

# UW Urology News

*A newsletter from the  
University of Washington Department of Urology*



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## News from the Chairman

**Paul H. Lange, MD, FACS**

At our Resident and Fellow Graduation banquet the first part of June, we said goodbye to many people including our two Chief Residents Tom Walsh and Marc Dall'Era. They are both taking fellowships and pointing towards academia. Every year at this event we congratulate them and ourselves for producing great people and urologists. This year was no exception; I have no doubt we will hear a lot about, and be proud of, these two fine men. We also said the first of several good-byes to Mike and Connie Mitchell. I say first because there will be other opportunities both before they leave at the end of June 2006 and hopefully in the spring when they return for a formal Festschrift for Mike.

We knew for at least a year that Mike wanted to step down as Division Head and devote more time to scholarship and work only part time so as to spend more time with family, especially the 7 grandchildren who live mostly in the Midwest and East. I thought he would stay around here for a while (despite the long plane trips back and forth especially for Connie) during that time and then we would approach our angle of consolidation and repose together. I felt sure his house would take some time to sell. But it was not to be. The house sold in a week and the lure of grandchildren and the unbelievable opportunity of working part-time in the



same hospital in Milwaukee as his son (who is a pediatric cardiovascular surgeon) was irresistible. Who could blame him? I would do the same thing!

When I became Chairman and the news broke around the country that the renown Mike Mitchell chose to join us, I kept hearing two things: 1) you don't deserve Mike Mitchell, and 2) no matter what you do while you are Chairman, no matter how long you are head, they will charac-

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## UW Urology: Leading the Way in Prostate Cancer Research

**Paul H. Lange, MD, FACS**

At first quietly, and then not so quietly, this department and others within the greater University of Washington (UW) environment, and later within the Pacific Northwest, have been working to build an important enterprise in prostate cancer research and service. Today it would be safe to say that this group, which now encompasses not only the UW, Fred Hutchinson Cancer Research Center (FHCRC), and the Institute of Systems Biology (ISB) in Seattle, but also the University of British Columbia, and the University

of Oregon ranks as one of the major prostate cancer multidisciplinary groups in the world.

To best understand what this organization entails is to understand it's origins, and like most histories, it has several versions. From the Urology department's view, it began many years ago at the University of Minnesota when the laboratory of Drs. Paul Lange and Robert Vessella did their early work on PSA. Later when they arrived at UW, this effort attracted the support of

the Lucas Family Foundation who has supported that laboratory's efforts in prostate cancer research for 17 years, most prominently in the development of what now are 20 human prostate cancer xenograft lines known throughout the world as the LuCaP series. When this effort began there were just 2 human prostate cancer animal models. This effort attracted many collaborators. One was Nick Bruchofsky, a world famous prostate cancer endocrinology researcher from British

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## Prostate cancer research, continued from page 1

Columbia. Soon that collaboration resulted in a large NIH O'Brien Centers Grant which ran for 10 years, and deepened the relationship with the Vancouver General Prostate Centre now directed by Larry Goldenberg and Martin Gleave. This group is without question the leading prostate cancer research enterprise in Canada.

Another collaborator became Leroy Hood, a world famous molecular biologist initially connected with UW and then later with his own Institute of Systems Biology in Seattle. Through this collaboration, a large effort to identify the genes of prostate cancer was launched with the support of Michael Milken's CaP CURE Foundation (later renamed the Prostate Cancer Foundation). This support has totaled over 11 million dollars so far and facilitated the acquisition of many federal grants and, more importantly, increased collaboration with other prominent prostate cancer researchers in the Northwest and also recruitment of renown researchers in other fields to do work in this cancer. One prominent group of prostate cancer researchers is that of Janet Stanford who already was leading efforts at FHCRC in prostate cancer. Currently over 40 advanced degree researchers are working in prostate cancer at UW, FHCRC, and the ISB and they hold over 35 million dollars in federal research funding. The most prominent funded grant is the NIH designated Special Programs of Research Excellence (or SPORE) in prostate cancer. It is one of 11 prostate cancer SPORES in the nation; the others being: Baylor, Harvard, Johns Hopkins, Mayo, MD Anderson, Memorial Sloan Kettering, Northwestern University, UCLA, UCSF, and the University of Michigan. These SPORES are large multidisciplinary organizations involving many clinical and research disciplines locally, and nationally the SPORES are united in many collaborative research efforts. Our SPORE is called The Pacific Northwest Prostate Cancer SPORE because it encompasses not only researchers from FHCRC, UW, and ISB, but also the prostate cancer research groups in Vancouver, and more recently the growing prostate cancer research group at the University of Oregon under the leadership of Tom Beer. Another important collaboration and grant is that associated with Dr. Vessella's laboratory and the Emory University group. Thus this department is

connected significantly with almost all of the large multidisciplinary research groups in the nation.

Over the last 8 years the FHCRC (one of the premier research cancer institutions in the world) and UW have combined forces on many fronts including prostate cancer. This association resulted in the formation of the Seattle Cancer Care Alliance (SCCA) which is a collaborative effort of FHCRC, UW, and Children's Hospital Medical Center in cancer innovation and service. A part of the SCCA efforts include two large prostate cancer clinics. One clinic is run by Tia Higano at the SCCA building close to the FHCRC campus and is concerned mostly with advanced prostate cancer trials. More pertinent here is the large multidisciplinary Prostate Cancer Center located on the UW campus in the Surgical Pavilion adjacent to the new Urology outpatient clinic. This has been one of my long-term dreams; a truly multidisciplinary clinic where clinicians, (whose major academic interest is prostate cancer) from all the pertinent disciplines including Radiation Oncology, Medical Oncology, Surgery, Social Work, and Psychology live and work together in intimate fashion with a large number of oncology and/or research nurses and data managers to enhance cutting edge patient care and accelerate the development and deepen the execution of clinical trials. Currently there are 10 physicians and over 30 people working in our Prostate Cancer Center. The physicians include 4 medical oncologists (Tia Higano, Bruce Montgomery, Pete Nelson, and Evan Yu); a radiation oncologist (Ken Russell); and 5 urologic oncologists Bill Ellis, Paul Lange, Dan Lin, Tom Takayama, and soon our new laparoscopic expert, Sangtae Park).

The protocols that have been, or soon will be, launched in these clinics are too numerous to mention but include trials for surveillance, neoadjuvant and adjuvant therapies around radical prostatectomy and radiation therapy, Quality of Life trials surrounding surgery, trials for early and late recurrence, and of course, many trials for advanced disease. The clinical trials that we are involved in emanate of course from cooperative groups (e.g. SWOG) but also from those developed and conducted by ourselves, and those more exclusive national protocols to which we have been invited because of our reputation and/or

connection with other research groups around the country (e.g. prostate cancer SPORES). Our goal is to have and offer a trial for almost every clinical situation and every patient. These clinical efforts are enhanced not only by our access to new drugs but also to newer technical innovations such as robotics and virtual reality, new methods of radiation delivery, and most recently, the development of a \$1.5 M computerized real time database system which will allow faster and more accurate analysis of treatment outcomes, translational research efforts, and in general will better coordinate dialogue between the bench and bedside.

The many more basic innovations that have already come from our group are also too numerous to detail except in very broad terms. Briefly they include: 1) the large LuCaP human prostate cancer xenograft series now used all over the world; 2) our rapid autopsy program (1 of 2 in the nation) that are acquiring the very important prostate cancer metastatic tissue so vital for analysis here and all over the world; 3) our efforts at finding the hereditary (family and polymorphic) genes associated with prostate cancer; 4) our elucidation of the gene expression profiles of various prostate cancer states; 5) our innovations which enhance pathologic tissue handling and analysis; 6) our work on the androgen receptor and its signal transduction pathways especially molecules related to insulin growth factor which in turn have resulted in several new systemic targeted therapy clinical protocols; 7) our work on the detection and elucidation of circulating prostate cancer cells from bone marrow aspirates; 8) our efforts at finding and categorizing the prostate and prostate cancer stem cells; and finally, 9) our efforts to improve the use of androgen ablation therapies most prominently the use of systemically administered estrogen.

All these activities and grants require the acquisition of large private and institutional financial resources, the continued recruitment of talented young investigators, and significant organizational efforts. This task has been amalgamated into the Institute for Prostate Cancer Research (IPCR); a cooperative effort of FHCRC and UW, and is headed by myself. One of its inaugural goals is a \$35M fund drive. To that end, two large prostate cancer survivor breakfasts were staged in 2004 and 2005 under the direction of UW Medicine's Devel-

# Diabetes-Associated Erectile Dysfunction: The Rising Need for Novel Treatment Options

Kanchan Chitale, PhD



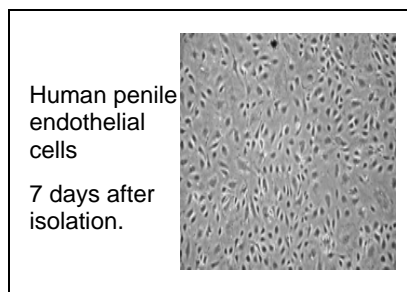
The presence of diabetes in the United States is rapidly reaching epidemic proportions. In a population based analysis of US men aged 20 and up, 49% of all men with diabetes reported erectile dysfunction (ED)<sup>1</sup>. The onset of ED in diabetic men is up to 10-15 years earlier than in the general population<sup>2,3</sup>, and <50% of men in this cohort respond adequately to PDE5 inhibitors. Thus it is clear that unmet medical needs remain in the field of ED.

Presentation of ED in diabetic patients is not only associated with a reduction in health-related quality of life and an increase in depressive symptoms, but may also be a harbinger for general cardiovascular disease<sup>4</sup>. In a recent survey of diabetic men with ED, impotence rated amongst the top three complications of most concern for patients, with only blindness and kidney disease being rated higher<sup>5</sup>.

Diabetes uniquely impacts all components of the erectile response, potentially having underlying psychogenic, neurogenic and vasculogenic mechanisms. Neural degeneration, penile smooth muscle cell death, tissue remodeling, heightened vasoconstrictor tone and endothelial dysfunction have all been proposed as mechanisms of diabetes-associated ED. Accumulating evidence suggests that penile endothelial dysfunction [often defined as attenuated levels of nitric oxide (NO)] occurs in both rat and mouse models of type I diabetes. This decrease in bioavailable NO may be a cause of the reduced responsiveness of diabetic men to phosphodiesterase type 5 inhibitors; as these agents only serve to enhance or prolong existent NO-induced dilatory signaling<sup>6</sup>. Despite the numerous mechanisms proposed to explain diabetes-associated ED, no unifying hypothesis yet exists. Thus, better defining molecular mechanisms that impair the normal cellular function of cavernosal tissue and cause loss of function in disease states could have important implications for patients.

At the University of Washington, researchers in the laboratory of Hunter Wessells MD and Kanchan Chitale PhD are working to elucidate potential novel therapeutic

targets for the treatment of diabetes-associated ED. Their research utilizes a wide range of techniques and animal models to examine diabetic-ED from the level of gene regulation through to physiologic function. Microarray analysis enables the wide-scale detection of gene expression changes in penile tissue from diabetic vs. non-diabetic patients and animals. Lab research technician, Karen Engel, has developed a successful method for the isolation and culturing of human penile endothelial and smooth muscle cells.

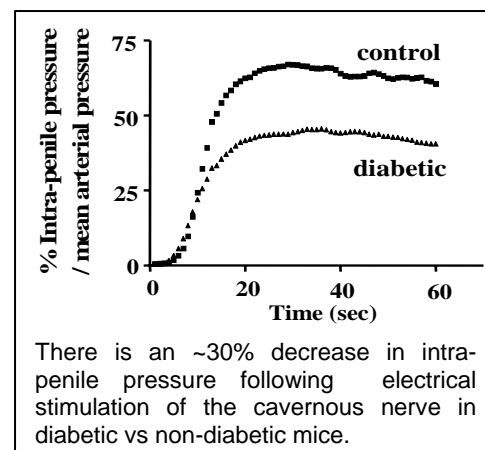


Human penile endothelial cells  
7 days after isolation.

These cells are derived from donor biopsy samples obtained from consenting diabetic and non-diabetic men by Dr. Wessells during penile prosthesis implantation or organ donation. The use of human penile cells enables the examination of signaling pathways at the cellular level, and supports the potential relevance and translatability of findings to the human.

Sophisticated methods designed to examine physiologic and pathologic protein function in animal models are also in use in the Wessells/Chitale lab and allow for more rigorous hypothesis testing not feasible in human patients.

Through *in vivo* measurement of intracavernous pressure following electrical activation of the cavernous nerve, lab research scientist, Ian Luttrell, is able to assess erectile function in anesthetized rats and mice. Using this technique, Mr. Luttrell has verified reports demonstrating decreased erectile function in rats made diabetic through drug-induced destruction of pancreatic islet cells.



The Wessells/Chitale research team also examines penile function at the specific level of endothelium-dependent dilatory capacity through the use of the small vessel organ bath preparation brought to the lab by Dr. Chitale. In this preparation, relaxation of penile tissue isolated from rats or mice is assessed in response to the selective endothelium-dependent dilator, acetylcholine (ACh).

Using this wide array of tools, the research team has exciting preliminary data identifying a potential novel target for the treatment of diabetic-ED. Through microarray analysis, Dr. Christopher Sullivan, a former post-doctoral research fellow in the lab, identified altered expression of genes in penile tissue from diabetic rats compared to non-diabetic controls<sup>7</sup>. In his analysis, Dr. Sullivan detected significant up-regulation of a multi-function copper-binding protein, ceruloplasmin (CP) in diabetic rat penile tissue. Initial studies from the lab using human penile endothelial cells, suggest that CP may inhibit activity of eNOS, a potent generator of NO, consistent with other reports. CP has also been shown by other laboratories to

# Traveling to Cameroon: A Resident's Perspective

**Stephen H. Culp, MD, PhD**



Since 2004, residents in the University of Washington Department of Urology have had the opportunity to travel to Cameroon during their research year. Approximately six weeks is spent working under the direction of Dr. George Brannen at a variety of hospitals in the northwest province of this West African country. A total of three residents, Drs. Mia Swartz, Stephen King, and myself, have so far made the 10,000 mile trek to Cameroon.

My voyage to Cameroon commenced during the African rainy season in the summer of 2005. Prior to this, I never before had visited the African continent, much less traveled to a developing country. I spent the majority of my time in Shisong, a small village located approximately 10 hours northwest of the main port city of Doula. Having just finished my third year of training, I felt prepared for the urologic procedures I would encounter. Yet, I assumed no limits to the amount of new culture and tradition that I would undoubtedly experience on my journey.

Walking through the hospital gate my first full day at Shisong, the guard quickly greeted me – “You are Welcome Doctor Steve”. After a few words of morning chatter, the guard directed me to the operating theatre. I walked along the outside corridor using my umbrella as a walking stick and admired the hospital courtyard in the early morning hours. The sun shone brightly on the many families washing clothes and preparing their morning meals. I passed by traditionally dressed patients seated on benches waiting to be seen. Our eyes would meet and although our only word spoken was “hello”, they could easily ascertain that I was a new stranger to their home, given my white skin and fascinated facial expressions.

I arrived at the changing room and was immediately thrust into another world. After valiantly trying to find matching scrubs and shoes that fit, I made my way to the operating theatre periodically adjusting my eyeglasses that kept fogging up over the cloth mask. As I opened the door to the theatre, a loud roar from the

staff instantly surrounded me – “You are Welcome Doctor”. Anyone who was not busy offered me a handshake with their left hand resting beneath their right elbow, a traditional sign of respect.

The first day in the operating theatre overwhelmed my senses. Although the cases for the most part seemed complex, the operating team managed to complete a dozen of them by noon. Everything worked like clockwork. There were no pre-packaged procedural kits – each surgical instrument had to be removed from its sterile container and placed on the respective Mayo stand. Making use of two beds in the room, technicians would wheel the next patient in and complete the prep prior to the completion of the other operation. Overall, the efficiency of the operating room staff, combined with the surgeon expertise, kept a pace completely foreign to me. On completion of our time in the theatre, I would join the surgeons on ward rounds or outpatient consults, gathering cases for the next day.

During my six weeks in northwest Cameroon, I operated at a total of three hospitals, the majority of time spent at St. Elizabeth General Hospital in Shisong. I spent one to two days a week operating at Banso Baptist Hospital in nearby Kumbo and one full week at a sister catholic hospital in Njinikum, located about four hours from Shisong. Although vastly limited in resources, the expertise of the staff far surpassed what I had expected. Everyone in the hospital welcomed me and enjoyed my partnership, but they did not “need” me. Though receptive and interested in how we perform procedures in the United States, the surgeons were quite comfortable with their own skills, many of which were quite foreign to me. I quickly learned to work without Bovie electrocautery, clamping off and tying each bleeding vessel. Suction was a luxury, used only when desperately needed. Retractors were few in type and number, thus the exposure left much to be desired when compared to what I was used to in America. It took awhile to retrain my hands to tie using every last bit of suture. And on local procedures, I learned to work fast, realizing that

the limited anesthetic would quickly dissipate, leaving the patient to feel pain.

On returning home my second night in Shisong, I found a collection of books located underneath the living room table. Most of these books were written in German so I consequently tossed them aside. However, there were a few books written in English dealing with Dr. Albert Schweitzer and Lambarènè, the hospital he established in neighboring Gabon in 1913. Although I had previously read some of Dr. Schweitzer’s work during school, reading it now in the African air within 50 yards of a similar hospital added color to the words and stories of this remarkable man. Even though 40 years have passed since Dr. Schweitzer’s death, the hospital that I now worked in shared many haunting similarities with that of Lambarènè.

Although patients at Shisong arrived by taxi or foot instead of by riverboat on the banks of the Ogowé River, their overall history and stories were markedly akin. Despite the numerous distinct lineages in Northwest Cameroon, the people, like those in Gabon, are all subject to an overall paternalistic tribal structure. This translates into a culture far different than what we are used to in the western setting. The cause of disease as well as its treatment differs widely from western culture secondary to the traditional beliefs of each tribe on witchcraft and traditional healing. Therefore, when a patient did arrive at our hospital door, they surrendered many of their native convictions in order to be diagnosed and treated. At first, I felt this resignation to be somewhat arbitrary, but as time progressed, I developed an awareness of how western medicine could coexist with the culture without having to conflict with the native tradition.

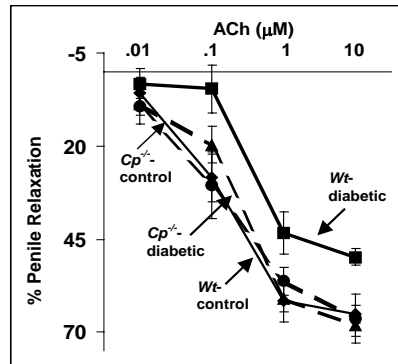
Overall, the people of Cameroon are hard-working, have a strong personal faith in religion, and are deeply appreciative of all that is done for them. Through my work and reading, I developed a respect for their culture and lives that I would not have gained otherwise had I not pursued this endeavor. Although I cannot predict my future in terms of ability to devote long term commitment, this brief personal involvement has forever changed my ideas and overall practice of medicine.

## Diabetes and ED continued

increase levels of oxidative stress. Both the inhibition of eNOS and the increase in oxidative stress lead to decreased NO bioavailability and attenuated penile dilatory capacity, and implicate a potentially deleterious effect of elevated CP on erectile function in diabetes.

Perhaps the most compelling data suggesting that increased penile CP in diabetes may contribute to decreased erectile function comes from recent physiologic studies in the lab using “knock-out” mice deficient in the Cp gene ( $Cp^{-/-}$ ).

upon drug-induced depletion of pancreatic islet cells. Although the CP-deficient mice are susceptible to the development of

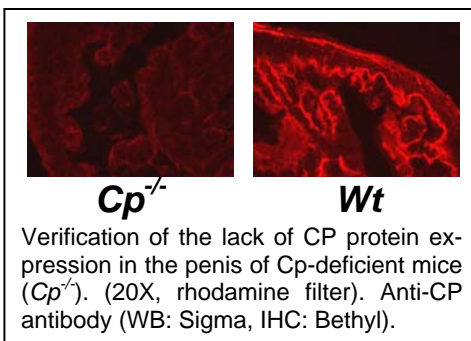


diabetes, intriguing initial data suggest that these mice are protected against the diabetes-associated penile endothelial dysfunction seen in their Wt littermates.

Thus, from the level of gene expression to physiologic function, these data suggest that increased CP in diabetes may contribute to diabetes-associated penile endothelial dysfunction. Although more research is necessary, the inhibition or removal of CP may be a potential therapeutic strategy to combat diabetes-associated ED.

As the incidence of diabetes is rapidly increasing, interventions to improve or prevent ED in men with diabetes will become increasingly important. Surgeon-scientist partnerships like that of Dr. Wessells and Dr. Chitale facilitate the study of underlying disease mechanisms in human tissue/cells as well as animal models, and increase the likelihood of successful, potentially translatable research.

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While in the research lab this past year, Dr. Stephen King, a 4<sup>th</sup> year Urology resident, demonstrated that both the  $Cp^{-/-}$  mice and their wild-type control littermates (Wt) have significantly elevated blood glucose

## News from the Chairman continued

terize as the major, if not the only, noteworthy event of your tenure as “you got Mike Mitchell to come to Seattle.”

Over the last 17 years I have been privileged to work alongside Mike building this department, and I must say, I think those predictions will be true. It has been a real privilege to become his friend and to watch as he showed us again and again that he is the best pediatric urologist in the world. A one-of-a-kind surgeon (often called the heir apparent to Hardy Hendren); a great thinker and innovator; holder of most of the leadership positions within Urology (e.g., ABU, RRC); a major reason this program has gained national prominence. Over these years he built a pediatric division which is now counted as one of the best in the country, and most

importantly, he is a genuinely wonderfully caring person; one who the more you know about him, the more you want to get to know him better. It is one of my great regrets that even though we met almost weekly when we were both in town, and we are fast friends, I still didn't get to know Mike well enough. And Connie also; one who gave great support and wise advice over the years. I will always be grateful to both of them for the tremendous, almost excessive, loyalty that they have shown to me and to this Department. My wife Lucy and I will miss them greatly.

But like all great enterprises, we move on and up. A search for a new Pediatric Urology Division Head is

already underway; one that hopefully will carry that Division to even greater heights not only clinically (if that is possible) but also investigationally. The newly created Mike Mitchell Endowed Chair, a growing endowment, and over \$3M in federal support under the tutelage of the Head of the Pediatric Urology Laboratory, Jim Bassuk, makes this goal almost guaranteed. And so it goes: more things to be proud of and support!

## Announcements

### Congratulations 2006 Graduates

The University of Washington Department of Urology extends congratulations to all of its 2006 graduates. **Drs. Marc Dall'era** and **Thomas Walsh** are graduating from the residency program. Both are heading to San Francisco for fellowship training at UCSF. Marc is starting a urologic oncology fellowship under the direction of Dr. Peter Carroll, and Tom will be training in andrology and infertility under the direction of Drs. Paul Turek and Tom Lue. **Dr. James Kuan** is completing his fellowship training in trauma and reconstructive urology with Dr. Hunter Wessells. James will be staying at the UW as a faculty member and will be practicing at Harborview and the Puget Sound VA, as well as continuing his research efforts in renal injury biome-

chanics and trauma outcomes. **Dr. Thomas Lendvay** is completing his fellowship in pediatric urology with Dr. Michael Mitchell. Tom is also staying on as faculty and he will be practicing at Children's Hospital where he plans to develop both the clinical and research aspects of the robotic surgery program. **Dr. Janice Lai** is completing her post-doctoral research training under the direction of Dr. Bob Vessella. She is currently in the midst of a job search, and is looking for a position that will include both research and teaching.

### Awards

**Dr. David Penson** was honored as the 2006 recipient of the Golden Cystoscope Award at the annual meeting of the AUA in Atlanta. David, currently an Associate Professor at USC, started his career as a

UW faculty member from 1999-2004.

**Dr. Kanchan Chitale** was awarded the 2006 American Physiological Society, Cardiovascular Section Young Investigator Award.

**Dr. Eva Corey** received the "Best Paper of 2005" award from Astra-Zeneca for her paper entitled "Comparison of Fc-osteoprotegerin and zoledronic acid activities suggests that zoledronic acid inhibits prostate cancer in bone by indirect mechanisms," which was published in *Prostate Cancer and Prostatic Diseases*.

**Dr. Glover Barnes** received an award from the National Association of Medical Minority Educators ( March 3, 2006), in " Recognition and Celebration of The Legacy Of Dr. Glover Barnes As A Diversity Trailblazer".

## 3rd Annual UW Urology Alumni Reunion, Atlanta, 2006



Join us next year in Anaheim!  
Time and location TBA

## UW Urology Publications in 2005

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## 2005 Publications continued

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## Prostate cancer research continued

opmental Office and Steve Fleischmann, a UW prostate cancer survivor. Close to a million dollars was raised at each event. At the last breakfast, the featured speaker was Lance Armstrong whose story about surviving testis tumor has inspired the world and energized all prostate cancer survivors. Over 1200 people attended this breakfast including many prominent members of the Seattle community. The prominence of the IPCR program was recognized and the prediction was made that like testis tumor, some day soon similar success stories will be recollected about prostate cancer. When that day comes, this department will be proud of the part that it has, will, and is playing in that historic accomplishment.

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## Change of Address? Feedback? Updates? Story ideas?

Please take a moment to fill out and send us the below form or email Michael Porter at [mporter@u.washington.edu](mailto:mporter@u.washington.edu). If you include any professional or personal updates and we will try to include your update in a future issue of *UW Urology News*

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Comments:

## Upcoming Events

Western Section AUA Maui, Hawaii	October 22-27
Northwest Urological Society Spokane, WA	December 8-9, 2006
4th Annual UW Urology Alumni Reunion At the AUA in Anaheim, CA	May 2006 Time and place TBA
UW Urology Graduation Banquet	June 2, 2006 (tentative)

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Volume 7, Issue 2

Spring/Summer 2006

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*A newsletter from the  
University of Washington Department of Urology*

