research studies. These include sample repositories and databases. In other fields this has been a central component of boosting research efforts.

For example, in the areas of non-cancer urological diseases there is a dearth of well documented samples available for investigators in the field to access for their studies. Even the studies of urological cancers would benefit from well documented samples and databases for benign diseases. There is an urgent need for the development and implementation of such resources.

Increasing the level of support for urology research. A major issue that continues to significantly limit recruitment, retention and research

progress in the field is an insufficient level of financial support from government, industry and philanthropy. Major initiatives, including this National Urology Research Agenda, have consumed significant effort and identified high priority areas for investigation.

With few exceptions, the resources to bring these priorities from concept to reality have not been realized. Directed funds are essential to make this a reality. It is also essential that a system of accountability be developed and put into place to evaluate how funds are spent and allocated, and to determine the impact of funding.

Among medical specialties, urology is one of the most diverse. This is an advantage as well as a disadvantage. Because of the field's diversity, and the intersection between urological diseases and syndromes with well-established basic science fields, such as neurobiology, vascular biology and endocrinology, it should be possible to rapidly assemble multi-investigator teams with a high level of capability.

However, the diversity also tends to balkanize the players in the field, creating islands of tiny sub-fields that do not interact effectively. Efforts to stimulate interaction among investigators with diverse interests, as well as identify specific core needs (such as tissue banks and databases) should improve this picture.

It is essential that attempts to reorganize aspects of the field at the national level occur alongside adequate funding opportunities for the assembly of investigators and resources into coherent networks.

Areas of research focus. As a first step, the urology community must identify and take advantage of programs that already exist in terms of tissue or serum banks, data resources, virtual databases and virtual networks of information.

Public health related issues, including disease prevention and outcomes research, are becoming increasingly important and must be considered priorities for urology research. With the focus nation-wide on the cost of health care, the importance of CER cannot be understated.

Clinical and epidemiological research is essential for progress across all priority areas, and urologists must increase their role in initiating and enrolling patients in clinical trials .

Funding opportunities that are more directed toward specific areas of research such as health disparity, pathology resource networks, clinical trials and other overarching themes need to be developed.

Involvement of urological researchers and urology clinical scientists in the activities of major clinical and translational research centers is essential. By collaborating on this scale, the urology research community may be able to interest non-urology researchers in forms of clinical and translational research that will significantly affect the way in which urological conditions are managed across the primary care and the specialty communities.



The AUA Foundation is the world's leading non-profit urologic health foundation and the Official foundation of the American Urological Association. Our goal is to promote health, provide hope and promise a future free of urologic disease, including cancer.

AUA Foundation Mission Statement:

The American Urological Association Foundation partners with physicians, researchers, healthcare professionals, patients, caregivers, families, and the public, established to support and promote research, patient/public education, and advocacy to improve the prevention, detection, treatment and cure of urologic diseases.



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