SSMR NEWS

October *Society for the Study of Male Reproduction* 2006

President's Message

Jon L. Pryor, MD, PhD

A warm welcome to SSMR members. We are coming off of a great 2006 SSMR meeting in Atlanta, which will be highlighted in this issue of SSMR News, and we have much to look forward to in the upcoming 2006 American Society of Reproductive Medicine (ASRM) meeting and next years 2007 SSMR meeting, both of which will be previewed in SSMR News. In this newsletter we will also announce the recent election results for the SSMR Board of Directors and discuss some upcoming issues.

We begin with the 2006 SSMR meeting held on Saturday, May 20th, 2006 in Atlanta that was chaired by Robert E. Brannigan, M.D., Assistant Professor at Northwestern University. Dr. Brannigan's theme for this year's program was "The Excurrent Ductal System: Pathway to Parenthood." It was an outstanding program with talks by Drs. Terry T. Turner on the anatomy and function of the epididymis, Peter Chan on epididymitis, Thomas F. Kolon on congenital epididymal abnormalities, Anthoney J. Thomas on vasal and epididymal surgery, Paul J. Turek on ejaculatory duct obstruction, Nancy Brackett on fertility in the spinal cord injury patient, and Stanley E. Althof on ejaculatory dysfunction treatment. A summary of this meeting follows in this newsletter. Many thanks go to Dr. Brannigan for his efforts that culminated in a great meeting. The celebratory SSMR banquet was held that night at Ruth's Chris Steakhouse and it sounds like everyone had a great time.

The SSMR banquet marked the end of Dolores J. Lamb, Ph.D. as President of the SSMR. Dr. Lamb guided us through the year that culminated with a wonderful program and banquet. We are thankful for all the work she has put into the society and I will look to her for advice as I ascend to the Presidency. The results of the election held earlier that day are Robert E. Brannigan as treasurer and Peter Chan as member-at-large. Congratulations to these new members and many thanks to those who ran and were not elected. I personally know that everyone who was nominated was outstanding and would have done a great job. We are lucky to have a deep bench of leadership in this society and those with a deep sense of purpose and self confidence who run for election when nominated, knowing that they may lose.

The ASRM meeting will be held in New Orleans October 21-25, 2006. A schedule of male infertility talks and events at the ASRM are previewed in this newsletter. The 2007 AUA meeting will be held in Anaheim, California from May 19th – 24th, 2007. Dr. Raymond Costabile, M.D., University of Virginia, is the program chair for the SSMR meeting which will be held on Saturday, May 19th, the opening day of the AUA. The title of that meeting is "Fine Wine or Wrong Time: Infertility in an Older Population Desiring Children." Dr. Costabile discusses the program in more detail in this newsletter. I know the program will be both practical and will contain new material that will make it a great learning opportunity for all of us. Aaron Spitz, M.D. is the local arrangements chair who is responsible for making sure we have a good venue and time at the banquet.

Harris M. Nagler, M.D., as Development Chair, has been working with Sue O'Sullivan and Donna Kelly from WJ Weiser and Associates, the group that manages SSMR. Despite a very challenging environment for fundraising with new rules and regulations for pharma, Dr. Nagler has managed to attain an 18% increase in fundraising over last year. This is truly remarkable and we are very grateful to Dr. Nagler. The SSMR industry partners who contributed to our society include GlaxoSmithKline/Schering Plough, Sigma-Tau Pharmaceuticals, Sexual Medicine Society of North America, Coast Reproductive, Pfizer, Surgical Specialties Corporation, and California Cryobank. Thanks to all these contributors that allow us to have such a great meeting. Dr. Nagler has started a Nurses Traveling Fellowship for 2007; this was initiated with a grant from Coast Reproductive. Please look for the details on this so we can support and encourage more nurses to attend the SSMR and AUA. Also, if you have any contacts for fundraising, please contact Dr. Nagler, or Sue or Donna at WJ Weiser and Associates.

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There are a few miscellaneous issues of note. Our vice president, Dr. Jay Sandlow, is looking into working on vasectomy guidelines. The SSMR secretary, Dr. Stan Honig is the head of our membership committee. There is a shortage of knowledgeable physicians in male reproduction, so if you know of any practicing urologists, nurses, residents, or others who want to join our society and learn more about male reproduction and related topics please contact Dr. Honig. Finally, voting for board members will be done on-line next year.

So many thanks again to all those who make the SSMR happen. If you have any issues you want us to consider, feel free to contact me. Enjoy the rest of the newsletter.

Jon L. Pryor, M.D., M.B.A.
President, SSMR ⌘

2006 ASRM Events of Interest

ASRM Annual Meeting | October 21-25, 2006 | New Orleans, LA

SUNDAY, OCTOBER 22, 2006

POSTGRADUATE COURSES:

8:00 a.m. – 5:00 p.m. Course 15: Androgens In Men And Women: Function And Dysfunction
Developed in Cooperation with the Society for Male Reproduction and Urology (SMRU)
Faculty:
Rebecca Z. Sokol, M.D., M.P.H., Chair
Glenn D. Braunstein, M.D.
Marilyn Y. McGinnis, Ph.D.

8:00 a.m. – 5:00 p.m. Course 19: Male Contraception: Past, Present and Future
Developed in Cooperation with the Contraception Special Interest Group (CSIG)
Faculty:
Michael A. Thomas, M.D., Chair
Kurt T. Barnhart, M.D., M.S.C.E.
Diana Blithe, Ph.D.
Christina C. L. Wang, M.D.

MONDAY, OCTOBER 23, 2006

12:15 p.m. - 1:15 p.m. INTERACTIVE SESSION
The Fetal Basis of Male and Female Reproductive Dysfunction
Society for Male Reproduction and Urology
Chair: Susan Benoff, Ph.D.
Speakers: Gail Prins, Ph.D., Hugh S. Taylor, M.D.

12:15 p.m. – 1:15 p.m. Round Table Luncheons

- M18. Y Chromosome Microdeletions: How Do They Affect Prognosis? Carin V. Hopps, M.D.
- M19. Varicocele: Red Flag or Red Herring? Marc Goldstein, M.D.
- M20. Ejaculatory Dysfunction. Wayne J.G. Hellstrom, M.D.
- M21. Non-obstructive Azoospermia: Fresh vs. Frozen? Craig S. Niederberger, M.D.
- M57. Premature Ejaculation. John P. Mulhall, M.D.
- M58. Microsurgical Techniques of Vasoepididymostomy. Joel L. Marmar, M.D.
- M61. Outcomes of Varicocele Repair. Harris M. Nagler, M.D.

1:30 p.m. – 2:15 p.m. Plenary Session
American Urological Association Bruce Stewart Memorial Lecture
"The Future of Reproductive Medicine: Genetics, Economics, Politics"
Lawrence S. Ross, M.D.

3:30 p.m. – 5:30 p.m. Concurrent Sessions
The Society for Male Reproduction and Urology Abstracts

5:00 p.m. – 5:30 p.m. SMRU Mini-Symposia
Russ Hauser, M.D., M.P.H.
"Exposure to Endocrine Disruptors on the Etiology of Male Infertility"

6:00 p.m. – 7:30 p.m. Poster Presentations/Reception

TUESDAY, OCTOBER 24, 2006

12:15 p.m. – 1:15 p.m. Interactive Sessions
Surgical Therapy of Male Infertility: Indications and Outcomes
(Varicocele, Vasectomy Reversal, Sperm Retrieval)
The Society of Reproductive Surgeons
Chair: Peter N. Schlegel, M.D.
Speakers: Marc Goldstein, M.D., Larry I. Lipshultz, M.D.

12:15 p.m. – 1:15 p.m Roundtable Luncheons

- T15. Sperm Processing and Reproductive Options in the Neurologically Impaired Patient. Nancy L. Brackett, Ph.D.
- T16. Sperm Retrieval in Nonobstructive Azoospermia. Paul J. Turek, M.D.
- T17. Reproductive Toxicants and Spermatogenesi Susan H. Benoff, Ph.D.
- T18. Genetic Evaluation of the Infertile Male. Robert D. Oates, M.D.
- T19. Nutrition and Male Infertility. Antoine Makhlouf, M.D., Ph.D.

PRESERVATION OF FERTILITY

- T40. Fertility Preservation: Ethical and Medical Aspects. Lynn M. Westphal, M.D.

- T41. Preservation of Fertility in Men. Herman Tournaye, M.D., Ph.D.

1:30 p.m. – 2:15 p.m. Plenary Session
CFAS John Collins Lecture
"Sperm DNA Damage and Male Infertility"
Armand S. Zini, MD

3:00 p.m. – 3:30 p.m. The Society for Male Reproduction and Urology Business Meeting

3:30 p.m. – 5:30 p.m. Concurrent Sessions
Male Reproduction and Urology Abstracts

5:00 p.m. – 5:30 p.m Mini-Symposia
Mark Sigman, M.D.
"Testing for Sperm DNA Integrity"

6:00 p.m. – 7:30 p.m. Poster Presentations/Reception

WEDNESDAY, OCTOBER 25, 2006

12:15 p.m. – 1:15 p.m. Interactive Sessions
Controversies in the Treatment of Male Infertility: When to Treat and When to Send for ART
Society for Male Reproduction and Urology
Chair: Harris M. Nagler, M.D.
Speakers: Robert D. Oates, M.D.,
Richard J. Paulson, M.D

12:15 p.m. – 1:15 p.m. Roundtable Luncheons

- W13. Varicocelectomy versus Embolization: A Comparative Look at Treatment Options and Outcomes. Robert E. Brannigan, M.D.
- W14. Optimizing Microtese Outcomes. Peter N. Schlegel, M.D.
- W15. Establishing a Sperm Bank. Cappy M. Rothman, M.D.
- W16. Medications That Impair Male Reproduction. Mark Sigman, M.D.
- W17. Methods for Testing Sperm DNA Integrity. Ashok Agarwal, Ph.D.
- W54. Acute Ejaculatory Dysfunction on the Day of Oocyte Retrieval. Stanton C. Honig, M.D.

1:30 p.m. – 2:15 pm. Plenary Session
SSR Exchange Speaker
"Profiling Gene Expression in the Testis"
Michael Griswold, Ph.D.

3:00 p.m. – 5:00 p.m. Concurrent Sessions
Male Reproduction and Urology Abstracts

4:30 p.m. – 5:00 p.m. Mini-Symposia
Dolores J. Lamb, Ph.D.
"Everything the Reproductive Specialist Wants to Know About Molecular Biology Techniques, but is Afraid to Ask"⌘

2006 SSMR Annual Program

"The Excurrent Ductal System: Pathway to Parenthood"
Saturday May 20, 2006
Summarized by Robert Brannigan, MD

The 2006 SSMR Program featured seven speakers addressing various aspects of the excurrent ductal system. The role of the excurrent ductal system in male reproductive health is essential but sometimes overlooked. As we proceed forward in this era of molecular medicine, where assisted reproductive techniques often overshadow other therapeutic modalities, it is important to revisit the male and examine new and exciting developments which offer promise toward optimizing male reproductive potential.

"The Epididymis: A State-of-the-Art Overview of Normal Anatomy and Function"
By Terry T. Turner, Ph.D.

Dr. Turner's talk provided a thorough and clinically applicable review of normal epididymal anatomy and function. He explained that the epididymis is embryologically derived from the mesonephric duct. It becomes a single, coiled tube which transports sperm from the testes to the vas deferens and urethra. He stated that the epididymis is divided into three regions, the caput (head), the corpus (body), and the cauda (tail). He added that the proximal caput epididymis is actually efferent duct tubule, and that true epididymal tubules are not present until the mid-caput region.

Dr. Turner next detailed the interdependence between the testis and the epididymis in generating a fertile ejaculate. The testis produces androgen and sperm, and it relies on the epididymis for sperm maturation and transport. The epididymis, an androgen dependent organ, absorbs testosterone via both the vasculature and the luminal compartment. Testosterone is then converted to dihydrotestosterone (DHT) by 5-alpha reductase, an enzyme located in the epididymal epithelium. DHT then binds to the intracellular androgen receptor, and this complex travels to the nucleus, binds to the promoter regions of genes with the Androgen Receptor Element (ARE), and drives gene transcription.

Dr. Turner next discussed the four key functions of the epididymis:

1. Sperm concentration
- 90%-95% of fluid leaving the testis is reabsorbed by the time the sperm reach the proximal caput.
- Most fluid reabsorption is by efferent ducts, which are of meso nephric tubule origin. The remaining fluid is reabsorbed by the epididymis ofmesonephric duct origin.

2. Sperm transport
- Sperm transport results from hydrostatic pressure driving fluid distally and proximal-to-distal peristaltic waves down the epididymal tubule.

- Sperm transport through the human epididymis is relatively rapid (2-6 days versus 10-15 days in most other species studied).
- More rapid transit occurs with higher sperm output by the testis.

3. Sperm maturation

- Sperm maturation increases in the mammalian epididymis as evidenced by:
  - A. Increased sperm motility (tail/metabolism maturation)
  - B. Increased zona pellucida binding (sperm membrane maturation)
  - C. Increased egg membrane binding (sperm membrane maturation).

4. Sperm storage

- Sperm storage occurs in the cauda epididymis and the convoluted vas deferens
- Over 50% of the sperm in the human epididymis are in the cauda awaiting ejaculation.
- Extended periods of time between ejaculations are detrimental to ejacu late quality.

Dr. Turner next turned to the issue of future directions for research. Basic science efforts are currently aimed toward gaining an improved comprehension of epididymal regulation of gene expression and cell signaling. A better understanding of these three processes will have potential clinical relevance for:

1. Contraception
2. Cryptorchidism
3. Epididymitis

Dr. Turner finished his lecture with an eloquent description of the segmental anatomical and physiological nature of the epididymis. Epididymal gene expression follows this same pattern, the changing microenvironment along the course of the tube necessary to enable sperm maturation and motility.

In conclusion, Dr Turner laid the foundation for the following speakers in his outstanding, state-of-the-art lecture.

"Epididymitis and Other Inflammatory Conditions of the Male Excurrent Ductal System"
By Peter Chan, M.D.

Dr. Peter Chan, the next speaker, addressed the issue of epididymitis and other inflammatory conditions in the male excurrent ductal system. He stated that epididymitis is a significant public health concern because:

- There are 500,000-600,000 cases of acute epididymitis per year
- Epididymitis is one of the most common reasons for days lost from work in men (Both in military and civilian life)
- 20% of Urological admissions in the military are due to epididymitis.

Dr. Chan explained that bacterial infections are the most common cause of epididymitis, and that the pathogens affecting adults are different than those affecting children.

Sexually transmitted diseases are a major factor in adults, and the incidence of STD's is rising despite awareness of HIV. He noted that the likely explanation is the younger age at which people become sexually active, the later age that most people marry, and the high divorce rate. All of these factors, in aggregate, favor higher numbers of sexual partners and a higher risk of contracting STD's.

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the most common pathogens for adult epididymitis, and less common causes include *Ureaplasma, E. Coli, Enterococus, and Pseudomonas.* E. Coli is rare in young, heterosexual men; however this organism is more common in men engaging in anogenital intercourse and also in older men. These infections are more prevalent in older men due to bladder outlet obstruction causing higher voiding pressure leading to reflux of infected urine through the vas deferens into the epididymis. He noted that, alternatively, reflux of sterile urine in this setting can cause a chemical epididymitis.

Dr. Chan next turned his attention to the potential deleterious effect of amiodarone, a class III antiarrythmic agent. Amiodarone can cause a chemical epididymitis, likely related to the fact that the concentration in the epididymis is > 300 times the concentration in the serum. He noted that this is a dose and duration dependent effect, and he added that antiamiodarone antibodies have been identified. These observations support the concept that a chemical or autoimmunue phenomenon is involved in the etiology of amiodarone epididymitis. Iatrogenic epididymitis can also arise from a variety of urological procedures, including instrumentation of the urinary tract, insertion of an indwelling urethral catheter, vasectomy, and prostate surgery.

Dr. Chan then explained the concept of stress-induced epididymitis. This particular theory is controversial, accounting for < 10% of cases of epididymitis in older series. Some more contemporary published series state that up to 70% of men with acute epididymitis reported an immediate/preceding event of heavy lifting. The mechanism behind this stress-induced epididymitis is thought to be reflux of sterile urine into the ejaculatory ducts and vas deferens to the epididymitis. Dr. Chan added that while in theory antibiotics may not be necessary in men with this particular variety of epididymitis, in practice these men should be treated due to the prevalence of infectious epididymitis in this age group. These men should undergo an initial urine culture, with antibiotics and anti-inflammatory therapy then initiated.

Dr. Chan described TB epididymitis. This is believed to be spread hematogenously. TB infectious processes often start at the epididymal tail, and it may present as a solid scrotal mass mimicking testis cancer. A number of fungal and opportunistic organisms are capable of causing epididymitis in patients with HIV or other immune suppressing states (post-transplantation immunosuppression, chemotherapy, and chronic illnesses/malnutrition).
These patients clinically may follow a difficult course, with their infections not responding to antibiotics against chlamydial/gonococcus. Imaging is often required, followed by drainage and special culture media. Infection may progress rapidly in these immunocompromised patients, and close clinical follow-up is essential. Dr. Chan briefly discussed Malakoplakia, Sarcoidosis, Xanthogranulomatous epididymitis, and Brucellosis. All of these conditions can all cause inflammatory pseudotumors involving the epididymis. Finally, he described Behçet syndrome, which is a systemic vasculitis with associated (noninfectious) epididymitis in 5-19% of cases.

Infectious vasitis is a rare condition characterized by benign nodularity of the vas deferens. Idiopathic vasitis nodosa is rare, and it more typically arises due to obstruction of the vas deferens with leakage of sperm and resultant inflammation. Iatrogenic vasitis nodosa is most often seen after vasectomy, it is indeed a very common entity (commonly referred to as a "sperm granuloma"). Dr. Chan cautioned that vasitis nodosa in this setting may reestablish continuity of the vas deferens and act as a channel for sperm to persist in or return to the ejaculate after vasectomy, thus leading to post vasectomy fertility in a small minority of men.

Infectious vasitis is a rare clinical entity, and it is most commonly associated with epididymitis or procedures. Clinically, infectious vasitis may present as a thick mass/cord in groin or spermatic cord. Iatrogenic vasitis may arise from vasal trauma. Interestingly, Dr. Chan noted that only 30 seconds of digital compression results in histological inflammation in all layers of vas, according to a study by *Shandling & Janik, 1981.* Additionally, vasography is a technique commonly performed during vasectomy reversal which may iatrogenically cause vasitis. Vasal inflammation can result, extending far beyond the site of injection. The mechanism is believed to be irritation due to the contrast and the pressure of injection. Vasography was first described by Belfield in 1913, and the technique is more refined now. The elimination of radiographic contrast, or the use of a water-soluble non-ionic contrast (better than oil-based contrast) is believed to minimize the risk of vasitis.

Dr. Chan concluded his lecture by addressing the significance of excurrent ductal inflammation in reproductive health. While a number of studies reveal conflicting evidence as to the impact of inflammation on male infertility, the bulk of the medical literature supports the concept that inflammation of the excurrent ductal system causes:

- "A decrease in the secretory function of the male accessory glands (i.e. seminal vesicles, prostate).
- A decrease in epididymal secretion of factors required for sperm binding capacity.
- The formation of anti-sperm antibodies.
- Direct impairment of sperm function as a result of bacterial activity *(E. coli* only).
- A decrease in the acrosome reaction."

Dr. Chan added that inflammation promotes changes in the excurrent ductal system, potentially leading to fibrosis, stenosis, and obstruction. Fortunately, we are well equipped with microsurgical techniques to correct many of these anatomical changes in the male.

"Congenital Epididymal Abnormalities"
Thomas F. Kolon, M.D.

Dr. Kolon presented an outstanding overview of congenital epididymal anomalies. The first portion of his presentation provided a summary of the various genital ductal appendages, including epididymal appendages, vas aberrans of Haller, testicular appendages, and par- paradidymis appendages. He discussed recent studies that concluded that the occurrence of appendages is variable, and that no significant difference in incidence and distribution of appendages exists between patients with a history of undescended testes and control patients. Dr. Kolon next addressed the topic of testis-epididymis fusion abnormalities. He stated that a closed, partially closed and open processus vaginalis are associated with an abnormal epididymis in 14, 36 and 69 % of cases, respectively (159 consecutive affected patients). In addition, epididymal anomalies are more frequent in this setting in association with undescended (72%) than descended (34%) testes. (Barthold JS and Redmond JF, *J Urol*, 1996). Furthermore, he added that epididymal anomalies occur with undescended testes 32-80% of the time. Anomalies are more common with a patent processus vaginalis, regardless of the position of the testis. Dr. Kolon noted that the link may be that androgenic stimulation may be required for processus vaginalis closure as well as epididymal development. He next presented the Children's Hospital of Pennsylvania series of 1219 patients who have undergone bilateral testis biopsy at the time of orchidopexy. In this group of young males, 73 had complete testis-epididymal nonfusion abnormalities. Of these 73, 47 had unilateral and 26 had bilateral undescended testes. Testis–epididymis complete non-fusion occurs in 6% of patients with undescended testes, and a higher incidence of complete non-fusion is seen in the setting of bilateral undescended testes versus unilateral undescended testis. He noted that his group of investigators had found a 4% incidence of contralateral descended testis non-fusion in pts with unilateral UDT. Upon histological review of the testis biopsies of this group of patients with complete testis-epididymal nonfusion abnormalities and undescended testes, the descended testes were found to have Ad spermatogonia and primary spermatocytes. In contrast, the undescended testes were found to have more gonocytes and no Ad spermatogonia. Dr. Kolon then noted that the testicular histology in undescended testes with complete testis-epididymis non-fusion is not significantly different than histology in undescended testes with normal testis epididymis fusion. He concluded this portion of his talk by adding that patients with complete testis epididymis non-fusion may benefit from ART.

Dr. Kolon next discussed general epididymal changes seen in patients with undescended testes. The ipsilateral epididymis is notable for a decrease in size of the efferent and epididymal ducts compared to age-matched controls. The cryptorchid epididymis grows more slowly during the transition to puberty, and histologically these young males exhibit underdevelopment of the epididymal muscular wall and decreased epithelial height in adults. (De Miguel et al. *J Androl* 2001;22:212-225). Dr. Kolon next related recent insights gained regarding a number of genes involved in epididymal function and development, including HOXA10, HOXA11, INSL2, GREAT, and LGR4.

Persistent Mullerian Duct Syndrome was next addressed by Dr. Kolon. This is an uncommon form of Male Pseudohermaphrodism, resulting in defective production and action of Muellerian Inhibiting Substance. This ultimately leads to retained mullerian remnants. In these individuals, production of and sensitivity to testosterone is normal. The testes of these patients are typically normally differentiated and contain normal germ cells. These testes manifest early abnormal germ cell maturation which may impact future fertility. Additionally, these patients also have ductal derangements. Finally, Dr. Kolon added that due to accompanying Leydig cell abnormalities, pubertal virilization should be followed.

Epididymal Reconstructive Surgery in the Era of IVF/ICSI
By Anthony J. Thomas, M.D.

Dr. Thomas provided an informative and critical analysis of epididymal reconstructive surgery in the era of IVF/ICSI. He began his talk by reviewing studies assessing cost-effectiveness of sperm extraction with IVF/ICSI vs. reconstructive surgery after vasectomy. Two studies were highlighted, one by Drs. Pavlovich and Schlegel and the other by Drs. Kolettis and Thomas. Both studies demonstrated an advantage for surgical reconstruction over sperm extraction with IVF/ICSI in terms of live birth rates and cost per live birth. In particular, increased financial costs associated with multiple fetus pregnancies account for a significant portion of this cost differential. Furthermore, the increased risk of complications such as cerebral palsy must be considered in the context of IVF/ICSI. The risk of cerebral palsy is 5 times higher in twin pregnancies and 17-29 times higher with triplets. For the mother, increased risks in the setting of multiple fetus pregnancies include hemorrhage, preeclampsia, and an increased risk of needing an emergent c-section. Dr. Thomas next addressed the fact that IVF/ICSI has changed in

recent years, with a progressive movement toward transferring fewer embryos. A reduction in multiple fetus pregnancies and the associated complications would be expected to follow. However, a review of the CDC's National Vital Statistics Report revealed an increase in twins and triplets and only a mild decrease in quadruplets born over the past six years. Moreover, these numbers were all higher than the expected or predicted number for each category. Finally, he noted that the SART 2003 data (the last available for analysis) revealed an overall live birth rate of 29.5% per IVF cycle.

Dr. Thomas next turned his attention to vasectomy reversal. He presented several studies detailing success rates vasectomy reversal, including patency (75%-90%) and pregnancy rates (45%-70%). Predictors of success with vasectomy reversal include: obstructive interval, age of spouse, method of anastomosis, same or different spouse, site of vasectomy, presence of sperm granuloma, and need for EV (epididymovasostomy). Dr. Thomas expanded on the parameter "time post vasectomy", noting that in two series the likelihood of needing a unilateral or bilateral EV in patients greater than 14 years post vasectomy was 62% in the Fuchs series and 43% in the Thomas series. Dr. Thomas noted that in men > 14 years post vasectomy in his series, the pregnancy rate was slightly higher if at least a unilateral EV (45% pregnancy rate) was performed vs. bilateral VV being performed (42% pregnancy rate). Dr. Thomas noted that in his unpublished series of 483 patients, the likelihood of needing EV was for 0% (0-< 3 years post vasectomy), 2.6 % (3-8 years post vasectomy), 26.3% (9-14 years post vasectomy), and 43% (> 14 years post vasectomy). He added that in the group of patients undergoing EV/VV, that patency and pregnancy rates were higher when normal sperm were found in the vasal fluid versus the finding of only sperm parts. Next, he addressed the issue of level of EV and patency rates. Briefly, the more distal the epididymal anastomosis, the higher the patency and pregnancy rates. This was particularly notable for noncaput anastomoses in the Cleveland Clinic series. The etiology of obstruction was also found to be a significant predictor of outcomes, with epididymal reconstructive surgery due to vasectomy or inflammatory processes having higher patency and pregnancy rates than reconstructive surgery done for congenital obstruction. The overall complication rate in the Cleveland Clinic series was 2.8%, with most of these being mild and self-limited. The incidence of serious complications was extremely low at 0.5%, consisting of one case of pulmonary embolism and one case of malignant hyperthermia. Dr. Thomas next summarized outcomes with end to side EV's in the Cleveland Clinic series, with patency resulting in 71% and pregnancy resulting in 42% of cases.

Dr. Thomas next asked the question: in 2006, is surgical reconstruction superior to sperm retrieval with IVF/ICSI? Surgery for obstructive azoospermia has the advantage of less multiple fetus pregnancies, with national twinning rates = 0.5-1.0/100, triplet rates = 1/8100, and quadruplet rates = 1/729,000. With ART, twinning rates are 30/100 and triplet rates are > 6-8/100. Surgical reconstruction yields higher pregnancy rates than IVF/ICSI programs overall. Dr. Thomas noted that only in the setting of unilateral pure caput EV, patency and pregnancy rates were 48% and 16 % respectively, and in this group sperm retrieval with IVF/ICSI may outperform surgical reconstruction in terms of outcomes. Reasons for choosing IVF/ICSI over surgical reconstruction may include: age of the female at time of presentation, time to sperm appearance in semen, insurance coverage for ART, tubal occlusion, significant ovulatory dysfunction, caput obstruction, and when the male partner refuses to undergo surgical reconstruction.

Dr. Thomas concluded his lecture by stressing the importance of treating each couple individually and assessing specific outcomes based on success rates for the particular urologist and IVF group actually providing care. Ultimately, the goal is to help a well informed couple make the decision that best suits their needs.

"Ejaculatory Duct Obstruction: Which are the Best Techniques to Diagnose and Treat?"
By Paul J. Turek, M.D.

Dr. Turek began his presentation with a concise review of normal ejaculatory duct anatomy and physiology. Much of the anatomical information discussed by him was drawn from a 1996 Journal of Urology manuscript authored by Dr. Turek and colleagues. The thick muscle wall of the seminal vesicle thins as it courses through the prostate and histologically becomes imperceptible as it courses distally. He noted that the maximum normal size for seminal vesicle width is 15 mm and ejaculatory duct width is 2.3 mm proximally. The ejaculatory ducts are surrounded primarily by collagen, and no muscular valve or sphincter is present at the ejaculatory duct orifice. Urinary reflux is prevented by duct wall coaptation and the acute angle of insertion of the ejaculatory duct into the urethra. Regarding ejaculatory duct physiology, Dr. Turek summarized a study conducted by his group using an in vivo rat model. He noted that seminal vesicle resting compliance, obtained via seminal vesicle filling, is triphasic and very similar to the bladder. The active compliance curve, obtained during nerve-induced contractile response, is biphasic and very similar to the normal heart (Starling curve). Dr. Turek noted that the seminal vesicle acts in many ways like a bladder, and the ejaculatory duct could be considered to be similar to the urethra. He added that this system could harbor abnormalities similar to those underlying bladder dysfunction, with both anatomical and functional abnormalities potentially leading to ejaculatory duct obstruction.

Dr. Turek next discussed semen parameter findings in the setting of obstruction:
Incomplete/Partial Ejaculatory Duct Obstruction: Low or low normal ejaculate volume, low sperm count, low sperm motility, and fructose present.
Complete Ejaculatory Duct Obstruction: Low ejaculate volume, absent sperm and fructose.
Functional Ejaculatory Duct Obstruction: Low ejaculate volume, absent or low sperm count, absent or low motility, and absent or low fructose.

He next presented a very useful algorithm for the diagnosis of ejaculatory duct obstruction (also printed in the syllabus). Briefly, these men typically present with complaints of infertility, hematospermia, ejaculatory pain, or perineal/scrotal pain. The physical exam for these men is usually normal, but may be notable for palpable prostatic cysts or palpable seminal vesicles. Semen testing should be performed, and serum FSH and Testosterone levels should be considered in cases of infertility. Relevant findings on semen analysis include low volume (< 1.5 mL) azoospermia, low volume oligoasthenospermia (< 20 million sperm per mL; < 30% motility), pH < 7.2, and low or absent fructose. During the diagnosis, other conditions to exclude are: collection error, CAVD, vasal agenesis, hypoandrogenism, retrograde ejaculation, and medication effects. TRUS is next performed, with EDO being suspected if dilated seminal vesicles are found (> 1.5 cm width), dilated ejaculatory ducts are observed (> 2.3 mm), or cysts/calcifications/stones

seen in the ejaculatory duct. Dr. Turek added the following caveats regarding TRUS:
"1. Not all men with obstruction will have these findings;
2. Men can have these findings without obstruction.
3. TRUS lacks specificity.
4. No single TRUS finding is pathognomonic."

Dr. Turek described adjunctive tests that can be performed during the TRUS (in the office under IV sedation). These additional tests include: Seminal vesicle aspiration, seminovesiculography (via fluoroscopy or plain film), and chromotubation (with flexible cystoscopy). Positive findings should then prompt TURED with TRUS guidance under anesthesia.

Seminal Vesicle Aspiration Key Points:
- Normal men have < 3 sperm/hpf of SV fluid;
- Obstructed men typically have > 3 sperm/hpf of SV fluid
- Men *should* ejaculate within the 24 hours prior to the aspiration
- Seminal vesicle aspiration does not localize the site of obstruction
- Seminal vesicle aspiration cannot differentiate physical and functional obstruction
- Seminal vesicle aspiration *can* confirm spermatogenesis in some azoospermic men.

Seminovesiculography Key Points:
- Perform by injecting 5-15 mLs of 50% Renograffin
- Need KUB or fluoroscopy to image.
- This does often allow anatomical localization of a point of obstruction.

Seminal Vesicle Chromotubation Key Points:
- This is essentially a "Whitaker test" of the ejaculatory ducts
- Perform TRUS and SV injection of 5-10 mL of a solution com prised of 1:1 saline and indigo carmine or methylene blue.
- The ejaculatory duct orifices are visualized via flexible cystoscopy.
- No need for x-rays.
- Can differentiate physical from functional obstruction.
- Can differentiate unilateral from bilateral EDO

Dr. Turek next discussed the TURED procedure. He does this under TRUS guidance using the brachytherapy stabilizing device with sterile drapes. A 24 French resectoscope is employed to resect the verumontanum until dye is visualized. Hemi-TURED is feasible, and he showed images from several cases demonstrating this technique.

Regarding outcomes, Dr. Turek stated that 60% of affected patients had relief of postcoital pain. 65-94% of patients with complete ejaculatory duct obstruction had improvement in semen parameters postoperatively, and 60-70% of men with incomplete ejaculatory duct obstruction had improved semen parameters postoperatively. Overall complications range from 15-20%, with UTI/Epididymitis being the most common, affecting 5-10% of patients.

Dr. Turek concluded his talk with the following observations:
"Ejaculatory duct obstruction can take several forms.
TRUS findings lack specificity. Adjunctive tests help.
Incomplete EDO is a difficult diagnosis.
With accurate diagnosis, creative surgical approaches are possible."

"Fertility in Men with Spinal Cord Injuries: New Insights"
By Nancy L. Brackett, Ph.D., HCLD

Dr. Nancy Brackett began her talk by providing very important information regarding spinal cord injury (SCI). First, she noted that the population most often affected are young men. In fact, in the United States, 80% of new injuries occur in males, and 62% of these men are 16-35 years old. Similar statistics are observed worldwide. While in women reproductive function is nearly normal after SCI, infertility is a major complication after SCI in men. In fact, 90% of men with SCI cannot father children via sexual intercourse. Fertility is affected by concomitant erectile dysfunction, ejaculatory dysfunction, and semen abnormalities.

Treatments for men with anejaculation include: penile vibratory stimulation (PVS), electroejaculation (EEJ), and sperm retrieval for use with IVF. Advantages of PVS include the fact that it is safe, and it is effective over 80% of the time for injury levels of T10 or above. PVS can be performed at home by most patients. Disadvantages are the relatively low (15%) success rate for men with spinal cord injuries below the T10 level.

Regarding EEJ, it is a safe procedure with costs generally similar to PVS. It is successful approximately 95% of the time. Disadvantages include the startup equipment costs ($21,000), the fact that it is invasive, and the requirement that it must be performed by a trained physician. Additionally, the total motile sperm count is typically lower than with PVS. Finally, surgical sperm retrieval requires no special equipment and may lessen the risk of autonomic dysreflexia in some patients. Disadvantages associated with surgical sperm retrieval include the high cost, the very low total motile sperm count yield, and the fact that this approach commits patients to the highest cost ART.

Dr. Brackett next presented a summary of a recent survey of health providers specializing in reproductive medicine. This group included both reproductive endocrinologists and urologists (3:1 ratio). The investigators found that 63% of those surveyed offer PVS, EEJ and surgical sperm retrieval. Interestingly, 28% of these practioners do not offer PVS or EEJ and use only surgical sperm retrieval for their anejaculatory men with spinal cord injury. Reasons cited for not offering PVS included: not having PVS equipment (45%), not being aware of PVS (39%), not being trained in PVS (39%). Reasons given for not offering EEJ included: not having EEJ equipment (60%), not being trained in EEJ (42%), referral presenting logistical problems (34%). Dr. Brackett noted that by not being offered men PVS and EEJ, these men and more importantly their female partners become committed to IVF with its associated degree of cost and invasiveness.

Dr. Brackett next addressed the issue of semen quality in men with SCI. Macroscopic and microscopic appearances are abnormal, and semen parameters are abnormal. She cited possible lifestyle issues that some investigators believe contribute to the impaired semen quality in men with SCI; these include: scrotal hyperthermia, method of bladder management, infrequency of ejaculation, method of ejaculation, and years post-injury. She noted, though, that mounting evidence suggests that lifestyle issues are not to blame for the low motility commonly seen in men with SCI. Dr. Brackett then referred to a manuscript by Drs. Ohl, Menge, and Jarow showing that abnormal transport and storage of sperm in the seminal vesicles of men with SCI may be at least partly involved. The authors performed seminal vesicle aspiration in men with SCI and found abnormally high numbers of sperm in the aspirates. Dr Brackett also cited data showing that vasal fluid quality, specifically motility and viability, were significantly lower in men with SCI compared to controls.

Compared to able-bodied men, men with a history of SCI have many changes in the seminal fluid including: decreased fructose, albumin, glutamic oxaloacetic transaminase, and alkaline phosphatase. Additionally, chloride and reactive oxygen species are increased in men with SCI compared to able-bodied men. Men with SCI also have increased levels of white blood cells in their semen, including lymphocytes, monocytes, and granulocytes. Furthermore, a number of cytokines have been found in significantly higher concentrations in men with SCI compared to controls. These cytokines include IL6, TNFá, and L1â. Dr. Brackett presented recent work from her group showing a statistically significant increase in sperm motility after treatment with monoclonal antibodies directed against these three cytokines.

Dr. Brackett closed her talk by noting that "progress in treatment of male factor infertility in general has led to a problem for couples with SCI male partners in particular." More specifically, the ejaculates of men with SCI are not being examined as a source of sperm for ART. Dr. Brackett added that surgical sperm retrieval is replacing PVS and EEJ as a first line of treatment for anejaculation. At this time, the majority of centers do not offer IUI to these couples. She stressed that the majority of men with SCI have reasonable yields (in terms of total motile sperm count) with PVS and/or EEJ to facilitate IUI, and IUI should ideally be offered to these couples as a treatment option.

"Ejaculatory Dysfunction Treatment: Counseling, Behavioral Therapy or Medicine"
By Stanley E. Althof, Ph.D.

Dr. Althof commenced his talk by defining ejaculatory disorders, including premature ejaculation and diminished ejaculation disorders (including delayed and retrograde). He presented a number of studies that conclude that premature ejaculation is a very common condition, with prevalence rates ranging from 4-38%. However, there is a puzzling issue, in that a large discrepancy exists between the number of men complaining of this disorder and the number of men seeking treatment. Possible explanations include the following: men are selfish and don't care about this problem, men are too embarrassed to seek treatment, unless pushed by their partner men don't seek treatment, men don't believe that there are effective treatments for this problem. Alternatively, the previously mentioned trials may overestimate of the prevalence.

Dr. Althof next presented the DSM IV diagnostic criteria for premature ejaculation:

- "Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect the duration of the excitement phase, such as age, novelty of the sexual partner or situation and recent frequency of sexual activity.
- The disturbance causes marked distress or interpersonal difficulty.
- The premature ejaculation is not due exclusively to the direct effects of a substance."

Additional considerations in making the diagnosis include:

- Lifelong vs. acquired premature ejaculation
- Generalized vs. specific occurrence
- Psychological or combined psychological and biological factors

Dr. Althof subsequently presented interesting data from a study he published in the J. Sex Med. on Intravaginal Ejaculatory Latency Time (IELT) distributions in men unaffected by premature ejaculation. This revealed:

- Mean IELT = 9.15 minutes
- Median IELT = 7.3 minutes
- Range = 0-53 minutes

This was followed by a presentation of IELT distributions for men affected by premature ejaculation:

- Mean IELT = 3 minutes
- Median IELT = 1.8 minutes
- Range = 0-41 minutes

He then dispelled the common misperception that premature ejaculation decreases in prevalence with age with data showing a steady prevalence with advancing age, even into men's 70's. Premature ejaculation is a significant problem because it commonly affects both the man and his partner. Common deleterious effects on the man include: Significant distress; Erosion of sexual self-confidence, satisfaction and self-esteem; Anxiety, embarrassment and depression; Difficulty in sustaining relationships or reluctance to establish new relationships; and Preoccupation with sexual performance.

Women, too, are effected and may suffer: Anger because the man has not been willing to seek treatment; Burden by some partner's need to give them orgasms through manual or oral stimulation which can lead to performance anxiety, further diminishing their sexual experience; Ambivalence regarding expressing their concerns for fear of injuring the man's already fragile self esteem versus suffering in silence. This condition can further manifest in strain on relationship with a developing mistrust of partner and perception of selfishness in the man, dissatisfaction with the sexual relationship, and an inability or lack of desire to communicate. Additionally, men suffering from premature ejaculation often have difficulty initiating and maintaining relationships.

Premature ejaculation occurs due to multifactorial etiologies, including both biological factors (Evolution, Central 5-HT levels, Sensitivity, Hormones, Penile Sensitivity, Ejaculatory Reflex) and psychosocial behavioural factors (Anxiety, Early Sexual Experience, Psycho-Dynamic, Frequency of Sexual Activity, Sexual Technique, and Context). Seminal emission, ejection and orgasm are all integrated into a complex pattern of copulatory behavior by several forebrain structures which include the medial preoptic area (MPOA), the Nucleus paragigantocellularis (nPGi), the Stria terminalis, the amygala and the thalamus. Several neurotransmitters are involved in these processes. Although the pathways are not entirely understood, we do know that dopamine facilitates sexual behavior/response. Dopamine agonists such as apomorphine and quinelorane facilitate erection and ejaculation whereas dopamine antagonists inhibit sexual responses. Furthermore, dopamine agonist synthesis and/or release are stimulated by testosterone. Dr. Althof added that Nitric Oxide may be a biochemical link or mediator between testosterone and the central dopamine pathways. Work in animal models has revealed that activation of the 5HT2C receptor delays ejaculation in rodents. Furthermore, activation of 5HT1A receptor may speed up ejaculation in rodents. This has led to speculation that in humans, primary premature ejaculation is due to either hypofunction of 5HT2C or hyperfunction of 5HT1A.

Some investigators have postulated that psychological factors may lead to premature ejaculation. These issues include early learned experience, interpersonal conflict, hostility to women, anxiety, performance anxiety, inability to tolerate intimacy, and fear of the vagina.

Pharmacotherapy for premature ejaculation includes the following agents:
- Clomipramine (Anafranil)
- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Sildenafil (Viagra)
- SS-Cream
- Prilocaine-lidocaine cream.

Next, Dr. Althof more specifically reviewed the efficacy of the SSRI class of medications.
Paroxetine > Fluoxetine > Sertraline > Clomipramine > Sertraline > Fluoxetine in terms of increasing IELT. He added that Nefrazadone and Fluvoxamine were not effective in delaying ejaculatory latency. He next highlighted data from work he did with Dr. Jon Pryor on dapoxetine revealing a 3 fold increase in IELT with the 30 mg dose and a 3.7 fold increase in IELT with the 60 mg dose. Questions remain with this class of agents as to whether daily dosing or prn dosing is optimal. Additionally, the question of the need for and efficacy of long term therapy for premature ejaculation remains unanswered. A 1999 study by McMahon et al revealed that IELT with daily dosing was higher than IELT with prn dosing. In May 2006, the FDA issued a warning statement re paroxetine that suicidal behavior and ideation in placebo-controlled clinical trials in adult patients with psychiatric disorders showed a statistically higher frequency of suicidal behavior in those treated with placebo. Dr. Althof noted that the overall number of events is small, and thus the data should be interpreted with caution. New directions for therapy include combination therapy with sildenafil and paroxetine, providing higher IELT's than paroxetine alone. He added that "delaying men's ejaculatory latency with off- label selective serotonin reuptake inhibitors is relatively straightforward, but restoring men's sexual confidence and enhancing sexual relationship satisfaction is more complicated."

Psychotherapy is another approach that provides therapeutic efficacy in men with premature ejaculation. Dr. Althof stated that the aim of psychotherapy is to:
1. Learn techniques to control and delay ejaculation
2. (Re)gain confidence in their sexual performance
3. Lessen performance anxiety
4. Modify rigid sexual repertoires
5. Surmount barriers to intimacy
6. Resolve interpersonal issues (that cause/maintain PE)
7. Come to terms with interfering feelings and thoughts
8. Increase communication
9. Turn conflict and useless friction into intimacy, fantasy and stimulation
10. Minimize or prevent relapse.

A number of studies provide outcomes data for treatment of premature ejaculation with psychotherapy. Masters and Johnson treated a cohort of 186 men with reported failure rates after treatment and at 5 year follow-up of only 2.2% and 2.7% respectively. Other studies include a report by Kaplan revealing that 80% of men were characterized as successful in overcoming rapid ejaculation immediately post-therapy. Hawton, another investigator, reported a 64% success rate immediately post therapy.

Unfortunately, the majority of studies with long-term follow-up document reduced success rates post-therapy, with success rates dwindling to 25% in many series. Factors that lend to successful outcomes with psychotherapy include the quality of the couple's general relationship (in particular the female partner's relationship satisfaction), motivation of the partners (in particular the male), absence of serious psychiatric disorder in either, physical attraction between the partners, and early compliance with the treatment program. Controversy exists, though, as to what constitutes success. Each of the following factors has been purported to constitute success: increased IELT, improved control of ejaculation, improved sexual satisfaction, improved partner satisfaction, treatment satisfaction, and a heightened awareness of arousal.

Dr. Althof next turned his attention to the topic delayed ejaculation. Delayed ejaculation is defined as "the persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity and duration." The disturbance causes marked distress or interpersonal difficulty, and is not better accounted for by another medical condition. Delayed ejaculation may be a lifelong or acquired phenomenon, global or situational, and due to psychological or combined psychological and biological factors. Three separate studies show the prevalence for delayed ejaculation to range between 3% - 8%. A variety of etiological factors may be responsible, including psychogenic, anatomic, infective, endocrine, and medication-related issues. A number of psychosocial factors may also come into consideration, including cultural and religious beliefs, unconscious or unexpressed anger, insufficient sexual arousal, preference for masturbation or an atypical masturbation style, and fear of pregnancy or sexually transmitted diseases. Psychological therapy is based upon the clinician's impression as to whether the delayed ejaculation is due to inhibition, lack of excitement, or atypical masturbation style. A closer look at these patients was undertaken by Dr. Perleman. In his six year retrospective chart review of 90 men, he found a high frequency of masturbation with 35% reporting masturbating = 1 time daily. An additional 25% reported masturbating 6-14 times per month. Furthermore, 40% of these patients also reported an atypical masturbation pattern which is not easily duplicated by the partner.

In some instances, delayed ejaculation is induced by SSRI medications. These effects can sometimes be offset by the addition of the following agents to the medical regimen:
- Amantadine
- Buspirone
- Buproprion
- PDE5 Inhibitors
- Cyproheptadine
- Yohimbine.

Dr. Althof noted that only a few studies exist assessing the efficacy of psychotherapy for the treatment of delayed ejaculation. Masters and Johnson reported an 82% response rate, and Schnellen reported an 81% response rate. Unfortunately, no long term follow up studies have been conducted.

Dr. Althof concluded his talk by noting that there is still a great deal to be learned about ejaculatory disorders. Issues such as pathophysiology, cultural differences, the definition of dysfunction, and efficacy of prn treatment remain to be elucidated and will provide fertile ground for research.

Post-Graduate Course, Sunday, May 21st
Evaluation and Management of the Infertile Male:
What's New and What's Essential?
Chair: Marc Goldstein, M.D.
Faculty: Dominick J. Carbone, M.D., and Jon L. Pryor, M.D.
Summarized by Jon L. Pryor, M.D.

The first talk, by Mark Goldstein, was why evaluate the Infertile Male in the Era of Art? There is a 37 time higher incidence of testis cancer in infertile than fertile men and a 30-100 time higher incidence of genetic abnormalities. Therefore, men need to be evaluated, not just for infertility, but because infertility may be a sign or symptom affecting their overall health. Varicoceles, if present can have an adverse effect on Leydig cell function resulting in low testosterone levels later in life which can result in decreased libido, energy levels, erectile function and osteopenia/osteoporosis. Finally, couples prefer naturally conceived babies.
Anatomy and physiology was the next topic. Key anatomic and physiologic points to remember include the following: (1) Blood supply to the testicle arises from the testicular, the deferential and the cremasteric artery; during inguinal varicocelectomy, the surgeon must remember that there may be 2 or 3 arterial branches at this level. (2) Testicular biopsy should be carried out in the medial or lateral surface of the upper pole, where risk of vascular injury is minimal. (3) Optimal qualitative and quantitative spermatogenesis requires the presence of both testosterone and FSH.

Evaluation of the infertile male was then discussed. The emphasis was that all men from infertile couples need to be evaluated by a detailed history (there are so many questions it's best to have a questionnaire), a targeted physical examination, and two semen analyses. If there are symptoms of an endocrinopathy, oligospermia, or an abnormal scrotal exam, a hormone evaluation is also obtained. Antisperm antibodies can be obtained if there is decreased sperm motility (asthenospermia), sperm agglutination or clumping, an abnormal post-coital test, or idiopathic infertility. There are other tests that can be performed for sperm function, such as the sperm penetration assay, but these are not widespread and in many cases are still in the investigation phase. We then discussed the workup of azoospermia, which is from ejaculatory dysfunction, blockage, or hypogonadism. In all cases make sure a hormone evaluation is obtained. Get a TRUS if you suspect ejaculatory duct obstruction (e.g. pain on ejaculation and/or low ejaculatory volume). If hypogonadotropic hypogonadism is suspected, get a MRI of the pituitary/hypothalamus.

The next lecture was an overall schema on how to categorize patients for treatment. Patients can be placed into one of four categories: normal, specific problem, idiopathic (minor or moderate) or idiopathic (severe) or a non-treatable problem. If the workup of the male appears normal, then focus on the female. Treat specific problems like a varicocele. If idiopathic (minor or moderate) try empirical therapy. If severe or a non-treatable problem, do IVF with ICSI, or adopt or pursue donor IUI.

We then discussed specific medical therapy of endocrinopathies, infections, and ejaculatory dysfunction. It was pointed out that some medications, such as metoclopromide, phenothiazines, and some antidepressants can elevate prolactin levels. Mild elevations of prolactin do not cause infertility and should not be treated. Hypogonadotropic hypogonadism is typically treated with hCG 1500 IU q MWF for six months and if no improvement, add hMG 75IU q MWF. Finally, when treating ejaculatory dysfunction from RPLND or diabetes with sympathomimetics (e.g. imipramine or pseudoephedrine), limit the drugs to ten days to two weeks around ovulation as they cause tachyphylaxis. In addition, if one drug doesn't work, try another sympathomimetic, as it has been clearly shown that patients may respond to one drug and not another.

Next, we discussed surgical therapy of male infertility. 35-40% of infertile men have varicoceles and 10-20% have obstructions. Therefore, over 50% of male infertility are surgically correctable. Microsurgical approaches allow sparing the testicular artery and lymphatics during varicocelectomy, thus virtually eliminating hydrocele and testicular atrophy as complications. Microsurgical repair of vasal obstructions now has patency rates over 90% and pregnancy rates of 80% up to 15 years after obstruction. Repair of epididymal obstructions using new microsurgical intussusception techniques yield patency rates of over 80% and pregnancy rates of 40% in the best of hands. Reversal of vasectomy frequently requires vasoepididymostomy and therefore reversals should be only be done by surgeons who are expert at vasoepididymostomy. Surgical treatment of male infertility is more cost effective than IVF and has comparable or better pregnancy rates. In addition, surgical treatment of male infertility will often upgrade couples from nothing to IVF/ICSI using ejaculated instead of testicular sperm, or from IVF to IUI, or IUI to a naturally conceived pregnancy.

Emperic therapy for male infertility was the next topic. Empiric therapy for male infertility may be divided into hormonal and non-hormonal treatments. Of the former, androgen supplementation, testosterone rebound therapy, gonadotropins, and GnRH therapy are not recommended for idiopathic infertility. Aromatase inhibitors, such as testolactone or anastrozole, may have some benefit in men with impaired testosterone to estradiol ratios. Therapy with clomiphene citrate remains controversial, though it may have some benefit in men with a low normal FSH level. Careful monitoring of individuals on clomiphene is required. Finally, nonhormonal treatments, including kallikreins, bromocriptine, pentoxifylline, and carnitine, have not been shown to be beneficial in randomized, double-blind, placebo controlled trials.

The urologist's role in assisted reproduction includes recognizing appropriate patients to refer for ART and to optimize sperm quality prior to ART. With regards to the latter, numerous studies demonstrate that varicocele repair prior to ART can upgrade sperm quality so that lower cost procedures, such as stimulated IUI, may be pursued rather than ICSI. With regards to the former, relatively clear cut cases best treated with ICSI include failure of conventional IVF, anti-sperm antibodies, and globozospermia. Finally, it is critical that specific patients (see below) undergo appropriate genetic screening prior to ICSI.

Basic genetics of infertility was then discussed. The talk centered around Klinefelters, CBAVD, and microdeletions of the Y chromosome. It was concluded that with IVF and ICSI, we can propagate genetic diseases, both those that cause infertility and other diseases. Even though there is no "cure" for genetic problems, patients want to know if they have a genetic cause for infertility and if it can be passed on to any of their progeny. If a man has less than 5 million sperm per ml, get a karyotype and test for microdeletions of the Y chromosome. If the patient has CBAVD or idiopathic epididymal obstruction, test for CFTR gene mutations.

The "Dos and Don'ts of Infertility" was a lecture to remind urologists of absolutes when treating infertility patients. Both the male and female of infertile couples need to be evaluated. The male should have a history and physical examination and two semen analyses.

Don't indiscriminately get other tests (e.g. scrotal U.S. or TRUS). Biopsy all azoospermic males, but do so only if you can harvest/freeze sperm at the same time for possible future use in IVF/ICSI. Don't do a vasogram at the time of testicular biopsy. Don't treat an infertility patient with testosterone- it's a contraceptive. Finally, practice the 3 C's: close follow-up, collaboration with the obstetrician/gynecologist and andrology lab, and good communication.

Coding for male infertility was the last topic of the course. Never use infertility as a diagnostic code. Infertility is a symptom, not a disease. Use the code for the etiology, physical findings, or pain, such as varicocele (456.4); testicular atrophy (608.3); epididymal cyst (222.3); or sperm granuloma of the vas deferens (608.4) for reversal patients (if present). Dictate your own detailed operative report. If a microscope is used, say so and indicate what magnifications were used. Code for all procedures, e.g. when coding for a testis biopsy to rule-out obstruction: testis biopsy—54505, microsurgical exploration of epididymis—54820 (if you inspected the epididymis under the operating microscope to look for dilated tubules), and code for sperm identification from testicular tissue—89264 (if you look at the tissue yourself under a 400X bench microscope to look for sperm).

Summary of AUA Instructional Course: Vasovasostomy, Epididymovasostomy and Sperm Retrieval Techniques
Course Instructors: Arnold M. Belker, M.D. & Christopher G. Schrepferman, M.D.
Summarized by Christopher Schrepferman, M.D.

Drs. Arnold Belker and Christopher Schrepferman served as co-instructors for the AUA Instructional Course entitled, "Vasovasostomy, Epididymovasostomy, and Sperm Retrieval Techniques." As the senior instructor, Dr. Belker began the course with an in-depth discussion of microsurgical techniques, particularly as they apply to microsurgical vasovasostomy and epididymovasostomy. He began with historical perspective on vasovasostomy, including a brief review of the importance of microsurgical repair when compared to macroscopic reconstruction. He particularly emphasized the importance of a well planned and well organized surgical field and offered a comprehensive review of instrumentation, options for suture placement, and pitfalls to avoid. He showed a number of intraoperative video clips to clearly demonstrate the importance of intraoperative preparation and precise suture placement.

Microsurgical vasoepididymostomy was also discussed, including a historical perspective on previously used techniques as well as recent advances in microscopic technique, including the more recently described intussusception technique and its various modifications. Again, high quality digital video was used to demonstrate precisely for the attendees some of the technical challenges associated with this difficult operation.

Finally, data on outcomes following microsurgical reconstruction were presented, with particular emphasis on expected patency and pregnancy rates. The audience was reminded that precise surgical technique and relatively high surgical volume are necessary to reproduce the high patency and pregnancy rates reported in the literature.

Dr. Schrepferman then spoke regarding sperm retrieval techniques currently available for men both with obstructive and nonobstructive azoospermia, including men with previous vasectomy or failed vasectomy reversal. Dr. Schrepferman emphasized the need for full evaluation by a trained urologist and/or male fertility specialist for patients with obstructive azoospermia in order to determine reversibility of the obstructing lesion. Techniques discussed included MESA, TESA, PESA, and TESE. For men with obstructive azoospermia, intraoperative images demonstrating MESA were provided, and a full digital video of a TESA procedure was presented. The audience was reminded of the importance of cystic fibrosis testing for CBAVD or idiopathic obstructive azoospermia. For men with non-obstructive azoospermia, an intraoperative intraoperative video clip of micro TESE was presented, courtesy of Dr. Peter Schlegel. The importance of obtaining a karyotype and Y-chromosome microdeletion study was emphasized.

Time was reserved at the completion of the course for an active question and answer period. Overall, the instructors felt the course was well-received.

Summary of AUA Instructional Course: Diagnosis and Treatment of Male Infertility
Course Instructors: Larry I. Lipshultz, M.D. and Paul J. Turek, M.D.
Summarized by Stanton Honig, MD

This course was a very thorough review of the clinical issues related to Male infertility directed to the general urologist with an interest in male infertility. The following are highlights of this instructional course:

- coital lubricants affect infertility and should be discontinued or switched to non toxic sperm lubicants
- All exogeneous testosterone (physiologic or pharmacologic) are male contraceptives
- If Clomiphene citrate is recommended for treatment, follow up is nec essary (FSH, testosterone, estradiol, Semen analysis)
- AZFb deletions have shown no sperm present on TESE
- Dr. Lipshultz suggests antisperm antibody testing in cases of : Sperm clumping, isolated defects in sperm motility, abnormal post coital test and unexplained infertility
- WBC's in semen may affect fertility by creating an increased amount of reactive oxygen species, that may result in a direct toxic effect to s perm and/or lipid peroxidation to membrane and DNA damage
- ROS may be scavenged by Vitamins E and C and NSAIDs,
- Low Strict criteria of sperm morphology seems to result in a lower IVF fertilization rates and may be improved by varicocele repair
- DNA damage may be measured in different ways: SCSA, comet, tunel assay.
- Increased DNA fragmentation may result in impaired fertility and may be improved by scavenging of reactive oxygen species, varicocele re pair or use of testicular sperm vs ejaculated sperm (controversial).
- Response to treatment for male infertility should be evaluated EAR LIER- maybe at 60 days due to new basic science data showing shortened transit time in testes.
- For clomiphene therapy, check FSH, T at 4 weeks, SA at 3 months
- Consider using clomiphene citrate in hypogonadotropic hypogonadism as first line therapy prior to hcG.
- Herbal and nutriceutical studies are very controversial and no definitive conclusions can be drawn.
- For Ejaculatory duct obstruction: Paul Turek recommends some form of diagnostic test beyond TRUS (which is very non specific) such as vasogram or seminal vesiculogram.
- Microdissection or FNA mapping may have slightly better success rates with sperm retrieval than standard open TESE.

Plenary Session: Monday, May 22, 2006
Leslie Schover: Parenthood After Chemotherapy
Summarized by Antoine Makhlouf, M.D. and Cathy K. Naughton, M.D.

Leslie Schover provided a succinct overview of the management of fertility in male cancer patients. Using a clinical vignette, she vividly illustrated the anxiety faced by young men grappling with a cancer diagnosis, and how easily the discussion about fertility can "fall through the cracks." In contrast to physicians' belief that cost is the primary barrier to pretreatment sperm banking, patient surveys identified the "lack of timely information" as the leading cause for failure to bank sperm. She stressed the importance of early sperm banking in the newly diagnosed testicular cancer patient, including the option of testis sperm extraction (TESE) at the time of orchiectomy in the 10% of patients who are azoospermic. Because chemotherapy and radiation damage germ cell DNA, she recommends that sperm banking either precedes these treatments, or occurs at least 6 months after therapy.

Beyond the prototypical young adult with testicular cancer, she discussed both older and younger patients who may benefit from fertility counseling. Due to the contemporary practice of earlier PSA testing and aggressive screening combined with the societal trends of delayed fatherhood and second marriages, the stereotypical image of the prostate cancer patient without fertility concerns may be falsely assumed by the treating urologist. Men with fertility concerns electing radical prostatectomy or external beam therapy should bank sperm prior to surgery, while those electing brachytherapy should be counseled that their fertility may be preserved. Furthermore, men on intermittent androgen ablation may regain spermatogenesis during treatment holidays. On the other end of the age spectrum, recent studies from the United Kingdom have addressed the factors affecting the ability of teenagers to provide semen samples for banking. Adolescents as young as 13 years of age were able to bank, provided their questions and anxieties about the collection method were addressed. She acknowledged the need for both parental consent and patient assent in these cases, and suggested the use of electroejaculation at the time of scheduled cancer surgery as an option when age considerations preclude collection by masturbation.
She closed with mention of ongoing research on spermatogonial stem cell transplantation. Cryopreservation of stem cells that may be later reimplanted after chemotherapy promises to preserve a man's ability to conceive naturally, without the need for assisted reproductive techniques (ART). However, at this time, sperm banking followed by ART remains the standard approach to preserve the fertility of male cancer survivors.

Tuesday, May 23, 2006
Poster Session 19: Infertility: Evaluation, Therapy and Basic Science
Summarized by Dolores Lamb, PhD

This session focused on several practical aspects of male infertility diagnosis and treatment, as well as upcoming advances in the basic science arena. Assisted reproductive technologies have changed our ability to treat a variety of male factor conditions. The use of cryopreserved sperm for IVF/ICSI provides a number of advantages for couples seeking to use sperm obtained by testicular sperm extraction with ICSI. Makhloulf, et al showed that the fresh sperm was not superior to the use of frozen sperm for successful fertilization in ICSI/IVF. Although a controversial area, it appears that fresh sperm may not provide an advantage to these couples. Testicular sperm extraction and ICSI is also used for men following secondary infertility due to chemotherapy. For these men (poster #1406) Okada, et al., showed that, the recovery of spermatogenesis is variable, although sperm could be retrieved in more than 40% of men with longstanding azoospermia following treatment and success varied by the drug regime used and whether or not radiation was used as well. Fujita, et al., (poster #1408) report that patients who have failed conventional TESE for non-obstructive azoospermia may still be candidates for testicular microdissection. Measurement of the seminiferous tubule diameter under optical magnification can improve sperm retrieval and minimize the amount of tissue removed (poster #1411, Zohdy) Microdisessection TESE may also have some side effects. Takada, et al. (poster #1409) reported that over the 12-month period following the microdissection procedure, that men had a decreased serum testosterone and increased LH and FSH concentrations, although the clinical significance of the findings for the patients is not clear.

Regardless of the source of sperm for ICSI, embryo quality did not appear compromised (Poster #1412, Borges, et al.,). Men with a normal motile sperm count of more than 20 million and a normal morphology by Kruger's strict criteria did not seem to require ICSI for successful fertilization in IVF. Kolettis, et al., examined the effect of female partner age on pregnancy rates for vasectomy reversal and concluded that if the women were less than 39 years old, pregnancy rates were good following vasectomy reversal. For vasovasostomy Hong, et al., (poster #1417) reported that the use of 8-0 nylon under loupe magnification has a lower success rate and a higher rate of vasal stricture compared to a microsurgical approach using 9-0 nylon.

Libman et al., (Poster #1407) report that bilateral varicocelectomy appears to be superior to unilateral repair resulting in improved semen quality and male fertility potential. Discussion was generated by the report of Marmar and Kessler (poster #1416) that complications could be avoided if a subinguinal microsurgical varicocelectomy and inline vasectomy could avoid the complication of testicular atrophy that can occur. Using some specialized new instruments, the authors report that no change in testicular size or blood flow resulted.

One area of interest and discussion focused around the reproductive tract anomalies that may be present in men with mutations in the CFTR gene that encodes and ion channel associated with cystic fibrosis (poster #1410, Karpman and colleagues). Various diagnostic approaches were compared to identify the mutations and results suggest that the common mutation screen used for cystic fibrosis may miss mutations present in CBAVD patients. Some patients had reproductive tract abnormalities that could be surgically reconstructed by epididymovasostomy.

In the area of basic science, transplantation of spermatogonial stem cells to restore fertility following secondary infertility resulting from chemotherapy has the potential to also transfer contaminating malignant cells despite a cancer cure. Poster #1418 (Fujita,et al.,) showed that flow cell sorting to removed leukemia cells from dispersed testicular cells prior to transplantation did not result in leukemia induction in the recipient. Nevertheless, more studies are required to permit a high degree of confidence that there are absolutely no contaminating cells present before translation to humans. Magnetic activated flow sorting enriched type A spermatogonia and fluorescence

activated sorting and characterized by Shefi, et al., (poster #1421) with the eventual goal of defining the molecular basis of spermatogonial cell differentiation in vitro.

The signal transduction pathways that regulate Sertoli cell function were defined in a series of investigations by Ishikawa and colleagues (posters #1419 and #1420) who defined the prostaglandin and cytokine signal transduction pathways in the Sertoli cell showing an autocrine amplifying loop involving IL1beta mediated by COX2 induction of several prostaglandins. These authors also showed that FSH interaction with the Sertoli cell activates the PKA pathway to increase cAMP levels and PKC pathway to regulate START-domain containing lipid transfer proteins.

Apoptosis is a key process that occurs during spermatogenesis. Huang, et al., (Poster #1423) showed in a rat model that hyperprolactinemia-induced impairment of spermatogenesis with an increased incidence of apoptotic spermatogonia. The effect of the chemotherapeutic agent, etoposide on sperm viability suggested that this agent disrupts mitochondrial membranes (poster #1424) and DNA damage as measured by TUNEL positivity with no morphologic changes noted in the sperm. Finally, sperm function also appeared to be adversely effected by alpha-blockers that may be administered to men with lower urinary tract symptoms associated with BPH and differences were noted between the actions of tamsulosin and alfuzosin or placebo (Hellstrom and Sikka, poster #1422).

Wednesday May 24, 2006
Moderated Poster Session: Infertility: Evaluation, Therapy, and Basic Science (II)
Summarized by Shane Russell, MD

The final infertility session of the AUA was an excellent review of new scientific research which fell roughly into 4 categories: clinical, diagnostic, basic science, and psychological aspects of male factor infertility.

Clinical

Dr Marmar and colleagues (abstract 1613) started off the session with a review of their clinical technique for testicular sperm extraction in men with non-obstructive azospermia (NOA). Using color/power Doppler ultrasound, guided biopsies were directed towards areas of the testicle with the highest levels of vascularity. Presumably, the enhanced perfusion of these areas allows a better chance for spermatogenesis to establish itself in these locations. In this study, the authors measured TP1 levels in these areas of biopsy. TP1 is associated with the presence of post-meiotic cells, and therefore a higher chance of finding retrievable mature sperm. In this study about 60 patients with Sertoli cell only syndrome (SCO) had 2 percutaneous testicular biopsies: one in a relatively vascular and another in a relatively avascular area. They found that TP1 levels were 10 times greater in areas located near an artery. As an aside, it was noted that sperm was found in 66.7% of these SCO patients using this biopsy technique, and of the patients with positive sperm, 32% achieved a positive clinical pregnancy with IVF/ICSI. The authors noted that all procedures were performed on an outpatient basis, using an 18g needle for tissue extraction after being given a local nerve block. No cases of significant post-biopsy testicular hematoma or atrophy were noted by the authors.

The next clinical paper was from Williams and colleagues at Baylor (abstract 1621). These authors performed a retrospective chart review of sperm bank data to evaluate semen parameters of 348 men (508 samples) who cryopreserved sperm after being given a diagnosis of having a malignancy. They found that men with testicular cancer (34%) had mean sperm densities of $24.9x10^6$ and mean motility of 52.6%. Men with all other malignancies (GI, CNS, leukemia/lymphona, sarcoma, prostate) had similar motilities, but higher mean densities ($>48.0x10^6$). The authors note that this represents the largest U.S. series of semen quality in men with cancer. Two possible sources of bias of the data which were brought up in the discussion session included the fact that azospermic men were not included (as their data was not available through the sperm bank). Another possible bias was that men who had malignancies that make them more clinically ill may be less represented in this study, as they may be unable/unwilling to produce a semen specimen for cryopreservation.

Ludwig and colleagues (abstract 1626) evaluated the possible effect of chronic pain syndrome/chronic prostatitis (CPPS/CP) on the acrosome reaction of sperm. The authors prospectively evaluated 56 patients with CPPS/CP who were divided into 2 groups: NIH IIIA and NIH IIIB, according the NIH classification. Both of these groups represent chronic nonbacterial processes, but NIH IIIA signifies an inflammatory state (with elevated levels of leukocytes in expressed prostatic secretions), and NIH IIIB is non-inflammatory. No significant differences were found between the 2 groups in terms of sperm density, motility, morphology, vitality, or overall acrosome reaction, though these patients did have decreased sperm densities and morphology compared to healthy controls. Although overall acrosome reaction between patients with NIH IIIA and IIIB were similar, the inducibility of the acrosome reaction was decreased in both groups, which was felt to be secondary to an increase in the rate of spontaneous acrosomal reaction. The etiology of this was unclear, but one possibility was felt to be the elevated levels of reactive oxygen species which are known to be present in this patient population and have deleterious effects on sperm quality and function.

The next clinical paper was by Lynne and colleagues (abstract 1630) which evaluated the options for assisted reproduction offered to infertile men with spinal cord injuries (SCI). A survey of local centers who provide reproductive services to SCI patients was performed. The types of physicians who responded to the survey were: Ob/Gyn/Reproductive endocrinologists 73%, Urologists 20%, Physical medicine and rehabilitation 1%, lab andrology/embryologists 6%. Methods used by these physicians for sperm retrieval included: surgical only (not use any ejaculated sperm) 28%, ejaculated and non-ejaculated sperm 63%, ejaculated sperm only 7%. Only 34% of the respondents reported offering IUI to patients. For the physicians who offer IUI, their minimal cut-off in total motile sperm (TMS) to offer IUI was: 1-4million TMS- 63%, 5-10 million TMS- 31%, 11-20 million TMS- 3%, and >20million TMS- 3%. Next, the authors retrospectively analyzed their own data on 451 SCI patients who produced 2,546 semen analyses by any method. Positive sperm retrieval with PVS was 54.9% (88% if level of injury was T10 or higher) and positive response to EEJ was 95%. Using a cut-off for IUI of 10 million TMS, sperm adequate for IUI was obtained in 68.8% of assisted ejaculation procedures in 86.9% of SCI patients. The pregnancy rate for these SCI patients undergoing IUI was approximately 17-18% per cycle, which is similar to non-SCI patients. The authors felt that many SCI patients are not offered IUI

as a choice for assisted fertility despite good potential outcomes, and called for greater education of reproductive endocrinologists and urologists concerning this.

The final clinically related paper was by Monoski and colleagues from Cornell (abstract 1632). This prospective study looked at the effect of varicoceles on SCSA (sperm chromatin integrity) levels in 72 men with a mean age of 37 years. They found that the grade of the varicocele was correlated to an increased in DFI % (gr2 – 13%, gr2 – 18%, gr3 – 22%). Patients with bilateral varicoceles also had a higher DFI% (22.78% vs. 17% for unilateral only), but this was not statistically significant. Sperm density and morphology also correlated with the presence of a lower DFI%. On multifactorial analysis, only sperm density in patients with varicoceles was predictive of DFI (with 50% of men below a density of 10million/cc sperm having DFI > 30% versus only 8% of men with sperm density > 10million/cc. The authors concluded that it appears that varicoceles have a detrimental affect on sperm chromatin integrity, and that this data can be used to counsel patients on making clinical decisions about treatment of their varicoceles. On post-presentation discussion, Dr. Nagler questioned whether the rise in DFI% could be positively attributed to the presence of a varicocele without the presence of a control group which had similar semen parameters but no varicocele.

Diagnosis

The first study on diagnostic techniques was by McCormack and colleagues (abstract 1617) who presented a new technology for basic semen parameter screening. They described a novel microfluidics device which attempts to assess both motility and count of present sperm (as opposed to just density assessment in off-the-shelf semen parameter screening devices currently available in drug stores). The microfluidics device is comprised of a semen sample reservoir which is connected to a small analysis reservoir by a thin fluid channel. Sperm labeled with a fluoroscene dye are placed in the sample reservoir where motile sperm then cross a fluid interface into the static fluid of the thin channel. The microchannel is visualized by bright field and fluorescent microscopy to evaluate sperm count and motility. 43 tests were performed on 15 fresh human semen samples and the results were found to correlate highly with CASA. Several concerns were raised in the study discussion, including whether such a test would be too complex to use by the general public, whether differing semen viscosities would affect motility readings, and if the relatively small diameter of the thin channel (60 microns) would cause shearing damage to the sperm, thus affecting results.

The next study was presented by Dr. Lamb and colleagues (abstract 1620) which looked at the presence of pre-clinical triplet repeat DNA expansions in patients with NOA and severe oligospermia. These triplet repeats have been associated with neurodegenerative diseases such as Kennedy disease and myotonic dystrophy. These triplet repeats are also known to increase with each successive generation, with the risk of developing the disease rising with the presence of more repeat sequences. Infertile men (from Texas and Australia) underwent testing of the length of triplet repeat tracts of 3 alleles (ataxin-1, ataxin-2, and dystrophia myotonica) and these were compared to known results from the general population. Infertile men had higher levels of these repeat triplet tracts than normal controls. Of 291 infertile men from Texas, 12 men had ataxin-2 levels in the disease range with another 25 harboring unstable alleles. 55 of 413 infertile Texas men had pre-clinical expansions of the dystrophia myotonica allele, and 4 of these men had enough repeats to be mildly symptomatic. 7 of 224 infertile Australian men had disease-length repeat expansions of ataxin-1. The authors concluded that triplet tract repeat expansions are more common in men with NOA and severe oligospermia, and that patients should be screened for and counseled on the possible increased risk of neurodegenerative disease in the offspring of these patients who can now potentially conceive with the assistance of IVF/ICSI.

Heshmat and colleagues (abstract 1623) presented the next study looking at seminal plasma lipocalin-type prostaglandin D synthase (PGDS) as a means to diagnose obstruction of the genital ducts. PGDS is produced by Sertoli cells and nowhere else in the genital duct system and, therefore, its absence in the ejaculate would imply a complete blockage of fluid whose origin is the testicle. Semen analyses from 61 patients with differing infertility issues as well as several with normal semen parameters were analyzed for the presence of PGDS. Groups with genital duct obstruction had significantly lower levels of PGDS than normal controls without any overlap. Patients with NOA and severe oligospermia exhibited a diverse range of PGDS levels, which did overlap with those of normal controls. The decrease in PGDS in patients with non-obstructive issues was felt to possibly be a result of Sertoli cell dysfunction or partial genital duct obstruction. The authors theorized that PGDS could potentially be used as a tool to detect genital duct obstruction in difficult clinical situations such as evaluating post-vasectomy patients with persistent rare non-motile sperm or assessing patency in patients following vasectomy reversal who have not had return of sperm to the ejaculate.

Another study evaluating genital duct obstruction was performed by Orhan and colleagues (abstract 1624). This group used technetium (Tc)-99m colloid seminal vesicle scintigraphy to diagnose ejaculatory duct obstruction (EDO). The authors stated that the colloid beads were approximately the size of sperm and should therefore theoretically predict the presence of clinically significant EDO better than contrast dye (which could slip past a partial ejaculatory duct obstruction too small for sperm to pass through). 12 patients suspected of having EDO (oligo- or azospermia with low ejaculate volume) underwent TRUS after which the seminal vesicles (SVs) were injected with 2cc of Tc-99m sulfur colloid under TRUS guidance. Seminal vesicle scintigraphy was then performed after colloid injection, and again following ejaculation. All 5 patients (100%) with TRUS findings consistent with EDO had SV volume decreases of Tc-99m sulfur colloid of < 30%. Of the 7 patients who had no TRUS evidence of EDO, only 3 (43%) revealed an SV volume decrease in Tc-99m sulfur colloid of < 30%. This seems to be a promising new technique in the controversial area of EDO where no gold standard currently exists for diagnosis. However, members of the audience pointed out that normal fertile control data are needed before for any meaningful conclusions from the data can be drawn.

The final study in the diagnostic section was reported by Fenig and colleagues (abstract 1631) on the comparison of duplex Doppler ultrasound looking for varicoceles in men undergoing evaluation for infertility because of abnormal semen analysis (group 1- n83) compared to documented fertile controls who presented for routine vasectomy (group 2- n49). Diagnostic criteria for the presence of a varicocele was the presence of two or more visualized veins with one having at least > 2.5mm diameter and a peak valsalva reversal of flow of > 10cm/s. Overall, group 1 patients had more total diagnosed varicoceles by ultrasound (69%) than

group 2 (43%). The incidence for left sided varicoceles was similar (group 1- 39% vs. group 2- 37%), but group 1 patients had significantly more (29%) bilateral varicoceles than did group 2 (6%). Varicoceles on either side were associated with decreased ipsilateral testis volume in both groups. The authors concluded that right-sided varicoceles are almost 5 times more common in men with abnormal semen parameters than normal fertile controls. It was not reported how many of these varicoceles were clinically palpable in this study, but Dr. Turek noted that the prevalence found in this study was much higher than the clinically palpable varicocele rates in infertile men generally reported in the literature. The topic then turned to the clinical evidence for repairing subclinical varicoceles, which at this point in time is weak at best. Dr. Goldstein stated that it would be interesting to do Doppler ultrasound studies on known fertile men without palpable varicoceles for comparison to see the prevalence of subclinical varicoceles in this patient population

Psychological

Two studies were presented evaluating the psychological impact of male factor infertility. The first study was by Russell and colleagues (abstract 1627) which evaluated couples undergoing workup for male factor infertility. 47 men and 26 women completed separate anonymous questionnaires which included validated measures of anxiety (STAI), depression (CES-D), and perceived strain on interpersonal relationships (RDAS). It was found that women were significantly more likely to report elevated levels of anxiety (56%) than the men (29.8%). Study women, but not men, had mean anxiety levels above that expected to be seen in the general population, though a small subset of men reported very high levels of anxiety. Both the study men and women reported elevated levels of depression above that expected in the general population. However, despite the increase in incidence of anxiety and depression, the study couples did not report an increased perceived strain on their interpersonal relationship with their partners. Overall, 46.8% of men and 76% of women reported some degree of elevated anxiety, depression, or both. The second study, by Ohebshalom and colleagues (abstract 1629), evaluated 39 men undergoing infertility evaluation or treatment for depression (CES-D) and quality of life (SF-36). The authors found that 23% of the study patients reported moderate depressive symptoms with another 8% reporting severe depression. These study patients also reported lower quality of life indices on the SF-36 than that expected in the general population. On multivariate analyses, improved quality of life was correlated with being married and a younger age. Both of these studies highlight the importance of clinicians recognizing the elevated risk of potential psychological problems in male factor infertility couples, as well as the need to have adequate referral resources to manage these issues effectively.

Basic science

The basic science section was started by Dr. Klaus Steger (abstract 1614) who reported on a study concerning imprinting disorders, such as Prader-Willi-Angelman and Beckwith-Wiedermann syndromes. These disorders result from aberrant resetting of imprinting marks on specific monoallelically expressed genes. There exists concern that IVF/ICSI combined with testicular sperm extraction in azospermic or severely oligospermic men may bypass some of the natural selection mechanisms which may normally afford some protection against passing on these abnormalities to offspring. The author therefore sought to evaluate at what level of development several imprinted genes (the maternally imprinted SNRPN gene and paternally imprinted H19 gene) were re-established in male germ cells. Taking precautions to prevent contamination by somatic Sertoli cells, the author found that genetic imprinting of these genes was already established in the spermatogonia of humans in both normal and abnormal states of spermatogenesis.

The next basic science study was by Nangia and colleagues (abstract 1615) which sought to evaluate whether vitamin D receptors (VDR) were present in testicular tissue. Using archived paraffin block specimens, the authors were able to show positive staining for the presence of VDR in spermatogenic (and mature sperm), Sertoli, Leydig, and testicular tumor (embryonal, seminoma, choriocarcinoma, and lymphoma) cells, but not on syncitiotrophoblasts or interstitial stroma. Using an in-vitro model of cultured human embryonal carcinoma cell line, the authors determined that the VDR was an active receptor, whose expression may be modulated by calcium levels. This receptor could be upregulated by the addition of vitamin D, and appeared to be down-regulated by testosterone. Further studies are needed to determine the clinical significance of these receptors.

Smith and colleagues (abstract 1616) studied pachytene nuclei in patients with NOA to evaluate for abnormalities concerning meiotic recombination in these cells, which is very important in the process of mature haploid sperm development. Meiotic recombination takes place in recombination nodules which can be identified in pachytene nuclei of developing spermatocytes, and this process requires the presence of the DNA repair enzyme MLH-1. The synaptonemal complexes (SC) also play a vital role in the formation of the recombination nodules, and the presence of gaps within the SC is felt to likely be detrimental to the process of meiotic recombination. Testicular biopsies were evaluated from 20 patients (5 patients with CBAVD, 5 with other forms of obstructive azospermia, 9 with NOA, and 1 patient with failure of emission). The number of SC gaps and MHL-1 (recombination) nodules was determined. Of note, only 2 of the 9 patients with NOA had spermatocytes which had not arrested before development to the pachytene stage. The recombination frequency was noted to be similar between all 4 groups evaluated. However, the number of SC gaps was significantly greater in the NOA patients compared with the other groups. The authors theorized that this higher prevalence of SC gaps could be a contributing cause to the increased level of DNA abnormalities, such as aneuploidy, found in the spermatozoa of NOA patients.

The next study was presented by Bertolla and colleagues (abstract 1619) who looked to evaluate whether mitochondrial dysfunction may play a role in poor sperm motility. Mitochondria are responsible for producing ATP, which is the primary source of energy for flagelar movement. The authors evaluated the specimens of 61 asthenozoospermic patients (group 1) and 69 healthy controls (group 2). Mean progressive motility was 26% for group 1 and 72% for group 2 by WHO criteria. Mitochondrial function was then evaluated using optic microscopy (counting at least 200 sperm cells), which the authors felt was more sensitive for diagnosing minor mitochondrial dysfunction than standard fluorescent microscopy and flow cytometry. The authors found that mitochondrial dysfunction was significantly more prevalent in group 1 as compared to group 2. The authors concluded that mitochondrial dysfunction may play a significant role in decreased sperm motility in some patients.

Margreiter and colleagues (abstract 1628) next sought to evaluate the clinical significance of deletion of the gr/gr genetic segment, which is located within the AZFc region of the Y chromosome and includes sections of both the DAZ and PBY2 genes. Prior studies had suggested that gr/gr deletions may have an independent negative impact on male fertility. The authors evaluated 1136 patients with oligospermia of azospermia for Y chromosome microdeletions

(YCMD). Of patients with normal karyotypes, 50 patients (4.4%) had AZFc deletions and 54 patients (4.8%) had gr/gr deletions. For comparison, 2 of 17 (12%) of fertile controls were noted to harbor deletions of gr/gr region. 27 (63%) of men with gr/gr deletions and 40 (69%) of men with AZFc deletions were azospermic, but 95% of AZFc deletion and only 70% of gr/gr deletion patients had sperm densities of < 1million/cc. No significant differences in mean sperm count, testosterone, FSH, LH, combined testicular volume, and distribution of testicular histology were noted between gr/gr positive and gr/gr negative groups. The authors concluded that the clinical profile and testicular histology of gr/gr deleted men was similar to those without Y microdeletions, and therefore gr/gr deletions do not represent an independent risk factor for male factor infertility.

The final study of the session was presented by Zini and colleagues (abstract 1625) who evaluated histone to protamine ratios in infertile men. Histones typically bind DNA in somatic cells. In sperm, protamine typically replaces the role of histones in DNA binding, although histones typically still account for around 15% of DNA binding in sperm. Protamines play an important role in sperm development, in that it allows a more compact binding of DNA in these cells, which likely plays an important role in sperm function, fertilization, and/or embryo development. The sperm of 20 infertile men and 10 healthy fertile controls was evaluated using nuclear protein extraction, densiometric analysis, immunoblotting and immunocytochemistry testing. The authors found that infertile men had sperm with significantly higher proportions of histone H2B to protamine (P1+P2) then did the fertile controls. Populations of sperm with differing histone to protamine ratios were found within the same infertile individuals, consistent with the presence of heterogeneous populations. The clinical significance of these findings still needs to be determined, as well as studies which might show changes in histone to protamine ratios following infertility treatments (such as varicocele repair). ⌘

6th Annual SSMR/SMSNA Traveling Fellowship Program

The 6th annual traveling fellowship program took place at the AUA in Atlanta and was a great success. This year was the second combined fellowship with the Sexual Medicine Society of North America (SMSNA).

I want to express the SSMR's gratitude to the SMSNA for their academic and financial support of the fellowship. These awards are designed to expose young urology residents to the field of sexual medicine, including male infertility and erectile dysfunction, and allow them to participate in many of the events at the AUA. The participants were able to come to both the SSMR and SMSNA annual meetings as well as a career breakfast held with several members of the societies. Ten travel fellows from various institutions were selected. The travel fellows this year were:

Jonathan Chan	University of Toronto, Toronto, Ontario, CANADA
William Conners	Albany Medical College, Albany NY
Hugo Davila	University of South Florida, Tampa, FL
Stephanie Harris	Medical College of Wisconsin, Milwaukee, WI
Tobias Kohler	University of Minnesota, Saint-Paul, MN
Vernon Orton	Virginia Commonwealth University, Richmond, VA
Jennifer Pugliese	Madigan Army Medical Center, Tacoma, WA
James Smith	University of Utah, Salt Lake City, UT
Jonathan Taylor	Eastern Virginia Medical School, Norfolk, VA
William Tran	SUNY Downstate Medical School, Brooklyn, NY ⌘

SSMR Board of Directors

Men's Health Traveling Fellowship Program 2007

Dear SSMR Members:

The Society for the Study of Male Reproduction (SSMR) and the Society for Sexual Medicine of North America (SMSNA) are proud to announce the seventh Annual Traveling Fellowship Program with the SSMR and the third combined award for the two societies. This will take place in conjunction with the 2007 AUA meeting in Anaheim, CA.

The SSMR and SMSNA, AUA-affiliated subspecialty societies, have a mission to promote the advancement of the science and treatment of male reproduction and sexual disorders through education of practitioners, public education, and informational exchange of research and new advances through meetings. The SSMR and SMSNA are committed to cultivating interest in sexual medicine treatment careers in trainees.

Our second combined program at last year's AUA was a huge success, and we wish to build upon that success. Our goal is to present residents in training with the opportunity, while attending the AUA meeting, to have a more intensive exposure to male sexual medicine issues. The Fellowship Program will include attendance at the SSMR and SMSNA educational programs and complimentary SSMR banquet participation and SMSNA lunch. Fellows will also attend an AUA post-graduate course in male infertility, erectile dysfunction and the infertility podium and poster sessions, as well as a symposium with fellowship directors and junior faculty members on how to prepare for a future successful career as a male sexual medicine specialist. The program will allow significant contact between Fellows and leaders in the field. Travel fellows will also be given an honorary membership to the SSMR for 1 year.

Preference will be given to those in earlier years of training. This does not mean, however, that senior residents and fellows cannot apply. Their applications will be considered along with the others. Participants accepted into the program are expected to take part in all components. This means that attendance at the meeting from Thursday afternoon until Monday or Tuesday evening will be required.

Meeting expenses covered by the program include airfare, hotel accommodations, SSMR and SMSNA meeting and banquet, tuition for the post-graduate course, and all special lectures. The maximum stipend will be $1,000 per Fellow. Overages are the responsibility of the Fellow or the home institution.

An application is attached, which needs to be completed by the applicant and signed by the director of the training program, assuring commitment from the Chief to allow full attendance of the Fellowship program, should the applicant be accepted. The applicant should solicit a letter of recommendation from a mentor of his/her choice. Applications are due by February 1, 2007. The awards will be announced by February 28, 2007.

We hope you will consider supporting this program through the application of trainees in your program. We look forward to another successful Men's Health Traveling Fellowship!

Sincerely,

Ajay Kumar Nangia, M.D.
Dartmouth Hitchcock Medical Center
Section of Urology
One Medical Center Dr.
Lebanon, NH 03756 ⌘

Application for the Men's Health Traveling Fellowship Program 2007

Saturday, May 19 – Wednesday, May 23, 2007
Anaheim, California

Please Print or Type.

Name:_____Degree(s):_____

Work Address:_____

City:_____State:_____Zip:_____

Home Address:_____

City:_____State:_____Zip:_____

Work Phone:_____Home Phone:_____

Fax::_____E-mail::_____

Current Position (resident/PGY year, post-doc):_____

Institution/Department:_____

Please attach the following:
1. Curriculum vitae
2. Personal statement (1 page or less)
3. Letter of recommendation from Chairman or selected mentor.

Signature of applicant:_____

Chairman signature: By signing below, I am supporting the application of the above-named member of our department as a Traveling Fellow of the SSMR and SMSNA. I understand that attendance at the AUA meeting will be subsidized by the award to a maximum of $1,000, and that attendance of the Fellow at all Traveling Fellowship functions is expected.

Signature of Department Chairman:_____

Send completed applications to:

Ajay Kumar Nangia, M.D.
Dartmouth Hitchcock Medical Center
Section of Urology
One Medical Center Dr.
Lebanon, NH 03756
Phone: (603) 650-5091
Fax: (603) 650-4985

Deadline: February 1, 2007

Mark Your Calendars!

2007 SSMR Subspecialty Society Program
"Fine Wine of Wrong Time; Infertility in an Older Population Desiring Children"
Raymond A. Costabile MD

Due to changing financial, educational and societal values in America, couples are increasingly delaying the start of their families and having children. In addition, our ever-lengthening lifespan has started the relatively new phenomenon of men (and women) desiring "trophy" children when they are in their 50's or 60's. Increasing interest in this issue has led to the topic of the 2007 SSMR Subspecialty Society meeting held at the AUA annual meeting in Anaheim on May 19, "Fine Wine or Wrong Time; Infertility in an Older Population Desiring Children". Program Chair, Raymond A. Costabile MD has gathered an enthusiastic faculty eager to discuss this interesting and relevant topic including Paul Shin MD, Ajay Nangia MD and Edmund Sabanegh MD. They will cover a myriad of issues involving the aging population who want children and how the male infertility specialist has had to adapt the subspecialty to this societal phenomenon.

The epidemiological aspects of delaying parenting in the United States will lead the discussion of what may be a societal induced epidemic of infertility. Presentations on physiological changes in reproductive capability in men and women will serve to provide a basic sciences background. The basic sciences discussion will be followed by a debate on the incidence and significance of birth defects and genetic abnormalities in children born to "older" parents. This should serve as an effective backdrop to extend our discussion into how the infertility specialist will need to adapt the evaluation and treatment of these "older" men and women desiring children. Finally the expert faculty and audience will be challenged by a series of patient scenarios to highlight this important topic in urology and reproductive medicine.

We invite all members of the Society as well as all attending the 2007 AUA annual meeting to attend this topical presentation which has wide appeal as well as significant coverage in the lay media.

ASRM Annual Meeting
October 21-25, 2006
New Orleans, LA

ASA 32nd Annual Conference
April 18-24, 2007
Hyatt Regency Tampa
211 North Tampa Street
Tampa, Florida

ASA Annual Meeting
April 21-24, 2007

Testis Workshop
April 18- 21, 2007

ASA Special Symposium
April 21, 2007

Andrology Lab Workshop
April 21, 2007

AUA 2007 Annual Meeting
May 19 - 24, 2007
Anaheim, CA

SSMR Annual Meeting at the AUA Annual Meeting
May 19, 2007
Anaheim, CA

The Society for the Study of Male Reproduction (SSMR) encourages organizations and individuals to link to www.ssmr.org.

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