SSMR NEWS

February *Society for the Study of Male Reproduction* 2006

President's Message

Dolores J. Lamb, PhD

As we begin another new year, it is important that we look towards the future of the Society for the Study of Male Reproduction! Our meeting will be in conjunction with the annual meeting of the American Urological Association in Atlanta, GA in 2006. Atlanta, the site of previous meetings of the AUA, offers our group a mixture of Southern charm and hospitality combined with a unique urban setting. Atlanta, once thought to be the heart of the Old Confederacy, today is a fast-paced modern city with skyscrapers designed by architects such as Phillip Johnson, I.M. Pei and Marcel Breuer.

The SSMR scientific meeting will be on Saturday May 20, 2006 from 1:00 pm-5:00 pm. The focus of this year's meeting is unique and one that has not been explored in depth at our meetings previously. Entitled, "The Excurrent Ductal System: Pathway to Parenthood", the program focuses on the genital tract, its pathology and treatment. Approaches to be presented include diverse aspects including development, anatomy, and function of the regions of the tract.

Dr. Bob Brannigan, this year's program director, has brought together an impressive collection of speakers internationally recognized for their expertise in the area of genital tract function and the meeting promises to provide many new insights into the basic biology, genetics and pathology of the tract. Dr. Terry Turner (University of Virginia Health System) will provide an overview on epididymal anatomy and function, followed by a focus on the pathologies frequently found and treated by urologists, namely congenital epididymal abnormalities (Dr. Tom Kolon, Children's Hospital of Pennsylvania) and inflammatory conditions of the male excurrent ductal system (Dr. Peter Chan, McGill University). Following a brief question and answer period, the focus will turn to therapy with Dr. Tony Thomas (Cleveland Clinic) speaking on vasal and epididymal reconstructive surgery in the era of ICSI/IVF and Dr. Paul Turek (University of California-San Francisco) providing insights in the best techniques to diagnose and treat ejaculatory duct obstruction.

Finally, ejaculatory dysfunction will be the focus of the final two lectures. Dr. Nancy Brackett (The Miami Project), a well-recognized expert in the treatment of infertility in men with spinal cord injuries will provide new insights into the management of these patients. This talk will be followed by the presentation of Dr. Stanley Althof (Case Western Reserve School of Medicine) who will focus on the treatment of ejaculatory dysfunction with counseling, behavior therapy or medicine.

After the end of our annual business meeting, we will meet at the Ruth's Chris Steak House at Centennial Park in Atlanta for our annual reception and banquet. Dr. Mike Witt, Ann Marie Bray and Debbie Roller of W.J. Weiser and Associates have planned a wonderful meal for us! Cocktails will begin at 6:30 p.m. followed by dinner at 7:30 p.m. The banquet is always a popular venue for our members so please be certain to make your reservations early!

A special thanks to all who provided insight and guidance into the program for this year's scientific meeting. Bob Brannigan worked tirelessly on our behalf to develop a novel and interesting program for our enlightenment and enjoyment. I would also like to thank Drs. Craig Niederberger (past-president) and Jon Pryor (vice president) for giving me such wonderful support and guidance this year. Jon has worked hard to put together the newsletters that are so useful for our members and Craig is working with the AUA to develop a fellowship match program for our subspecialty fellows. Ajay Nanjia continues to head our very successful traveling scholars program to attract training urologists and scientists to the field and we are indebted to him for his efforts to ensure the continuing success of this important program. In addition, I need to thank Debbie Roller, Ann Marie Bray, Alison Heimburger at W.J. Weiser, Inc. for trying to keep me on schedule and providing such important assistance.

Importantly, Dr. Harris Nagler (Beth Israel) has undertaken a difficult task for the society and agreed to serve on the executive committee as the Director of Development for the SSMR to provide a centralized and

See ***President's Message,*** *cont. on page 2*

CONTENTS

focused effort. Certainly, the economic reality faced by today's pharmaceutical companies limits our ability to obtain support for the important educational missions of our society. The industry backing of our society is critical to the success of our educational missions for the meeting and travel awards and daily operating expenses. Our ability to focus on presenting state-of-the-art science and technology, as well as innovations in the clinical diagnosis and treatment of male reproductive issues is enhanced by their funding and of course the support and efforts of our members.⌘

Review of ASRM 2005

Contributions by Justin Cohen; Stanton Honig, MD; Dolores J. Lamb, PhD; Cathy Naughton, MD; Craig Niederberger, MD; Robert Oates, MD; Jon L. Pryor, MD; Shane Russell, MD; and Jay Sandlow, MD.

SUNDAY, OCTOBER 16, 2005

Post-Graduate Course #16: Sperm Quandries
Summarized by Craig Niederberger, MD

This year's Society for Male Reproduction and Urology Postgraduate Course, "Sperm Quandaries," was chaired by Craig Niederberger, with Dolores Lamb and Robert Brannigan as co-faculty. The course was designed to highlight both new and old controversies in male reproductive medical diagnosis and therapy.

Dr. Brannigan began with a comprehensive overview of the varicocele, "The Varicocele: Does Is Matter, Does Fixing It Work?", concluding that: (1) varicocele is a common problem associated with impairment in spermatogenesis and steroidogenesis, (2) diagnosis is easily made on physical exam, (3) microsurgical inguinal and subinguinal varicocele ligation are effective, have low recurrence rates and low complication rates, and that (4) varicocele ligation is cost-effective in the era of IVF/ICSI.

Dr. Niederberger continued with a review of the various methods for obtaining sperm and cryopreservation for IVF/ICSI, "Testicular Sperm for IVF: How to Get It, Can You Freeze It?", concluding that: (1) the type of azoospermia (obstructive versus nonobstructive) directs the extraction technique, with FSH and testis axis predicting which type, and that, in most cases, a testis biopsy is unnecessary, (2) epididymal or testicular sperm may be used in ICSI with similar outcomes, and (3) cryopreservation may be used with good outcomes.

Dr. Lamb presented a thorough discussion of genomic assessment for male reproductive dysfunction in "Genetic Testing for the Male: Does it Matter?", concluding: (1) there are many genetic causes of male and female infertility, but there are laboratory tests currently available to diagnose just a few defects, (2) bypassing nature's natural barriers to defective sperm with ICSI may contribute to systemic problems in the offspring that can not be diagnosed with a pediatric genetic evaluation, and (3) patients need to be counseled that although the studies to date on the safety of ICSI are reassuring, there are no guarantees of a perfect baby, even with advanced genetic testing.

In the afternoon, Dr. Niederberger began with an overview of male reproductive assays in "Measuring Male Reproductive Potential: What Do the Assays Really Mean?", concluding: (1) screening for endocrinopathy is important, but can be limited to a semen analysis density of less than 10 million/ml, (2) the traditional bulk semen analysis thresholds have low sensitivity, and a dual parameter approach may be more effective, (3) semen volume is a very important parameter, and (4) sophisticated assays, including ROS and DNA integrity, will lead to new ways of assessing sperm function.

Dr. Lamb continued with a discussion of the controversy of globally declining sperm counts in "Sperm Counts: Are they Falling?", concluding: (1) most of the studies arguing for declining counts are flawed in a selection bias, the statistical model used for analysis, methodological inconsistencies, inconsistencies with abstinence, potential regional and ethnic variations in quality and in study design, (2) semen analysis is not a test of fertility, and (3) there is a need for further research to test the hypothesis that male reproductive health has declined using prospective multicenter studies.

Finally, Dr. Brannigan finished with perhaps the most controversial topic, Medicine Today?", concluding: (1) both partners from an infertile couple should undergo medical evaluation, (2) a semen analysis alone is not a sufficient assessment for a male with suspected infertility, (3) male factor treatments include counseling, medical therapy, surgical procedures, and assisted reproductive techniques, (4) many couples have more than one treatment available and should be counseled about all of their therapeutic options, and (5) the urologist and reproductive endocrinologist form an important team, and, when working together, provide the optimal patient care experience.

Substantial time was given to questions and answers and a panel discussion at the end. An exciting element of the course was the high level of audience participation, including such well-known individuals as Drs. Amelar, Belker, Nagler, Evenson, and many others. In a very real way, the course was taught by all in attendance.

MONDAY, OCTOBER 17, 2005; 10:45 A.M. – 12:00 P.M.

Interactive Sessions: Diagnosis and Treatment of Endocrine Developmental Disorders in the Male, Society for Male Reproduction and Urology, Chair: Rebecca Z. Sokol, MD, MPH
Summarized by Justin Cohen and Stanton Honig, MD

Rebecca Z. Sokol, MD, MPH, chaired the session, and began by described the physiology of normal development of the reproductive system in the male. Sokol described the course she would take in diagnosing and treating three patients with infertility. The first presented to her office with anosmia and ambiguous genitalia since birth. His uncle shared his diagnosis of Kallman's syndrome. LH, FSH, testosterone were low and the patient was treated with testosterone replacement. She noted that hCG and hMG could also be used if fertility was desired. The second patient presented with impotence and infertility, and had normal genitalia but abnormal progression through puberty, with gynecomastia and a eunuchoid body habitus. Labs showed low testosterone, and increased FSH and LH, representative of the patient's Klinefelter's syndrome (XXY) secondary to a nondisjunction during mitosis, which re-

sponded to testosterone therapy. The third patient was an African-American female presenting with primary amenorrhea, scant pubic hair, and a history of hernia repair in childhood. She was diagnosed with the x-linked recessive complete androgen insensitivity. Dr. Sokol recommended leaving the gonads in place until after puberty, recognizing that they have an increased risk for cancer.

Stuart S. Howards, MD, then presented an overview of normal male reproductive anatomy and surgical options for treatment of congenital anomalies. He described the complications of epispadias, which include infertility secondary to the bladder neck not closing at ejaculation, chordee, and injuries to the vas deferens during surgical repair of the epispadias. He then explained in great deal the standard Cantwell repair with partial penile dissection, and the newer Mitchell repair, which involves complete penile disassembly. Cryptorchidism, was reviewed, specifically timing of surgical repair. This should occur between 7 and 12 months of age, although no studies have shown decreased fertility if corrected later in childhood. After a successful unilateral orchiopexy, patients have normal fertility, but after bilateral orchiopexies, only 30-80% of patients are fertile. Dr. Howards then described micropenis, which must be differentiated from buried penis. The most common cause of this is GNRH deficiency, and evaluation should include karyotype, labs, and testosterone administration to determine if the penile size responds. Surgical treatment offers only limited benefit.

Michael K. Skinner, PhD, presented on the epigenetic transgenerational actions of endocrine disruption on male reproduction and disease development. He described his mouse model of Vinclozolin, an anti androgenic fungicide used to protect grapes. In his studies, mice born of first-generation mice exposed to Vinclozolin were infertile for many generations. This did not appear to be due to classic genetic factors; rather, the epigenetic methylation of DNA seemed to cause the infertility. Dr. Skinner then raised the argument that epigenetic factors may account for infertility in selected individuals.

MONDAY, OCTOBER 17, 2005; 10:45 A.M. – 12:00 P.M.

Society for Male Reproduction and Urology: (SMRU) Traveling Scholars Abstracts
Summarized by Robert Oates, MD

O-11: Sperm mitochondrial DNA copy number and integrity in infertile men: A comparison with nuclear DNA integrity. Song et al. University of Rochester Medical Center.

In this study, Song et al. measured the copy number, multiple deletions and integrity of mitochondrial DNA (mtDNA) and nuclear DNA fragmentation index in sperm of 54 infertile men. The authors observed an increased mtDNA copy number and poor mtDNA integrity in men with abnormal semen parameters. There was no clear correlation between mtDNA integrity and nuclear DNA fragmentation, although men with multiple deletions in mtDNA had greater amounts of nuclear DNA fragmentation.

O-12: Functional evidence of mismatch repair deficiency in non-obstructive azoospermia. Chu et al. Baylor College of Medicine.
Dr Chu and colleagues prospectively analyzed 18 samples of cultured testicular fibroblasts from men with NOA for survival following exposure to an alkylating agent. Their hypothesis was that the cell lines would be resistant if there were defects in DNA mismatch repair and their results supported this. These lines were also tested for MSH2 and MLH1 expression (two DNA mismatch repair pathway proteins) by immunohistochemistry (abnormal in the patient samples). As put so well in their conclusion, "Genetic defects associated with cancer predisposition in testicular failure patients are more common than previously expected and these men may be at risk for cancer development, ... their "mutator" phenotype may have other unrecognized consequences for the offspring."

O-13: 46,XX male patients – clinical and genetic findings in six patients. Alukal et al. Boston University School of Medicine.
Dr Alukal presented a total of seven men with 46,XX male syndrome. He described their genetic features and the mechanism of SRY translocation to the tip of an X chromosome. He also described their clinical features: male phenotype but azoospermia. The most important conclusion was that all men with NOA should have a karyotype and Y chromosomal microdeletion performed prior to any invasive testicular procedure. In the specific case of 46,XX male syndrome, there is no chance that sperm will be found upon TESE, as these men are missing nearly the entire Y chromosome and certainly those regions and their contained genes that are known to be involved in sperm production (AZF a, b, c).

O-14: Expression and function of two-pore domain potassium channels in non-human primate sperm. Chow et al. University of Washington.

Two-pore domain potassium channels are an integral part of cell-signaling pathways. The authors demonstrated with elegant bichemistry that these channels are present and functional in non-human primate sperm. This opens up a new avenue of research into their significance and role on spermatozoa.

O-15: Should all men with vasospermia at the time of vasectomy reversal be offered vasoepididymostomy? Singh et al. Mount Sinai Hospital Toronto.

The authors readdressed the longstanding question of what to do at the time of a vasectomy reversal if the fluid expressed from the testicular end of the vas does not contain sperm. They challenged the idea that VE should not be performed if the fluid was clear. Their findings demonstrated that their patency rates were much better if VE was performed in all cases of sperm absence – even if the fluid was clear. It was also noted that the success rates for VE were higher for first-time surgery as compared to redo-surgery. Finally, there was discussion about terminology, with most audience members disagreeing with the word "vasospermia" to describe this circumstance. The term "intraoperative azoospermia" was preferred.

MONDAY, OCTOBER 17, 2005; 1:30 P.M. – 2:15 P.M.

Plenary Session: American Urological Association/Bruce Stewart Memorial Lecture. "Drug Discovery and Development: A New Era?" Kenneth Watson, MD, MBA
Summarized by Jon L. Pryor, MD

Kenneth G. Watson, MD, MBA, from Astellas, presented the American Urological Association/Bruce Stewart Memorial Lecture entitled, "Drug Discovery and Development: A New Era?" Though working for Japan's second largest pharmaceutical company with sales of 7.5 billion (U.S.), Dr. Watson strived to present an unbiased view of the problems that pharma faces with drug development. Twenty-seven percent of total costs are attributed to the initial drug discovery and 38% to clinical development (i.e. Phase 1-3 studies). Surprisingly, 58% of all drug targets are based on what other companies have published; it is not novel development, as many assume. Some trends include more drugs focused on

intracellular targets, use of pharmacogenomics (i.e. use of genomic information to target areas for development), and pharmacogenetics (genomic information to target sub-populations for increased drug efficacy or decreased risk). Dr. Watson presented data to suggest there is less discovery output. He surmises this is because discovery is complicated, there is too much focus on drug economics (is it going to be a big winner?), and a robotic approach has replaced an intellectual approach to drug development. With 45 blockbuster drugs coming off market from 2003-2005 due to patents expiring, the industry is in potential trouble. There are 10,000 compounds that are explored for every one compound that makes it to market; the final price tag for the ones that make it is 800 million dollars and is expected to increase to 1.5 billion dollars by 2015. Some strategic options to deal with this problem are to increase the pipeline, decrease time to market, or somehow improve success rates of drug approval.

Finally, Dr. Watson talked about the World Health Organization (WHO) of essential drugs – these are essential drugs where money should be invested. Interestingly, virtually all countries accept the "essential drug" concept except well-developed nations, like the United States. He concludes 1) drug discovery is very risky, highly inefficient, and costly, 2) mega-mergers result in big companies, but not big pipelines, 3) the image of pharma is at a historic low, and 4) use of the WHO Essential Drug Lists counterbalances the pharmaceutical's over-marketing. He thinks that the pharmaceutical industry will evolve (e.g. reorganize R and D, downsize its sales force) and that the industry's future remains bright.

MONDAY, OCTOBER 17, 2005. 3:45 P.M. – 6:30 P.M.

The Society for Male Reproduction and Urology Abstracts
Summarized by Jay Sandlow, MD

O-26
Organ-sparing microdissection for non-palpable testicular cancer.

Hallak, et al performed screening scrotal ultrasounds on men presenting for infertility evaluation. They found eight non-palpable testicular lesions and explored six of them. This yielded a benign Leydig cell tumor in four, a Sertoli cell tumor in one, and a seminoma in one. All pts were either azoospermic or severely oligospermic. MicroTESE was positive in three of the four azoospermic pts.

Take home message: Microdissection can be utilized to remove testicular masses without orchiectomy, allowing for sperm retrieval (when necessary), and avoiding unnecessary testicular loss.

Discussion: Centered on the use of routine scrotal ultrasound in infertile men, particularly when most data (including this report) demonstrates that most non-palpable lesions identified are benign.

O-27
Does TESE improve IVF outcome in setting of virtual azoospermia?

Bendikson, et al reviewed the charts of all couples with virtual azoospermia that went through IVF cycles with both freshly ejaculated sperm and TESE. Sixteen couples were identified, with 48 cycles (27 fresh ejaculates, 21 TESE). Fertilization rates were equivalent, as were the number of embryos. Although pregnancy rates appeared to favor TESE, no statistical difference was seen. When couples were paired with their own data for ejaculated vs. testicular sperm, there was a significantly improved fertilization and pregnancy rate. The authors also found that as the total sperm count declined, so did the pregnancy rate.

Take home message: In couples with virtual azoospermia, there might be a slight advantage to utilizing testicular sperm, particularly following a failed IVF cycle with ejaculated sperm.

O-28
Computational model for predicting IVF outcome with surgical retrieved sperm.

Wald, et al derived a model based on multiple factors to predict IVF outcome. They used 83 "training" cases and 30 "test" cases, all with similar frequencies of various factors, including maternal age, source of sperm, fresh vs. frozen, and type of male factor involved. They determined that maternal age was the most significant factor. No other factor was statistically significant, although the source of sperm approached significance. This model is currently available on the web at www.urocomp.net.

Take home message: This model may be utilized to come up with an odds ratio for success of an IVF cycle based upon factors entered.

Discussion: One question was whether the results would be different if the input factors from other institutions were utilized as the training set. Of note, this was a multi-institutional study.

O-29
Outcome of vasovasostomy in presence of only sperm parts in the intravasal fluid.

Kolettis, et al examined the outcomes for vasovasostomy when there were either only sperm parts (heads or head with partial tails) or sperm parts on one side and intravasal azoospermia on other. The patency rate, defined as the presence of sperm, was 80%, with a pregnancy rate of 39%. No effect of obstructive interval was seen on the outcome.

Take home message: When sperm parts are noted in the vasal fluid, vasovasostomy is likely the right procedure unless only rare heads are seen.

Discussion: Questions regarding fluid interpretation, particularly in the identification of sperm heads, were raised. Also discussed distinguishing rare sperm heads (more likely to be epididymal obstruction) from many sperm heads (more likely to be vasal obstruction).

O-30
Outcomes following repeat vasectomy reversals.

Sandlow, et al examined outcome of redo reversals to determine if the obstructive interval affected the type of redo procedure, patency, or pregnancy rate. All initial procedures were vasovasostomies (VV) except for two, which were VV/EV. Overall, the patency rate was 88%, with no significant difference between <10 yr and >10 yr obstructive interval. No significant difference was seen in the need for EV based on obstructive interval, and although pregnancy rates appeared to be less for longer obstructive intervals, this was not statistically significant. There was a higher incidence of late failures in the redo procedures as compared to first-time reversals.

Take home message: Redo reversals have similar success rates to first-time reversals, and the need for EV is not based on obstructive interval. Based upon this, the authors would also recommend VV for first-time reversals, even in the presence of intravasal azoospermia, if the surgeon is not facile in performing EV, as this is unlikely to have an adverse impact upon subsequent redo procedures (if they become necessary).

Discussion: Could the late failures be due to ischemic injury, possibly from first reversal? The group stressed the importance of assuring an adequate blood supply to the vasal ends.

O-31-34
Gonadotoxin effects on male fertility.

These abstracts examined the effects of various gonadotoxins, including air pollution, tobacco smoke, heavy metal, and ibuprofen on various seminal parameters and/or pregnancy outcome. Lichtenfels, et al found an altered female/male ratio when air pollution levels were higher. This was seen in both human and murine studies. Burkman, et al determined that chronic tobacco smokers were found to have altered sperm binding, as measured by the hemi-zona assay (HZA). They then calculated a "smoking load index" and found that those with a lower load had 71% positive HZA compared to 18% with a higher load. Wirth, et al (as part of the FINS Study Group) examined heavy metal levels in men who consumed fish from the Great Lakes. Although levels such as mercury were higher, no effect was seen on seminal parameters. Finally, Robinson, et al examined ibuprofen use and its effect on seminal parameters, need for ICSI, and ART pregnancy rate. They demonstrated that ibuprofen had no significant effect on any of these outcomes.

Take home message: Although gonadotoxin exposure may alter seminal parameters, no data exists to demonstrate an effect on fertility. However, it is still recommended to optimize outcomes with smoking cessation and the avoidance of potential gonadotoxins.

O-35 Leukocytospermia and DNA integrity.

Moskovtsev, et al examined the presence of leukocytospermia (LCS) and its possible effect on semen parameters and DNA fragmentation. They showed a significant negative effect on seminal parameters, including concentration, motility, and morphology, and a very weak effect on DNA fragmentation index (DFI). The authors concluded that other factors might play a larger role in DNA fragmentation.

Take home message: Although LCS might have a negative effect on seminal parameters, it might not play a major role in DNA fragmentation.

TUESDAY, OCTOBER 18, 2005; 1:30 P.M. – 2:15 P.M.

Plenary Session. CFAS John Collins Lecture "Sperm DNA Damage and Male Infertility." Armand S. Zini, MD
Summarized by Jon L. Pryor, MD

On Tuesday, October 18, Dr. Armound S. Zini, MD, an assistant professor from the Department of Urology at McGill University, presented the John Collins Lecture entitled, "Sperm DNA Damage and Male Infertility." Dr. Zini began by asking why we even care about assessing sperm integrity. He thinks that conventional semen parameters do not tell all and we need other tests to assess the ability to conceive, that we need new markers to predict success from IVF, and that we need to determine the influence of DNA damage on the health of any offspring. He showed how there is specific DNA-protein composition that is presumed to establish precise gene expression post-fertilization. Dr. Zini then reviewed the various indirect and direct approaches to estimating DNA damage in sperm, including their limitations, the most obvious being that any sperm you have assessed its DNA integrity cannot be used for IVF with ICSI. All of the assays described to measure DNA damage measure different things, but their results correlate with each other. And they suggest that sperm DNA damage correlates with infertility. However, the degree of damage and nature of damage and its specific correlation to infertility has not been explored. Semen abnormalities, in particular protamine deficiency and Reactive Oxygen Species (ROS) has been associated with sperm DNA damage. Protamine deficiency and ROS, in turn, can occur from numerous etiologies, including genetic, gonadotoxins (e.g. cigarette smoking), increased environmental temperatures, and multifactorial causes. Dr. Zini feels that the SCSA holds promise as an assay that measures DNA damage. Looking at a large series of assays for DNA damage, he thinks that DNA damage is not associated with decreased fertilization rates, but may be contributors to abnormal embryo development and decreased pregnancy rates. Clinical utility, today, is that these assays may be good predictors of poor outcome for conception. On an individual level, assessing DNA integrity of sperm might be useful for longitudinally following an individual, toxicology studies, and following offspring in those parents who have been shown to have increased DNA damage. There might be treatment options for those with increased abnormal DNA damage: eliminate the goandotoxin, vitamins (e.g. C and E) that lower ROS, antibiotics if there is semen infection, varicocelectomy in those with a varicocele, and possibly using sperm directly from the testis for those who need ICSI. In summary, there is a subset of men with increased DNA damage, our understanding of the nature of DNA damage is rudimentary, and patients with increased DNA damage and their offspring should be followed prospectively.

TUESDAY, OCTOBER 18, 2005; 3:45 P.M – 5:00 P.M.

Podium Session.
Summarized by Christopher G. Schrepferman, MD

O – 178

Drs. Sukkarieh and Sheynkin reported on a case series of 11 patients found to have non-palpable testis masses on routine scrotal ultrasonography for male infertility. A total of eight patients had surgery: six with needle localization and microsurgical excision and two with radical orchiectomy. Of the eight tumors, six were Leydig cell tumors or nodules, one was malignant germ cell neoplasm, and one was scar only. Testicular sperm extraction was performed successfully in two patients with Leydig cell tumor. These findings emphasize the likelihood of benign histology in non-palpable testicular masses in a small number of patients. Audience members questioned the utility of routine scrotal ultrasound in male infertility patients. A trial of testosterone therapy, particularly in men with no possibility of sperm retrieval, was suggested as a way to help distinguish Leydig cell tumors and avoid unnecessary surgery, as the tumors should resolve with testosterone. Concerns were also raised about the possibility of multi-focal CIS, particularly in cases with seminoma.

O – 179

Dr. Roudeboush *et al* reported on the association between reproductive hormone levels (total testosterone, LH, FSH, and prolactin) and severity of obesity based on body mass index (BMI) calculations. Total serum testosterone was found to be inversely correlated with BMI, while no other reproductive hormones correlated. No data were reported on free testosterone or sex-hormone binding globulin levels, which are particularly relevant in men with elevated BMI.

O – 180

Dr. Agarwal *et al* investigated the role of inhibin B as a marker for male infertility. Inhibin B, FSH, LF, testosterone, and prolactin levels were assayed in control subjects and a diverse group of infertile men. Inhibin B and testosterone levels were significantly lower in infertile men, and inhibin B levels showed strong correlation with testicular volume and semen parameters. Inhibin B may be a better marker for fertility than FSH and LH.

O – 181

Drs. Whitten, Nangia, and Kolettis reported on their clinical experience using clomiphene citrate therapy in 11 men with hypogonadotrophic hypogonadism (HH). Clinical responses were best in men with adult-onset idiopathic HH, as three of four men demonstrated normal FSH, LH, and testosterone levels and a mean sperm density of nearly 70 million/cc, leading to two pregnancies. Patients with Kallman's syndrome responded better to injectable gonadotropins. The authors suggest that clomiphene citrate may be an effective and inexpensive alternative to injectable gonadotropins in some men with HH, particularly if partial HH exists.

O – 182

Dr. Tanaka *et al* presented their technique to isolate spermatogonial stem cells (SSC's) from neonatal mice. Cell suspensions of neonatal testicular tubules were selected by density gradient and exposed to a magnetic bead conjugated monoclonal antibody followed by separation in a magnetic field (MACS system). SSC's were isolated well but proliferation after plating was minimal. The authors demonstrate an important laboratory technique for use in the eventual treatment of azoospermia.

TUESDAY, OCTOBER 18, 2005; 5:15 P.M. – 6:30 P.M.

Male Reproduction and Urology Abstracts and Lecture: "Evolution of Ejaculatory Dysfunction Treatment – A Shocking Story"
Summarized by Cathy Naughton, MD

Three abstracts were presented in this session before the mini symposium. Dr. Paul Turek and colleagues **(O-183)** found abnormal meiosis in men with maturation arrest compared to obstructive men with normal spermatogenesis (O-183: Is Progression Through Meiosis Normal in Men with Nonobstructive Azoospermia?). However, whether the number of cells demonstrating varying specific stages of meiosis is a global versus percentage difference is not known.

Can Anti Mullerian Hormone (AMH) and Inhibin B levels improve the predictive value of FSH to the irretrievability of spermatozoa in testis biopsies of men with non-obstructive azoospermia? Dr. Sathanandan and colleagues **(O-184)** asked this question (O-184: Anti Mullerian Hormone and Inhibin B: Discriminatory Markers of Azoospermia?); however, were only able to state based on a pilot study that Inhibin B is a better discriminatory marker than AMH in differentiating obstructive versus non-obstructive azoospermia.

USP26 is a testis-specific gene, located on chromosome Xq26, involved in the Ubiquitin-Proteasome Pathway. This pathway is a mechanism of discarding abnormally folded molecules by proteolysis. Dr. Paduch and colleagues **(O-185)** found a mutation (1090C-T) in the USP26gene in 10% of men with non-obstructive azoospermia (NOA) (O-185: A Specific Mutation in the USP26 Gene is Associated with Poor Sperm Recovery in Men with Non-obstructive Azoospermia). Men with this particular mutation were less likely to have successful sperm retrieval at TESE compared to men with a different alternation in the same USP26 gene (363ACAinsertion) or men with no identifiable chromosomal defects.

This mini symposium by Dr. Dana Ohl, Professor of Urology at University of Michigan, Ann Arbor, was an informative discussion through the history of electroejaculation (EEJ) and penile vibratory stimulation (PVS), two available treatments for ejaculatory dysfunction. He highlighted the three resultant problems of erectile dysfunction, ejaculatory dysfunction, and poor semen quality in men with spinal cord injury (SCI). There are approximately 10,000 new cases of SCI yearly, 82% of afflicted are men. The majority of men are in their reproductive years (ages 16-30 years), highlighting that infertility becomes an important issue.

Almost 100% of men with SCI lose the ability to ejaculate, contributing to male infertility. In the past, intrathecal neostigmine was a successful but undesirable form of therapy due to autonomic dysreflexia and death from cerebral hemorrhage. Electroejaculation is a technique adopted from animal husbandry in the 1930s. Steven Seager introduced the potential idea of using electroejaculation in human after he successfully performed EEJ in a paraplegic poodle following a MVA. He then created a SCI monkey model and noted that he could retrieve preserved sperm production by EEJ.

Dr. Carol Bennett was responsible for bringing this technology to the bedside, and performed EEJ with Steven Seager on a SCI human patient. The first pregnancy resulting in a live birth was reported in 1984 in the United States. Dr. Bennett developed human protocols, established safety of the procedure, as well as a collaborative effort with obstetrics and gynecology to show the efficacy of this technique in the treatment of male infertility due to SCI.

Higher success rates with EEJ are observed with patients with thoracic lesions, complete lesions, and patients who perform intermittent catheterization for bladder management. The samples obtained from EEJ have extremely high sperm concentrations, but extremely low motility and viability.

Penile Vibratory Stimulation (PVS) was developed to overcome the limitations of EEJ, and provide another treatment option. The technique rests on the principle of stimulating the pudendal nerve causing seminal emission through T11-L2 and projectile ejaculation through the sacral cord, S2-4. Reported success rates in the literature (19-91%) are erratic and variable. Part of the immense variability in success rates using this technique was the inconsistency in the amplitude setting. A study using 2.5mm versus 1.0mm amplitude resulted in 96% versus 32% success ejaculation rates using this device. The ease and efficacy of this technique lead to development of the FertiCare Device, from Multicept A/S, Denmark. Successful antegrade ejaculation with PVS device is more likely in patients with spinal cord lesions above T10, upper motor neuron lesions, intact bulbocavernosa and hip flexion reflexes. Unfortunately, the limitations of low pregnancy rates and poor sperm quality still exist with the PVS technique.

Dr. Ohl was involved in numerous studies to determine possible etiologies of poor sperm quality from SCI patients using EEJ and PVS. Theories of aberrant hormone levels, autoimmunity, electrical injury during EEJ, and higher prevalence of UTIs in this patient population were shown not to be critical in causing poor sperm quality. It appears from Dr. Ohl's and Dr. Nancy Brackett's (Research Associate Professor of Neurologic Surgery and Urology, Miami Project to Cure Paralysis) studies that poor

sperm quality in spinal cord patients is secondary to disordered sperm storage in the seminal vesicles from a neurological etiology, and is not related to ejaculation frequency.

Dr. Ohl provided the audience with a clinical treatment algorithm for sperm acquisition in spinal cord patients. He recommends PVS first, and reserves EEJ for PVS-non-responders, as he found higher antegrade ejaculation viability and more favorable SPA penetration test results using PVS. Further, almost all patients prefer PVS to EEJ, as less pain is experienced using the former. In comparing pregnancy rates using IUI versus IVF, he recommends a limited number of IUI cycles in SCI patients who do not require anesthesia for ejaculated sperm acquisition before proceeding to IVF, as this algorithm has been shown to be more cost-effective than proceeding straight to IVF. However, in patients who require anesthesia for sperm acquisition, such as sensate men who have undergone retroperitoneal lymph node dissection, he recommends proceeding directly with testis sperm extraction techniques in combination with IVF.

WEDNESDAY, OCTOBER 19, 2005; 10:45 A.M. – 12:00 P.M.

Interactive Sessions. Making Sense of Sperm Morphology. Society for Male Reproduction and Urology.
Summarized by Shane Russell, MD

Dr. Nancy Brackett began this session with a historical analysis of the development of sperm morphology evaluation dating back to the 1930s. Two pervasive trends identified throughout this time period included the recognition of significant lab variability in judging sperm morphology, as well as the increasingly strict definitions of what constitutes a normal sperm shape. Whereas in the 1930s, fertile men were thought to have between 70-90% normal forms by the prevailing classification schemes, andrology labs today using Kruger strict criteria have decreased accepted cut-offs for normal fertility to as low as 4% normal forms.

Dr. William Roudebush then explored the controversies surrounding the clinical use of sperm morphology in predicting fertility outcomes. A major theme has been the continuing problem with consistency in andrology lab outcomes when grading sperm morphology. Some reasons postulated for this included the numerous existing classification schemes in use, inadequate training and quality control, use of improper or outdated techniques, inconsistencies in quality control, and conflicting or ambiguous references and standards. It was concluded that more practical and reproducible methods and standards need to be developed.

A key component of clinical utility of sperm morphology is the establishing of threshold values for normal and abnormal forms. An "ideal" threshold would be a number below which no pregnancies would occur and above which patients without a female factor could consistently expect to achieve pregnancy. Unfortunately, no such "ideal" threshold will likely ever be found, and the best that we can reasonably attain will be a threshold number below which significantly fewer pregnancies will occur, and above which significantly more pregnancies will occur, and the inevitable overlap between them will be minimal. Another factor in setting thresholds is that they would be expected to differ depending on whether natural intercourse or some form of ART is being used.

The original Kruger strict criteria cut-off of 14% normal forms was established for predicting outcomes with standard IVF. Percent normal forms above 14% (and in later studies, 5%) were found by Kruger et al. to be associated with improved fertilizations rates (FR) and pregnancy rates (PR). A review of IVF studies looking at the 14% strict criteria cut-off found that four of five reviewed studies showed an improved FR with % normal forms above 14%. However, only two of eight IVF studies showed improved PR with using a cut-off of percent normal forms >14%. A review of studies using a 5% normal forms cut-off found similar results. Overall conclusions for the use of morphology is that it seems better at predicting FR outcomes than PR outcomes in couples undergoing IVF, but that its use as an isolated parameter seems limited. It was suggested that the clinical utility of sperm morphology could be enhanced by using it in combination with other studies, such as DNA fragmentation studies, sperm function assays, or other standard semen parameters.

Sperm morphology as a predictor of intrauterine insemination (IUI) outcomes were next evaluated by Dr. Roudebush. A review of 11 IUI studies showed that seven of these studies showed an improved PR with normal forms above a cut-off that ranged between 4% and 15.5%. Studies have suggested that total motile sperm (TMS) counts and motility may be better predictors of IUI outcomes than morphology. It was also suggested that morphology might only be predictive of IUI outcomes if TMS counts were over five million. It was again concluded that morphology seemed to have limited predictive value of IUI when used in isolation.

The predictive value of sperm morphology in predicting pregnancy by natural intercourse showed that lower morphology was, in general, associated with subfertility, but has limited value when used as an isolated factor. An extensive review of the literature in 2002 found 265 articles related to the subject, but only four of these has had sufficient power to be evaluated. Of these four articles, two (50%) found that morphology had predictive value in natural intercourse outcomes. The cut-off for normal threshold range remains unclear, but a range of between 3% to 12% was suggested. The problem in establishing an ideal threshold is that, because of the extensive overlap between groups, when the threshold level is raised, then positive predictive value was reduced, while any drop in threshold value results in a corresponding drop in sensitivity.

In conclusion, Dr. Roudebush stated that when used in isolation, sperm morphology is a poor diagnostic test for determining whether a man will be fertile or infertile. A low morphology in general does not exclude the ability to achieve pregnancy by any technique, but does have a relationship to outcomes with each of them. At this time, no strong general recommendations for percent normal form cut-offs can be given, and the suggested best approach is to correlate your own andrology lab's thresholds with conception rates in one's own practice to serve as a guide.

Discussion overseen by Dr. Sigman at the end of the talks brought up several interesting, relevant topics. One included the phenomenon that as criteria for grading sperm morphology has become increasingly strict, the number of patients with "normal" morphology parameters seen in clinic is becoming vanishingly small. This prompted discussion as to the clinical relevance of a test in which such a small percentage of patients have a normal value finding. Dr. Turek questioned the relevance of the standard cut-offs for the Kruger strict criteria in severely oligospermic patients, because the original studies were performed in patients with otherwise fairly normal semen parameters. In clinical practice, poor sperm density and motility are almost invariably associated with significantly decreased morphology, so Dr. Turek questioned the impact of the morphology component in terms of pregnancy outcomes in this patient population. Finally, Dr. Lamb brought up the statistical problems with sperm morphology grading when only 200 sperm are counted out of a population of often millions of sperm.

WEDNESDAY, OCTOBER 19, 2005; 4:30 P.M. – 5:45 P.M.

Male Reproduction and Urology Lecture: The Male Biological Clock by Dr. Harry Fisch, MD
Summarized by Dolores J. Lamb, PhD

Dr. Harry Fisch presented a talk on the male biological clock. The age of parenthood has increased for both men and women, and fertility declines for both genders with advancing age despite the fact that men do not undergo total cessation of their fertility as occurs in women. Sex hormone levels gradually decline, affecting both fertility and man's sense of well-being. Treatment of "andropause" with testosterone replacement is increasing to diminish problems such as libido and erectile dysfunction, loss of muscle mass and strength, and weight gain. Nevertheless, there is concern that the indiscriminate use of testosterone replacement products may present risks for patients.

Studies show that 35-year-old men are twice as likely as 25-year-old men to be infertile. Similarly, fertility treatments with IUI required a longer treatment for older men to achieve a pregnancy. Of note, the risk of miscarriages appears to rise with increasing paternal age, and there are specific genetic and genomic diseases, such as schizophrenia and Down's Syndrome, for example, that also increase in incidence for aging fathers. Studies indicate that reproductive aging is not a problem only faced by women and that there needs to be a new awareness of the male biological clock. Research is needed to define effective methods to delay this reproductive aging, or at least lessen the potential for an adverse genetic consequence for the aging male father. ⌘

Needs & Objectives for the 2006 SSMR AUA Program

Needs Statement:

Urologists must be knowledgeable of the following:
1. The basic anatomy and physiology of the epididymis, vas deferens, seminal vesicles, and ejaculatory duct.
2. The changes that arise in the epididymis as a result of inflammation and obstruction.
3. The pathophysiology and treatment of ejaculatory dysfunction.
4. The best diagnostic technique(s) and surgical treatment for ejaculatory duct obstruction.
5. The role of epididymal reconstructive surgery in the era of IVF/ICSI.
6. The best technique(s) for sperm retrieval in the obstructed male.

Learning Objectives:

At the conclusion of this continuing medical education activity, participants should be able to:
1. Describe the anatomy and physiology of the genital ductal system.
2. Discuss the numerous anatomical and physiological changes that occur in the epididymis as a result of obstruction and inflammation.
3. Summarize the epidemiology and pathophysiology of ejaculatory dysfunction, as well as available treatment options.
4. Analyze the diagnostic modalities available for the evaluation of men with ejaculatory duct obstruction.
5. Appraise the role of epididymal and vasal reconstructive surgery vs. IVF/ICSI for couples attempting to initiate a pregnancy.
6. Determine the best sperm extraction technique(s) for the obstructed male. ⌘

This scientific program will offer 2.75 category 1 credits

Special Assistance
We encourage participation by all individuals. If you have a disability, advance notification of any special needs will help us better serve your. Call 847-517-7225 if you require special assistance to fully participate in this activity.

SSMR 2006 Meeting at the AUA

Commitments as of 1/16/06

This activity is supported in part through educational grants from:

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Agenda for SSMR at the 2006 AUA

Saturday, May 20, 2006

1:00 p.m. – 4:00 p.m.

Annual Business Meeting will be held from 4:00 p.m. – 5:00 p.m.

Georgia World Congress Center – Room A311/312
Atlanta, Georgia

"The Excurrent Ductal System: Pathway to Parenthood"

Program Chair: Robert E. Brannigan, MD

1:00 p.m. – 1:05 p.m. **Introduction**
Robert E. Brannigan, MD
Assistant Professor of Urology
Department of Urology
Northwestern University,
Feinberg School of Medicine
Chicago, Illinois

1:05 p.m. – 1:20 p.m. **"The Epididymis: A State-of-the-Art Overview of Normal Anatomy and Function"**
Terry T. Turner, PhD
Professor of Urology and Cell Biology
University of Virginia Health System
Charlottesville, Virginia

1:20 p.m. – 1:35 p.m. **"Epididymitis and Other Inflammatory Conditions of the Male Excurrent Ductal System"**
Peter Chan, MD
Director of Male Reproductive Medicine
Division of Urology, Department of Surgery
McGill University
Montreal, Quebec

1:35 p.m. – 1:50 p.m. **"Congenital Epididymal Abnormalities"**
Thomas F. Kolon, MD
Assistant Professor of Urology
Department of Urology,
Division of Pediatric Urology
The Children's Hospital of Pennsylvania
Philadelphia, Pennsylvania

1:50 p.m. – 2:00 p.m. **Question and Answer Session**

2:00 p.m. – 2:30 p.m. **"Vasal and Epididymal Reconstructive Surgery in the Era of IVF/ICSI"**
Anthony J. Thomas, Jr., MD
Head, Section of Male Infertility
Cleveland Clinic Glickman Urological Institute and
Cleveland Clinic Department of Obstetrics and Gynecology
Cleveland, Ohio

2:30 p.m. – 2:50 p.m. **"Ejaculatory Duct Obstruction: Which are the Best Techniques to Diagnose and Treat?"**
Paul J. Turek, MD
Associate Professor
Department of Urology
University of California, San Francisco
San Francisco, California

2:50 p.m. – 3:00 p.m. **Question and Answer Session**

3:00 p.m. – 3:10 p.m. **Break**

3:10 p.m. – 3:25 p.m. **"Fertility in Men with Spinal Cord Injury: New Insights"**
Nancy Brackett, PhD, HCLD
Research Associate Professor, Neurological Surgery and Urology
The Miami Project to Cure Paralysis at the Miller School of Medicine
University of Miami
Miami, Florida

3:25 p.m. – 3:45 p.m. **"Ejaculatory Dysfunction Treatment: Counseling, Behavioral Therapy, or Medicine?"**
Stanley E. Althof, PhD
Professor of Psychology, Case School of Medicine
Executive Director, Center for Marital and Sexual Health of South Florida
West Palm Beach, Florida

3:45 p.m. – 4:00 p.m. **Question and Answer Session**

4:00 p.m. – 5:00 p.m. **Annual Business Meeting**

Dear Urology Residency Directors and 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 Sixth Annual Traveling Fellowship Program with the SSMR and the second combined award for the two societies. This will take place in conjunction with the 2006 AUA meeting in Atlanta, Ga.

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 first 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.

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 Saturday through Tuesday 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 enclosed, 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. **The application deadline has been extended to February 10, 2006.** The awards will be announced by March 4, 2006.

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, MD
Dartmouth Hitchcock Medical Center
Section of Urology
One Medical Center Dr.
Lebanon, NH 03756

You are invited to attend the 2006 SSMR Annual Banquet!

Saturday, May 20, 2006

Ruth's Chris Steakhouse

Embassy Suites Hotel

267 Marietta Street, Atlanta, GA 30313

Register for the banquet quickly and easily online at www.ssmr.org!

Ruth's Chris Steak House is situated in the lobby of the Embassy Suites hotel just across the street from the Georgia World Congress Center, CNN and Phillips Arena. This Ruth's Chris restaurant in downtown Atlanta offers dramatic views of Centennial Olympic Park (the home of the 1996 Summer Olympics).

Cocktails 6:30 p.m. – 7:30 p.m.
Dinner 7:30 p.m.

If you have any dietary needs, please contact the SSMR office at (847) 517-7225 prior to April 21, 2006.

Business casual attire is appropriate.

# of people attending _____ x $75.00 per person = $ _____ (on and before April 21, 2005)

# of people attending _____ x $85.00 per person = $ _____ (after April 21, 2005)

Name:_____Spouse/Guest:_____

Address:_____

City:_____State:_____ Zip: _____

Phone:_____Fax:_____

Method of Payment:

❒ Check (payable to the SSMR) ❒ Visa ❒ MasterCard

Card #:_____Exp. Date:_____

Signature:_____

Please return this form to the SSMR office no later than April 21, 2006.

SSMR
1111 N. Plaza Drive, Suite 550
Schaumburg, IL 60173
Phone: (847) 517-7225
Fax: (847) 517-7229
E-mail: ssmr@wjweiser.com
Website: www.ssmr.org

Mark Your Calendars!

31st Annual Meeting of the American Society of Andrology
April 8 - 11, 2006
Hyatt Regency Chicago on the Riverwalk
Chicago, Illinois

ASA Annual Meeting
April 8 - 11, 2006

Andrology Lab Workshop
April 8, 2006

Postgraduate Course
April 8, 2006

American Urological Association Annual Meeting
May 18 – 25, 2006
Atlanta, Georgia

SSMR Meeting at the AUA Annual Meeting
May 20, 2006
Scientific Program: 1:00 p.m. – 4:00 p.m.
Annual Business Meeting: 4:00 p.m. – 5:00 p.m.
Atlanta, Georgia

Society for the Study of Male Reproduction
1111 N. Plaza Drive, Suite 550 ♦ Schaumburg, IL 60173
Phone: 847-517-7225 ♦ Fax: 847-517-7229 ♦ Email: ssmr@wjweiser.com ♦ Website: www.ssmr.org

SSMR
1111 N. Plaza Drive, Suite 550
Schaumburg, IL 60173-4950

Application for the Men's Health Traveling Fellowship Program 2006

Saaturday, May 20 – Wednesday, May 24, 2006
Atlanta, Georgia

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, MD
Dartmouth Hitchcock Medical Center
Section of Urology
One Medical Center Dr.
Lebanon, NH 03756

Deadline: February 10, 2006