Translational and Basic Science Research in Pediatric Urology: A Conversation

FROM THE GUEST EDITOR

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The world-wide technological explosion of the last 25 years has opened new methods and opportunities for basic, translational and clinical research in pediatric urology. Advances in molecular biology, the sequencing of the human and mouse genome, tissue engineering, stem cell research, and nanotechnology, to name a few, have paved the way for exciting research within pediatric urology. The academic push of pediatric urology fellowships within the United States to incorporate 1-2 years of basic, translational and/or clinical research training has been instrumental in raising the physician standard. While not all pediatric urology fellows choose to continue research after training, these efforts have contributed to the increase of successful physician scientists in the US. Here, this is evidenced by the increasing number of pediatric urologists with NIH-funded training grants and as NIH-funded independent investigators. Indeed, we also owe great thanks to the many physician researchers in related medical fields and PhDs who have devoted their work to topics within pediatric urology.

In this issue of the Dialogues, esteemed colleagues from both the US and abroad share their thoughts on the past, present and future of research. Each contributor was asked to ponder on the current state of research in general and specifically on a given genitourinary organ. These contributors stress the crucial role clinicians play in the identification and recruitment of patients to research studies. Hopefully, we as pediatric urologists will organize into national and international multi-center groups to achieve research studies of high impact.

Trying times may lay ahead as grant budgets are trimmed and fewer grants are given. But the zeal is still strong. Basic, translational and clinical research in pediatric urology should and will continue – for the kids.

FROM THE EDITOR

Anthony A. Caldamone, M.D.

Whenever I venture to read an article on translational research, I am reminded of the words of Frank Zappa: “Reality is an optional experience.” The reality that I continued to struggle with is how a busy clinical pediatric urologist can direct a productive basic science research laboratory. In this issue we have seven examples of just that reality. Each tells us how they were able to become successful at both clinical and basic science endeavors. In addition each contributor, under Dr. Baker’s direction, tells us how their research will change our approach to clinical pediatric urology.

Dr. Baker and her contributors are to be congratulated, not only for this excellent issue, but also for their persistence in trying to make us better clinicians.
1. What do you consider the two most major basic science discoveries in pediatric urology in the last 10-20 years? How have they shaped clinical management?

Our nephrology colleagues have done the bulk of this type of research and to them we owe our gratitude and respect. There is no question that the single most important recent discovery in kidney research is the clinical application of RAS inhibition. Inhibiting angiotensin converting enzyme as well as antagonism of both the angiotensin types I and II receptors has shown impressive renoprotective effects. This inhibition of the RAS has been pivotal in our understanding of both the pathogenesis as well as the treatment of progressive renal damage.

Also important is the discovery of specific genes that are involved in specific kidney diseases. A few examples are nephrin in congenital nephrotic syndrome; collagen defects in Alport’s disease; PKD genes in polycystic kidney disease; GDNF-c ret interaction in ureteric budding and the aquaporin genes in regulating water reabsorption. These genes give us powerful diagnostic tools which do not necessarily allow prevention of the disease but give us the ability to better study the disease processes and as in patients with APCKD, give us the ability to diagnose and counsel the patients and families.

Finally, the development of animals with genetic deletions/transgenics has really redefined how we study and understand specific factors that may affect renal development and impact on renal injury and its evolution as well as treatment options.

2. What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?

The obvious answer in this day and age of stem cells, organ construction, and regenerative medicine is renal replacement therapy. The most devastating disease processes in our field are the ones that lead to renal insufficiency. While renal transplantation and advances in dialysis technology today make survivability more realistic than in the past, they are not without significant risk and are not physiologically ideal. Renal replacement with direct tissue or some other novel delivery system that could enable the body to replace the millions of nephrons lost to disease would be the single most society and practice changing feat that I can imagine within our specialty. Unfortunately, this is a monumental task as the kidney is functionally much more complex than other potential engineered organs, such as the bladder. The kidney has so many highly differentiated functioning cells that not only would researchers have to replicate each individual cell type but also organize them in such a way that they could function together to perform the many functions of the glomerulus and collecting system.

Other intriguing urological avenues for kidney research include investigation to gain a better understanding of genitourinary development and embryology. This understanding could then provide the tools to better study congenital developmental anomalies. An example of this is the manipulation of genetic signaling in the interaction between the ureteral bud and metanephric blastema. If we could affect this interaction, we could possibly prevent the congenital anomalies that result from aberrancies in this signaling pathway. Discovering prognostic indicators to identify those at risk for renal deterioration secondary to significant renal disease such as urinary tract obstruction or vesicoureteral reflux would also be a major breakthrough. Current available radiographic diagnostic tools are highly unreliable in identifying which patients with hydronephrosis are at risk for deterioration of renal function. This makes it difficult for the clinician to decide which patient with hydronephrosis to treat aggressively with surgery and which one to follow conservatively. However, if we had urinary biomarkers that would identify which patients were at risk, we could much easier know who to treat and when to do so. Biomarkers could also help us decide who was at risk for renal deterioration from other disease processes such as acute renal failure, diabetic nephropathy, and renal transplant rejection, among other things.

Finally, in patients with congenital or aquired renal disease, it would be a major accomplishment if we could find new and better ways to prevent or slow progression of their renal deterioration, ultimately avoiding end stage renal disease and the need for renal replacement. For example, if one could prevent or slow the progression of interstitial fibrosis and tubular cell atrophy, two primary hallmarks of progressive renal disease, the progression to fulminant renal failure could be significantly delayed if not stopped altogether.

These are just a few examples of things that if studied and brought to fruition, would have a significant impact on our patients and would alter the way we practice medicine in untold ways.

3. Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?

It’s all about ideas and scientific method. If we don’t ask ourselves questions then there will be no research. The key is to help the clinical urologist realize that he is half of the research puzzle and without his input, we are severely limited in our ability to move research forward. Often, the questions we ask ourselves in a typical day of clinical practice are ripe for investigation in the laboratory if we only get the ideas out there on the table. There are many ways to do this in the current era of information technology. Online forums (chat rooms), blogs, and video conferencing are just a few examples of how ideas could be disseminated and discussed. Clinician X takes an idea to Scientist Y and they discuss the problem and come up with a hypothesis to test. Scientist Y runs into a problem during the research process and goes back to Clinician X to ask his advice and discuss the situation. All in all, they both win AND the knowledge in our field is advanced. I should also mention, that to avoid hurt feelings in the long run, I always discuss scientific ownership on the front end with all of my collaborators. That way, when the abstract is presented or the paper is written, there are no misunderstandings. Scientist Y must give Clinician X his due or Clinician X walks away mad never to return and Scientist Y has lost an invaluable ally.

(continued on next page)
4. In 10-20 years, how do you envision basic science research will be used in daily pediatric urology practice?

To continue with the examples I used to answer question #2, renal replacement therapy would give patients with end stage renal disease from posterior urethral valves or prune belly syndrome a better quality of life and a brighter outlook for the future. Biomarkers would enable us to order a simple test to help decide which patient with hydronephrosis is at risk for renal deterioration and who would thus benefit from surgical intervention. That ability would make our current diagnostic tools potentially obsolete. In 2007, there is no question that we outrageously over treat patients with vesicoureteral reflux. In the future, thanks to someone's research efforts, we will hopefully be able to identify patients at risk for pyelonephritis and renal injury and thus be better able to focus our therapeutic efforts. Once we identify the cause of progressive renal deterioration in our patients we can find a way to treat them to slow or altogether stop this progression lessening the need for transplantation and/or renal replacement. These are just a few examples of potential findings from the laboratory that could ultimately be used in clinical practice to benefit our patients. Obviously the sky is the limit when it comes to ideas and potential findings that could be translated from the lab to patient care.

5. Some say there is a chiasm between the knowledge of the basic science researchers and most pediatric urologists. How can we eliminate this chiasm?

I touched on this a bit when answering question #3, but we must keep the clinical urologist interested and involved in our research endeavors or we are finished. We cannot afford to place ourselves higher on the intellectual pedestal and make the things we learn in the laboratory seem foreign and uninteresting. This is where the concept of translational research comes into play. Translational research is generally described as the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of disease or injury. Its value is usually determined on the basis of likelihood that completion of exploratory or developmental research objectives will move towards effective therapies. The translational researcher, such as myself and many other physician scientists, is charged with the task of bringing the world of basic science together with the world of clinical medicine. As such, it is our job to keep those who consider themselves primarily clinicians involved in the loop. At our institution we have a biweekly lab meeting where basic scientists, clinical physicians, and translationalists come together and discuss research. It is an environment full of energy and excitement due to the ideas discussed and the collaborative attitude of all those involved. Ideas discussed in these meetings are then taken to the lab, experiments performed and the results brought back to the meeting for all to discuss. It is this type of interaction that we as pediatric urologic researchers need to foster.

Translational research is generally described as the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of disease or injury.

6. How have you been able to balance your clinical responsibilities with your research efforts? Has there been pressure to generate clinical income of late – and how does one prevent those pressures from overcoming research time?

First of all, I must stress that true research cannot be accomplished without the entire program, from the individual researcher to the division or group practice to the institution itself, giving these efforts value and committing the appropriate resources in that direction. One person cannot take on the task of developing a given division's research program. Everyone involved must be on board and supportive. I have a great commitment to my research endeavors but I also have the unwavering support of my partners. I am given protected time – true protected time that is more than just lip service with no substance to back it up. My partners take care of my clinical responsibilities if I am in the lab. Initially, when I came to Vanderbilt, 75% of my time was protected. Now, 10 years later, it is only 25%, but the commitment and supportive attitude is still the same. They take phone calls for me, they see my patients who wander into clinic on the wrong day. They answer the nurses’ questions. They go to the ER and see consults for me if I am on call and unable to go, and the list goes on and on. This is what is involved in truly protecting one’s time. In addition, I am not punished financially for doing more lab and less clinical work. Again, however, this is a group decision NOT to put more value on clinical work than on academic work. Finally, collaborative research efforts with other investigators within one’s institution are key to more efficiently using research time and are critical to the success of physician scientists. Collaboration is defined as working jointly with others or together in an intellectual endeavor. Pediatric urologists receive very little if any formal lab training. As such, we need an environment in which to learn, grow, and flourish. Thus, collaboration gives us the advantage of working with senior, established investigators who can serve as mentors and a source of scientific intellect. In addition, new lab techniques as well as grantsmanship skills can be learned and fostered in this environment. Finally, space and resources can be shared saving expense and increasing efficiency.

7. Where do you think more research efforts should be directed in pediatric urology?

The main problem with suggesting where more pediatric urology efforts and money should be directed in terms of kidney research is that we are competing with the nephrologists, who have much more formal research training and who often times devote 75-100% of their time to their research activities. Pediatric urology practices are rarely if ever set up that way – few of us could sustain a successful surgical practice if we were only “on service” one or two months out of the year. That being said, the nephrologists provide fabulous collaborative resources and in my experience are thrilled at being able to help provide mentorship and intellectual crosstalk. An example – one lab’s focus can be on the anatomical and developmental components of kidney disease while another’s focuses more on the changes within the glomeruli and interstitium of the kidney. Medical and surgical kidney disease will always have their own unique place, but bring the two worlds together and great things can be accomplished - it’s a natural union whereby both sides benefit. As I discussed in question #2, renal replacement and biomarkers are two perfect examples of where these two research worlds should collide.
The Bladder

1. What do you consider the two most major basic science discoveries in pediatric urology in the last 10 to 20 years? How have they shaped clinical management?

There have been many important discoveries in bladder research during the last two decades, and it is difficult to rank their significance. The in vivo observation of bladder's ability to regenerate and differentiate into a functional organ was critical for pediatric urology in that it ushered in the exciting research of tissue engineering. Although it has not yet made a direct clinical impact, its potential translational value is enormous. The second discovery of importance was the characterization of bladder-specific molecular markers, such as uroplakin. Although it has not resulted in a direct impact on clinical practice, it will undoubtedly pave the way for the subsequent research in understanding the bladder development and regeneration.

2. What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?

The mechanism of bladder fibrosis must be understood better. Clinically, what leads to the loss of bladder capacity and compliance is fibrosis, not simply cell proliferation. Much work has been done studying the role of bladder smooth muscle cells, but clinical observations suggest that bladder function is a very complex process that will likely involve an interactive participation of multiple cell types, including urothelium, smooth muscle cells, resident fibroblasts, nerves, blood vessels, and possibly circulating/resident stem cells. Characterization of these inductive interactions and integrative physiology will lead to translatable ideas that will possibly impact clinical practice.

3. Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?

The modern basic science research requires sophisticated support infrastructures, especially in regards to the regulatory guidelines set by the government, such as radiation safety, recombinant technology, laboratory animal care facilities, and biological material handling/storage. It is, therefore, unrealistic for private practice pediatric urologists (who will comprise a significant portion of our labor force in the upcoming years) to engage in basic science investigations.

In academic settings, the basic science investigation requires protected time (for those doing the research) as well as financial resource and support. Although there are various ways in which research activities can be funded, many of the innovative ideas during the early stages will require seed money to generate preliminary data. Because this may involve setting aside of departmental revenues for research, there must be a strong sense of collective ownership by the entire group in investing for such basic science research endeavors. A constant dialogue must exist, such as joint research/clinical case conferences, whereby translatable ideas are continuously refined. Clinically relevant questions must be translated into a testable and fundable set of hypotheses, and laboratory-derived findings must be translated into clinically applicable ideas. Whether the discoveries turn into publications, more grants, or business opportunities, there must be a shared ownership by all involved.

4. In 10 to 20 years, how do you envision basic science research will be used in daily pediatric urology practice?

Relatively speaking, the basic science research efforts have been sparse in the field of pediatric urology, when compared to other fields such as oncology, cardiology and nephrology. Even in fields where the research activities have been intensely pursued, however, the examples of true “bench-to-bedside” translation have been extremely rare. The field of tissue engineering has brought the possibility of translational research closer to reality, and study of bladder cell/molecular biology may impact the clinical practice by accelerating the progress in tissue engineering.

5. Some say there is a chiasm between the knowledge of the basic science researchers and most pediatric urologists. How can we eliminate this chiasm?

Philosophically, a rigorous scientific investigation requires a “reductionist” mindset, whereby the problem at hand must be reduced down to the smallest components, whose significance can be tested. The more one can reduce the complexity of a problem into independent and individual components, the more likely one can evaluate critically the potential mechanisms underlying the problem. The clinical practice of medicine, however, is by nature integrative. We tackle a clinical problem by thinking globally, rather than at an individual molecular level. It is only logical then that ideas generated by reductionistic approach will fail to yield a significant impact at the global, clinical level. A rigorous science of reduction and hypothesis-testing will often appear irrelevant to clinicians who are trying to solve a patient’s problem. There must be a concerted effort by both scientists and clinicians to integrate the individual components into a whole. The only way to do this is by engaging in a constant, on-going dialogue. The physician-scientists, even at an elementary level, can and must serve as interpreters between the two worlds.

6. How have you been able to balance your clinical responsibilities with your research efforts? Has there been pressure to generate more clinical income of late - and how does one prevent those pressures from overcoming research time?

In the current climate of withering grant supports, creative solutions for financial support are more critical than ever. In academic institutions, a dedicated effort at developing a solid philanthropy base is important. Not only does it provide a bridging fund to sustain a research effort in financially difficult times, but it also serves to free up resources to develop new ideas that may mature into other fundable projects. For translational projects, small business venture grants and contracts can also provide needed financial resources.

7. Where do you think more research efforts should be directed in pediatric urology?

Developing clinically pertinent disease animal models is very much needed in pediatric urology, especially in bladder diseases. A surgically created obstruction, for example, does not provide a relevant setting to test the in vivo significance of the molecular pathways and therapeutic targets.
The Ureter

1. What do you consider the two most major basic science discoveries in pediatric urology in the last 10 to 20 years? How have they shaped clinical management?

In the field of ureter research, major basic discoveries have been made in the understanding of the pathophysiology of vesicoureteral reflux - one of the most common pathological conditions a pediatric urologist is confronted with. And this has not only shaped clinical management, it has changed clinical management completely. The introduction of bulking agents in the use of suburothelial injections at the ureterovesical junction in order to seal this region and to avoid reflux to the upper tract and to protect it from reflux has completely changed almost all algorithms that existed so far for the management of children with reflux.

Basic research in that field revealed new possible underlying pathophysiological mechanisms, such as a deterioration in the muscular coat of the very distal ureter thus leading to incompetence in closing the ureterovesical junction actively and preventing reflux.

2. What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?

More and deeper insight into the microanatomy and microbiology behind different pathological conditions will probably facilitate both basic science and clinical management. But to understand different pathologies, it is necessary to learn how the different structures of the ureter, all the way from the renal pelvis to the bladder, develop under so called normal conditions. This is only possible using modern biotechnologies, nanotechnologies, reproductive technologies and other modalities that we are even not able to think of at the moment. Currently basic researchers are starting in that field to understand about the host defense mechanisms that are responsible to prevent urinary tract infections and thus to rule out children that are at risk for developing upper tract deterioration. The above mentioned strategies may help to come to a much more distinguished and individualized approach.

3. Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?

Pediatric urology is a very young recognized subspecialty. It is inevitable and mandatory that clinicians and basic science researchers are contributing to promote this young subspecialty and bring pediatric urology a step forward. Without the clinical view gained during every day practice, the basic scientist will not be able to understand the clinical problems, and without basic research to rule out possible pathophysiological mechanisms that contribute to different clinical conditions, the clinician will not be able to offer modern diagnostic and therapeutic strategies to the affected children. So research in both fields, clinical and basic science are depending on each other, and only multidisciplinary strategies will help to bring basic research into clinical progress.

4. In 10 to 20 years, how do you envision basic science research will be used in daily pediatric urology practice?

I can envision that hopefully we will be able to sort out who of the many refluxing children is at risk for recurrent febrile urinary tract infections and subsequently renal deterioration and who really needs to be treated. Currently we are treating definitively too many children with antibiotic prophylaxis, subureteral injections or even open surgery because we fear possible kidney damage. And the major goal is to preserve renal function and to avoid further deterioration. So optimistically, modern technologies will be available for daily clinical and routine practice to come to an individualized approach in the treatment of different pathological conditions.

5. Some say there is a chiasm between the knowledge of the basic science researchers and most pediatric urologists. How can we eliminate this chiasm?

There is definitively an existing chiasm between the knowledge of basic science researchers and many pediatric urologists. Many researchers are working without connection to clinical units. On the other hand they are also performing basic research which has absolutely no input for the pediatric urologist because of the lacking link between them and those who are dealing with the real problems in every day clinical life. I guess that only strong interaction between basic research institutions and clinical units will help to eliminate this problem. Therefore, it is compulsory that pediatric urologist run through a research department during their training. Both sides will profit from this interface.

6. How have you been able to balance your clinical responsibilities with your research efforts? Has there been pressure to generate more clinical income of late - and how does one prevent those pressures from overcoming research time?

In an academic hospital it is an every day struggle between the tremendous amount of routine work load on the one hand and the possibility to find space and time to do research. Administration is putting a lot of pressure to generate more clinical income but we have to tell them that without basic research, development of new diagnostic and therapeutic strategies it will be impossible to generate any income in the long run, because others will do it and patients do move a lot and have much more information about different approaches than previously. Internet has changed a lot of things and patients are looking for that information actively and sort out upfront where they are going.

7. Where do you think more research efforts should be directed in pediatric urology?

Since pediatric urology is such a young recognized subspecialty, there is a huge amount of work that has to be done. There is not a single field within pediatric urology that has solved all the underlying pathophysiological mechanisms behind the different conditions. Additionally most of the diagnostic and therapeutic algorithms that we are using today have to be questioned since there is a tremendous lack of evidence based data that we can really rely on.
**The Testis**

1. **What do you consider the two most major basic science discoveries in pediatric urology in the last 10 to 20 years? How have they shaped clinical management?**

   a) In my own area of research the main basic science advance in the last 20 years was the discovery of Sry gene in 1990 (Sinclair et al, 1990), [who now works in my own institute and collaborates in our management of gender disorders]. This provided the first step in understanding the genetic switch controlling sexual differentiation in the embryo.

   Sry was a gene in the sex-determining region of the Y chromosome that was found to trigger testicular development in males. At the time there was euphoria in molecular biology, as sexual development was presumed to now be easily understood. However, despite the realization that embryonic development is exquisitely complex, and even now only a handful of other genes involved have been identified, this discovery changed the way babies with disorders of sexual development (DSD) were managed. Our diagnostic approach to these children is now firmly based on genetic analysis as well as hormone levels.

   The current state of the art in this area is well described in a recent review of Wilhelm and Koopman (2006) that I recommend to urologists who care for babies with DSD.

   b) The second major basic advance in testicular biology was the discovery of insulin-like hormone 3 (Ins3), and its role in the first phase of testicular descent. Ins3, an analogue of insulin, was previously called relaxin-like factor (RLF), and was known to be present in the testis, but with unknown function. Knockout mice with a mutant Ins3 gene, however, had interruption of the transabdominal phase of descent and absence of the gubernacular swelling reaction. The gene was found about the same time by labs in Texas and Holland (Zimmermann et al, 1999; Nef and Parada, 1999), and its discovery triggered vigorous research (Adham and Agoulnik, 2004). The full role of Ins3 in sexual development remains to be elucidated, but only a few children with intraabdominal testes have mutations in the gene (Baker et al, 2002).

   Both these molecular discoveries highlight one of the main areas of advancement to be expected in understanding genital anomalies in the near future.

2. **What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?**

   Three different areas spring to mind in response to this question, arising from completely different parts of science.

   a) One area completely outside biology which promises much change is in the physics of ultrasound and magnetic resonance imaging. These basic sciences could deliver major advances in imaging, allowing changes in antenatal diagnosis as well as in the anatomical understanding of anomalies.

   b) Certainly molecular biology, one of the engines of scientific advancement at present, will continue to find new genes involved in testicular development, as well as other areas of sexual differentiation, which should impact on screening and understanding of DSD.

   c) Meanwhile, the unraveling of the molecular pathways in normal and abnormal development is very likely to lead to new (and unexpected) treatments, such as the use of folate supplements to prevent neural tube defects. In my own area of research, for example, the finding that the neurotransmitters, calcitonin gene-related peptide (CGRP) can cause inguinal hernia closure suggests that herniotomy may not be needed in the future (Hutson et al, 2000).

3. **Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?**

   With the expanding knowledge base in medicine, we need to develop teams of people with complementary expertise, as it is no longer possible for groups to have all the skills required. We urologists need to team up with molecular biologists, all biologists and/or embryologists, depending on the area of research. Such a team would have the link to important clinical problems (which basic scientists often lack), as well as the resources to address the research questions.

   In some centers, the paediatric urologist’s role in the team will be to provide clinical samples for analysis or access to patients for potential clinical trials. However, the most productive circumstance may be as the senior clinical investigator, driving the research with the help of the basic science team.

4. **In 10 to 20 years, how do you envision basic science research will be used in daily pediatric urology practice?**

   In the near future an increasing number of children will be enrolled in prospective data bases to provide both the broad epidemiological data about different anomalies, as well as the specific information about rare variants. These 2 aspects will enable a 2-pronged attack on genetic links to anomalies, particularly disorders of sexual development with incomplete virilization and severe hypospadias. The rare “experiments of nature” provide molecular clues while the population-wide review (linking information from many units) can overcome the low numbers in any one centre, which is the key problem in paediatrics preventing introduction of evidence-based practice.

5. **Some say there is a chiasm between the knowledge of the basic science researchers and most pediatric urologists. How can we eliminate this chiasm?**

   The key to overcoming this barrier is to recognize that the 2 groups speak different languages – what is needed is the interpreter. What form this person should take will vary in different places, depending on local circumstances, although here are some simple suggestions:

   a) Regular interdisciplinary meetings.

   b) Employment of a junior clinical fellow with basic science training to translate for the rest of clinical staff.

   c) Rotation of junior clinical fellows through basic science departments for exposure to research problems, scientists and their technology, so that they have made the links which can be maintained after they return to clinical work.

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d) Establishment of a committed research leader in each clinical department, so that clinicians who are intimidated by basic scientists can interact with a surgeon-scientist instead.

e) Improve the basic science opportunities for future paediatric urologists early in their training before they get caught up in clinical work.

f) Honorary appointments in local university departments.

g) Encouragement of sabbatical leave in local university department.

6. How have you been able to balance your clinical responsibilities with your research efforts? Has there been pressure to generate more clinical income of late - and how does one prevent those pressures from overwhelming research time?

I was fortunate early in my career in that I had a year as a research fellow during my surgical training (with Robert Fowler as my supervisor). This exposed me to the excitement of research and opened different career options. After completing my surgical training I spent 3½ years in full time research, 3 of which with Pat Donahoe in Boston. On return from overseas I had a scholarship that allowed me to spend the first year establishing my laboratory. After this training it became clear to my seniors that I was serious about research and so I was given a ½ clinical/½ research appointment, which effectively I still have. This enabled me to maintain significant personal research effort despite mounting clinical and administrative pressures. Of course, I was not exposed to the income-generating pressures faced by American surgeons, but, not surprisingly, my salary was still considerably less that the income of my colleagues in private practice.

The funds for my research salary come from the Royal Children’s Hospital Foundation (and hence private donations) rather than the clinical budget. This seems to be a great model for other institutes, many of which have independent research institutes with separate funds.

The key to preventing clinical pressures overwhelming research output is to have separately funded research time. This needs to have research performance standards to keep people productive, as long as this is balanced by a high enough salary level to encourage the right people to stay in research.

7. Where do you think more research efforts should be directed in pediatric urology?

Paediatric urologists have a deeper understanding of urological embryology and anatomy than anyone else in medicine, and hence bring special skills to the research world. In my view we should capitalize on these strengths and concentrate our efforts in the understanding of normal and abnormal urogenital development, using the full range of biomedical research approvals available. These range from microarray analysis through to fetal and neonatal post-mortem dissection, as well as experimental study of relevant animal models.

Alternative strategies include development of new surgical approvals to old problems, but these are more uncertain of success, as the problem itself can change suddenly if fashions or technology change. I think one of the key places for increased effort is the establishment of large tissue banks and multi-unit data bases to overcome the low frequency of index anomalies.

References


The Penis

1. What do you consider the two most major basic science discoveries in pediatric urology in the last 10 to 20 years? How have they shaped clinical management?

UCSF has a rich tradition in translating anatomical studies of the urinary tract to clinical application. For example, groundbreaking work by Drs. Emil Tanagho and Tom Lue has directly influenced the surgical approach to the penis, ureterovesical junction and bladder neck. Specific procedures have been developed from these anatomical studies to treat bladder extrophy, incontinence, vesicoureteral reflux, erectile dysfunction and Peyronies disease. Anatomical studies in conjunction with physiology have lead to an understanding of the mechanism of micturition resulting in the groundbreaking work that founded the field of neuromodulation. This rich tradition at UCSF has been the catalyst for further anatomical studies on normal penile and clitoral anatomy and the anatomy of hypospadias.

Histologic analysis of human fetal specimens has led to modifications in surgical techniques in hypospadias surgery, specifically, the correction of penile curvature by dorsal midline plication at the 12 o’clock nerve free zone. Understanding neuronal distribution has also been germane for the surgical treatment of patients with congenital adrenal hyperplasia and other disorders of sex development. The basic surgical principle that the nerves should not be disturbed has allowed the translation of anatomical studies to clinical practice.

Another important concept that is germane to understanding hypospadias, which is the second most common congenital anomaly in children, is the impact of environmental agents or endocrine disruptors on normal genital development. It is now clear that the incidence of hypospadias over the last three decades has increased. This cannot be explained simply by genetics implying that exogenous factors such from the environmental are responsible. Scientific studies, specifically using the mouse model have shown that the genital tubercle (developing phallus) is quite sensitive to a number of environmental agents. Furthermore, data suggest a genetic susceptibility with the concept that patients with specific genotypes, if exposed to environmental agents, are more likely to develop hypospadias. Although we are hard-pressed to devise an in utero treatment for hypospadias at this time, knowing that specific genotypes in conjunction with specific environmental agents may cause congenital anomalies could lead to a preventative program, thereby decreasing the incidence of hypospadias.

2. What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?

Understanding how cells communicate and interact will be critical to developing future therapeutics for pediatric urologic diseases. This is a tried and true paradigm in medicine, which has proved to be successful in respect to translational research. For example, in respect to the penis, a better understanding of the mechanism of erection has revolutionized the treatment for erectile dysfunction. This has lead to treatment with papaverine, prostaglandin, phen tolamine, and now a new class of medications, PDE 5 inhibitors. I can envision this approach being used to understand, for example, the ideology of smooth muscle hypertrophy/bladder fibrosis, hypospadias and in the future, even cancer.

3. Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?

I feel strongly that physician scientists in conjunction with basic scientists and clinicians will advance the field of pediatric urology. For example, our most common disease process, urinary tract infections and vesicoureteral reflux, which is ubiquitous to all our practices, has little evidence-based support for our present treatment and therapies. Our community can participate by multi-institutional studies and careful prospective evidence-based research projects. Pediatric urologists in both the university and community should collaborate by providing clinical data, tissue, blood, and/or urine specimens in a prospective fashion for outcomes studies and genetic research.

4. In 10 to 20 years, how do you envision basic science research will be used in daily pediatric urology practice?

In the future, we will be genotyping our patients to look for susceptibility for specific diseases. Genotyping may predict prognostic outcomes and direct treatment options. We are already seeing this in the field of oncology where chemotherapy is now being tailored to the genetic expression pattern of specific cancers.

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1. What do you consider the two most major basic science discoveries in pediatric urology in the last 10 to 20 years? How have they shaped clinical management?

Tissue engineering research in urology is still in a nascent stage, as is the entire field, and has not seen “major basic science discoveries”. However, as surgeons at the forefront of innovative technology, urologists have adopted the use of tissue substitutes as part of routine surgical practice (such as human cadaveric dermis, porcine small intestinal submucosa). There is also awareness of the need for bladder substitutes, as well as the feasibility of such research efforts. Diverse research groups, such as materials scientists, polymer chemists, biomedical engineers, nanotechnologists, and cell biologists are collaborating in joint research which should make such discoveries possible in the next 10 to 20 years.

2. What basic science investigations do you feel hold the greatest potential to shape clinical practice in the future?

In general, research about common problems is likely to have the widest impact on clinical practice. In pediatric urology, one such area is urinary tract infections and reflux. In our own practice, reconstruction and tissue replacement are likely to have a major effect. Hence areas of interest are biocompatible materials, smart polymers, and the basic science of cell survival and differentiation, with a view to organ and tissue formation.

3. Most pediatric urologists do not have facilities for basic science research. How can these pediatric urologists aid the physician scientists/basic science researchers?

It would be useful to form “focus groups”, through the SPU, AAP, SFU etc, aimed at bringing pediatric urologists with similar interests together. The discussions can be continued through internet based message boards or email groups. This can be an avenue for those who are interested (but without their own “labs”) to follow the research, as well as to contribute ideas. This will also help younger pediatric urologists, just out of fellowships, to find suitable mentors.

(continued on next page)
4. In 10 to 20 years, how do you envision basic science research will be used in daily pediatric urology practice?

As in other fields of medicine, there will be more of a “tailored approach” based on risk assessment for most of the common diseases treated, as well as malignancies. For example, with reflux, there should be enough information available (both genetic and UTI susceptibility), to determine the need for antibiotics or other intervention. Tissue engineering advances should leave us with several reconstructive options for both renal and bladder replacement.

5. Some say there is a chiasm between the knowledge of the basic science researchers and most pediatric urologists. How can we eliminate this chiasm?

This is a common problem across disciplines and not confined to pediatric urologists. This can only be addressed by more dialogue between the clinicians and researchers, developed over time. The trend towards more emphasis on translational research or research collaborations between clinicians and scientists is an encouraging one. One of the advantages of being part of an adult urology department is the availability of a much larger group of investigators with varied interests.

The most important factor is the commitment from the leadership of the department/division, and the institution, to foster an appropriate environment to allow research faculty to thrive, especially in the first 3 to 5 years. An appropriate mentor should be available, and would greatly facilitate this process. With NIH funding at low ebb, we have turned to private philanthropy to bridge the gap, and this has been helpful in getting diverse projects off the ground.

6. How have you been able to balance your clinical responsibilities with your research efforts? Has there been pressure to generate more clinical income of late - and how does one prevent those pressures from overcoming research time?

There always seems to be an erosion of research time with every passing year as one’s clinical practice gains momentum. Not to mention the subtle pressures that even large academic centers are under, to generate more clinical income, leading to ever increasing emphasis on clinical work. I have resorted to mostly using personal time (evenings and weekends) to make up for lost research time. My practice has also evolved to more of an outpatient type surgical practice or minimal inpatient stays except for the major reconstructive procedures. With an efficient nurse who handles most phone calls and prescription requests, this helps to save time that can be directed towards research.

The most important factor is the commitment from the leadership of the department/division, and the institution, to foster an appropriate environment to allow research faculty to thrive, especially in the first 3 to 5 years. An appropriate mentor should be available, and would greatly facilitate this process. With NIH funding at low ebb, we have turned to private philanthropy to bridge the gap, and this has been helpful in getting diverse projects off the ground.

7. Where do you think more research efforts should be directed in pediatric urology?

I believe our highest yield will come from studies of the embryology of the genitourinary tract, hormonal influences on the development of external genitalia, tissue engineering, genetics of reflux and hypospadias, and UTIs.
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Guest Editor: Linda A. Baker, M.D.

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