NEWS

SSMR

SOCIETY FOR THE STUDY OF MALE REPRODUCTION

SSMR NEWSLETTER FALL 2004

PRESIDENT'S MESSAGE

CRAIG NIEDERBERGER, MD, FACS

Welcome, members of the SSMR, to another year of advancement in the field of male reproduction. Ours is truly one of the most exciting subspecialty areas in Urology, moving rapidly into the science and medicine of the future. Encapsulated in this newsletter for your reading pleasure, our Vice-President, Dolores Lamb, organized a team of reporters who have summarized the salient points in each of the male reproductive sections of the recent annual American Urological
Association meeting in San Francisco.

Mark Sigman organized a compelling and highly useful Scientific Session during the afternoon of Saturday, May 8. The basic science topic was presented by Marcel Cedars, "What the Urologist Needs to Know About Ovulation Induction," and the clinical science session included targeted talks on seminal assays designed to give the clinician a focused understanding of how and where these tests are best used and interpreted. Peter Chan reported a fascinating survey of current techniques of sperm extraction in use by urologists and ART laboratories. Mark's hard work was clearly evident in a successful, interesting, and manifestly useful session.

Peter Chan is organizing the 2005 SSMR Scientific Session, which promises to be interesting and practical for the practicing urologist. Details will follow in the spring newsletter, which will be sent prior to the 2005 annual AUA meeting. Please encourage your urological colleagues who may not be members of the SSMR and who will not receive our newsletter to attend this Scientific Session, as it is designed to be appealing to all.

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Paul and Ashley Stiles Turek hosted a wonderful SSMR banquet Saturday night following the Scientific Session. From a perch dizzyingly high in San Francisco's sky, our friends and colleagues mixed and mingled surrounded by spectacular views of the city below. Paul and Ashley's choice of the restaurant and their gracious hosting provided a truly memorable evening. Edmund Sabanegh and Dolores Lamb will co-host the SSMR banquet at next year's AUA meeting in San Antonio, at what will certainly prove to be an enjoyable and entertaining event.

Jay Sandlow has turned the reins of the SSMR Traveling Fellowship Program to Ajay Nangia. Jay's work in initiating, organizing and promoting the Traveling Fellowship Program over the years resulted in a truly outstanding educational event that fostered many young urologists in developing male reproductive medical careers. We all are truly indebted to Jay for his substantial efforts, and offer our great thanks. Likewise, Ajay's agreeing to continue this wonderful program and resource for the future of our field is deeply appreciated. If you are involved in resident training, please encourage your residents to apply for this outstanding program.

We are entering an era when finding external financing for our Society is becoming increasingly challenging. Pressures from many sides are limiting the traditional sources of income that provide all of our educational programs. The executive committee is currently considering structural changes to consolidate and augment fundraising efforts. If you have any ideas or sources of funding, please contact our Treasurer, Jay Sandlow, to coordinate efforts. Everyone's help is very much needed and deeply appreciated.

Finally, I would like to personally thank Bob Oates, our past president, and Peter Schlegel, who preceded him. Bob made a dazzling array of improvements to our Society, and his educational efforts last year were well considered and clearly successful. Peter continued to work extraordinarily hard for our Society, and his dedication is seen it its smooth function and evolution. Both leave impossibly large shoes to fill, and we all continue to owe debt to these remarkable individuals.

I hope your summer was wonderful, and I look forward to working with you for a promising, enjoyable and fruitful year for the science and medicine of male reproduction. ◆

4th Annual SSMR Traveling Fellowship Program

The 4th annual SSMR Traveling Fellowship program took place at the AUA in San Francisco this year and was a great success. These awards are designed to expose young urology residents to the field of male infertility, and allow them to participate in many of the events at the AUA. Nine participants from various institutions were selected. The fellows attended the SSMR Postgraduate Course and banquet, went to all of the infertility plenary, podium, and poster presentations, took the Male Infertility Postgraduate Course, and participated in a roundtable discussion with some of the up-and-coming leaders in the field of male infertility, including Cathy Naughton, Ajay Nangia and Christopher Schrepferman. The experience culminated with an informal cocktail party, where the fellows were able to meet with many of the SSMR members. The program allowed these young urologists-in-training to attend the AUA meeting, as well as gain exposure to the field of male infertility. The fellows who participated this year were:

Sean T. Corbett, MD	Dartmouth University
Beneranda Sophia Ford, MD	State University of New York-Buffalo
Mohit Khera, MD	Baylor College of Medicine
Antoine A. Makhlouf, MD	University of Virginia
Jennifer L. Maskel, MD	University of Wisconsin-Madison
Sergio G. Moreira Jr., MD	University of South Florida
Jay D. Rayman, MD	Weill Medical College of Cornell University
Nikhil Lalit Shah, MD	Henry Ford
Charles J. Viviano, MD	University of Connecticut

There will be some changes for the future. We plan to have the activities earlier in the week so that more junior level residents can participate. Sessions regarding erectile dysfunction will be included, and the fellows will receive a talk on one of the mornings by an expert in the field. Finally, the reins will be passed to Dr. Nangia, who will assume the chairmanship of the award committee. It has been a privilege to hold this position over the last four years, and I will continue to serve on the committee. Next year's program in San Antonio will be a great one and we hope to have many applicants.

The feedback has been tremendous and we will continue to offer this great experience to all urology residents. Questions may be directed to Ajay K. Nangia (Ajay.K.Nangia@Hitchcock.org).

Jay Sandlow, MD
Medical College of Wisconsin ◆

2004 ASRM Events of Interest

ASRM Annual Meeting
October 16-20, 2004
Pennsylvania Convention Center
Philadelphia, Pennsylvania

Saturday, October 16, 2004
Postgraduate Course #8: The Role of the Andrologist in the Era of ART
Faculty:
Peter N. Kolettis, M.D., Chair
Jay I. Sandlow, M.D., Co-Chair
Peter N. Schlegel, M.D.
Michael P. Steinkampf, M.D., M.P.H.

Saturday and Sunday, October 16 – 17, 2004
Postgraduate Course #4: Male and Female Sexual Dysfunction-Contemporary Thought and Interventions
Faculty:
William D. Petok, Ph.D., Chair
Jeanne Leventhal Alexander, M.D.
Barry W. McCarthy, Ph.D.
Abraham Morgentaler, M.D., F.A.C.S.

Monday, October 18, 2004; 10:45 a.m. – 12:00 p.m.
Society for Male Reproduction and Urology (SMRU) Traveling Scholar Abstracts

12:00 p.m. – 2:00 p.m. Roundtable Luncheons

- Varicoceles and ART (M31)
- Sperm Retrieval in Non-obstructive azoospermia (M32)
- Genetic Evaluation of the Infertile Male (M33)
- Cancer and Male Infertility (M34)
- Role of Sperm DNA Integrity Testing in Human Assisted Reproduction: Evidence-based Medicine (M35)
- How to Upgrade Male Fertility to Lower the Grade of Assisted Reproduction (M36)
- Managing Ejaculatory Duct Obstruction (M76)

2:00 p.m. – 3:15 p.m. Male Reproduction and Urology Abstracts

4:00 p.m. – 4:30 p.m. William C. Andrews Wyeth Endowed Lectureship "Endocrine Aspects of Reproductive Aging in Men and Women"

4:45 p.m. – 6:00 p.m. Male Reproduction and Urology Abstracts

Tuesday, October 19, 2004

8:00 a.m. – 8:45 a.m. American Urological Association Bruce Stewart Memorial Lecture
"Laparoscopic Surgery: Past, Present, and Future"

10:45 a.m. – 12:00 p.m. Workshop
Testosterone Supplementation or No Supplementation in Men and Women
Chair: Sheryl A. Kingsberg, Ph.D.
Presenters:
Allen D. Seftel, M.D.
Rogerio A. Lobo, M.D.

12:00 p.m. – 2:00 p.m. Roundtable Luncheons

- Options to Preserve Fertility in Male Cancer Patients (T24)
- Processing Testicular and Epididymal Samples for ICSI (T30)
- Microsurgical Reconstruction for Obstructive Azoospermia (T31)
- Effect of Sperm Source on ART Outcomes (T32)
- Conservative Testicular Surgery for Germ Cell Tumors (T33)
- Cryopreservation of Testicular Samples for ICSI: Surgical and Laboratory Techniques (T34)
- Complementary and Alternative Medicine in Andrology: An Evidence-based Analysis T35)
- Ejaculatory Duct Obstruction: Diagnosis and Management

2:00 p.m. – 3:15 p.m. Male Reproduction and Urology Abstracts

4:45 p.m. – 6:00 p.m. Male Reproduction and Urology Abstracts

Wednesday, October 20, 2004

2:00 p.m. – 3:15 p.m. Society for Male Reproduction and Urology Abstracts

4:45 p.m. – 6:00 p.m. Society for Male Reproduction and Urology Abstracts

6:00 p.m. – 6:30 p.m. Society for Male Reproduction and Urology Business Meeting

10:45 a.m. – 12:00 p.m. Workshop
Stem Cell Technology for Male Infertility Treatment
Chair: Dolores J. Lamb, Ph.D.
Presenters:
Pasquale Patrizio, M.D.
Kirk C. Lo, M.D. ◆

2004 AUA REVIEWS

SSMR Meeting
Mark Sigman, M.D.

For the first time, the complete PowerPoint files, the audio recordings of the discussions after the presentations, and a more detailed summary of all of the talks may be downloaded for free to SSMR members at **www.ssmr.org**.

Ovulation Induction: What the Urologist Needs to Know
Mark Sigman, M.D.

Marcel Cedars presented "Ovulation Induction: What the Urologist Needs to Know." She reviewed the methods of assessing ovarian reserve. A day 3 FSH < 9 mIU/ml, and estradiol < 50 mIU/ml, and a day 10 FSH < day 3 FSH were reassuring prognostic factors. Dr. Cedars felt that an antral follicle count of < 4 during a non-stimulated cycle is the most useful prognostic indicator of poor ovarian reserve. Age > 40 years old is an independent poor prognostic indicator even with favorable FSH and E2. For women whom have had prior stimulated cycles, the oocyte number and quality are important factors. Ovulation induction regimens were reviewed: long Lupron, the flare protocol, and the antagonist protocol. Finally, there is new interest in less aggressive regimens of oocyte stimulation.

The Biology of Fertilization
Mark Sigman, M.D.

Dr. Vanessa Rawe presented "The Biology of Fertilization." The sequential steps involved in this process were reviewed: capacitation and the acrosome reaction; sperm/egg binding and fusion; sperm incorporation into the oocyte; egg activation; completion of the oocyte meiotic maturation; the extrusion of the egg's 2nd polar body; sperm aster formation; pronuclear formation; genomic apposition; beginning of first cell cycle; genomic union during first cell division of the zygote. Fate and importance of the sperm components were reviewed. Dr. Rawe classified sperm defects into two categories: Systemic, which are very homogeneous being present in the majority of the spermatozoa in a given semen sample; in contrast, non-systematic defects are usually secondary to pathologies that affect the normal function of the testis or the seminal pathway.

Andrologic Lab Test Panel
Mark Sigman, M.D.

A panel with Drs. Michael Witt, Harris Nagler, and Craig Niederberger, and moderated by Mark Sigman, discussed common andrologic lab tests. For each test the panelists were to answer several questions. What is the test? What does it measure? What are the indications? What information does it yield that cannot be obtained or predicted from the results of a standard SA? Do the results affect management of the couple any differently than results from the standard SA? Tests reviewed were semen volume, pH, fructose, sperm functions tests, viability assays, antisperm antibody testing, sperm cervical mucus interaction assays, and sperm DNA integrity assays.

Dr. Chan reported the results of a survey of andrologists and IVF embryologists about the selection and use of testicular sperm extraction techniques in patients with non-obstructed azoospermia. Micro-TESE was the most commonly employed first technique followed by multiple testis biopsies. An embryologist was always present in the OR in for 70% of respondents. Once received in the embryology laboratory, 64% utilized sharp dissection of the tissue. Sperm retrieval was performed only in conjunction with egg retrieval (fresh) in 36% centers, while both fresh and frozen sperm were utilized in 36% of other centers. Sperm retrieval success rates were similar between different approaches and it was not possible to determine a "most successful approach."

Monday Plenary Session: State-of-the-Art Stem Cell Transplant in Male Infertility
Dolores J. Lamb, Ph.D.

Dr. Victor Trey Brugh presented an overview of adult stem cells transplantation as a potential treatment for male infertility in the future. Adult stem cells are defined by their unique properties of prolonged proliferation, self-renewal, generation of differentiated progeny, maintenance of developmental potential and proliferation in response to injury. They offer the potential of restoration of spermatogenesis after toxic insult. Genetic or acquired stem cell defects are recognized etiologies of male infertility. Potentially, patients with secondary infertility due to exposure to testicular toxicants, such as after chemotherapy or radiation therapy or following accidental occupational exposures, could realize benefits from restoration of spermatogenesis after spermatogonial stem cell transplantation. It is proposed that patients could undergo a testis biopsy for cryopreservation of testicular stem cells prior to chemotherapy. Subsequent transplantation after recovery could then restore spermatogenesis otherwise damaged by treatment. Primary infertility patients with stem cell defects in primordial germ cell migration during development or those with defects in stem cell renewal during adult spermatogenesis could also potentially benefit from this type of therapy. Dr. Brugh summarized the current research status of spermatogonial stem cell purification, a necessity for translation of the studies using mouse models to human male infertility. Because an autologous transplantation of spermatogonial stem cells retrieved prior to chemotherapy is likely to be one of the first applications of spermatogonial stem cell transplantation, it is critical that purification techniques be optimized to ensure that contaminating cancer cells are not inadvertently transplanted back to the patient along with the adult spermatogonial stem cells. This is a rapidly advancing field that should benefit patients in the near future.

Defining the Standard for Vasectomy Success
Jay Sandlow, M.D.

Dr. Harry Fisch presented Defining the Standard for Vasectomy Success. Dr Fisch outlined some of the controversies regarding the standard of care for vasectomies. He stated that there is an underlying failure rate of 0.1%. Early failures are typically due to residual sperm, whereas late failures are typically due to recanalization. He then presented data that demonstrated that post-vasectomy, approximately 72% of men are azoospermic at 3 months. This number increases to 85% at 6 months, and 99% at 12 months. He stated that the type of vasectomy did not affect when azoospermia occurred (although recent data suggests that fascial interposition prevents recanalization). In regards to post-vasectomy semen analysis, motile sperm represents either error or recanalization, whereas non-motile sperm is typically due to residual sperm in the excurrent ductal system. The risk of pregnancy in this case is approximately 0.05% (1 in 2000). Therefore, if occasional non-motile sperm are detected, these likely represent residual sperm and not recanalization. He then asked the question, should we centrifuge post-vasectomy specimens. This is recommended by the WHO, but may not represent the current standard of care for

vasectomy, particularly in light of the above data.

Dr. Fisch summarized as follows. Sterility after vasectomy is not guaranteed. Post-vasectomy semen analysis should be checked at 3-6 months, as the vast majority of men with be azoospermic (or severely oligospermic) at this point. Although sperm may occasionally reappear, if they are rare and non-motile, they most likely do not represent recanalization. Centrifugation of post-vasectomy specimens is not the standard of care. If the neat sample demonstrates azoospermia, that is adequate for sterility. The bottom line is that all patients must be counseled regarding the importance of the post-vasectomy semen analysis and the possibility of pregnancy, even when samples are azoospermic.

Case Studies in Male Infertility/ Azoospermic Men
Craig Niederberger, M.D.

Case Studies in Male Infertility/ Azoospermic Men was chaired by Harris Nagler. Faculty included Dolores Lamb, Craig Niederberger, Robert Oates and Jon Pryor. Four clinical scenarios involving azoospermia were discussed. In the first, Dr. Nagler presented a patient with ejaculatory ductal obstruction. Dr. Lamb discussed the semen analysis, and Dr. Oates discussed the clinical evaluation and treatment of ejaculatory ductal obstruction. Salient points revealed in the case included that low ejaculate volume azoospermia may be due to ejaculatory ductal obstruction, congenital bilateral absence of the vas deferens and ejaculatory dysfunction, that seminal volume and pH indicate the diagnosis and that fructose may not be necessary. There is no need for testis biopsy to make the diagnosis, and various treatment options may be employed.

In the second case, Dr. Nagler presented a patient with azoospermia and a varicocele. Dr. Pryor presented the endocrine evaluation, and Dr. Oates discussed treatment issues and options. Summary points included a discussion of the hormonal evaluation of azoospermia, including pituitary versus testicular dysfunction, and endocrine patterns in obstructive versus nonobstructive etiology. Also noted was the genetic evaluation of nonobstructive azoospermia including karyotype and Y-chromosomal microdeletion analysis, and that varicocelectomy without testis biopsy is recommended.

In the third case, Dr. Nagler presented a patient with Klinefelter's syndrome. Dr. Pryor presented the genetics and histopathology of Klinefelter's syndrome, and risk of transmission to progeny. Dr. Niederberger discussed sperm acquisition techniques should the patient and his wife opt for sperm retrieval and in-vitro fertilization with intracytoplasmic sperm injection. Summary points included the genetics of this disorder, risk to offspring, recommendation of simultaneous sperm extraction for in-vitro fertilization with diagnostic biopsy if performed, and methods of sperm acquisition for non-obstructive azoospermia.

In the final case, Dr. Nagler presented a patient with congenital bilateral absence of the vas deferens (CBAVD). Dr. Niederberger presented the clinical findings accompanying this diagnosis, and Dr. Lamb presented the molecular genetics of CBAVD. Dr. Niederberger concluded with the clinical evaluation of the patient and sperm acquisition, should the couple decide with genetic counseling to attempt conception. Concluding points included that the diagnosis of CBAVD is made by physical examination, and that a genetic basis for the condition is assumed. Evaluation of the partner is required, and any technique may be used to obtain sperm.

The Treatment of Adolescent Varicoceles
Jay Sandlow, M.D.

The treatment of adolescent varicoceles, a discussion lead by Lawrence Baskin and debated by Evan Kass and David Diamond, centered on the controversy surrounding the adolescent varicocele. The potential implications of the untreated varicocele include the effects on testicular growth and future fertility. Dr. Kass presented some historical data regarding the effects of varicocele repair on testicular growth, utilizing the concept of catch-up growth to provide support for early repair. He then presented the hypothesis that early repair reduces the risk of infertility in selected boys. He cited data showing Leydig cell scores are different in adolescents as compared to adults, representing an early opportunity to prevent later injury. He also demonstrated that testicular volume loss is more common in older boys with grade 2 varicoceles, but that almost all boys with grade 3 varicoceles will have volume loss in both testicles, even with a unilateral lesion.

Dr. Diamond countered with epidemiologic data demonstrating that perhaps only 1 in 10 adolescents will benefit from repair. Based on this data, since only 1/10 will benefit, and we cannot select that one, 9 will undergo potentially unnecessary surgery. Furthermore, the GnRH stimulation test doesn't correlate with volume loss. In addition, testicular volume loss does not correlate with seminal parameters and future fertility. Although it has been stated that varicoceles are a progressive lesion, there is no good prospective data regarding the effect of the adolescent varicocele on seminal parameters and testicular volume over time.

Dr. Kass rebutted with data demonstrating that boys in their late teens with varicoceles had significantly decreased seminal parameters, and for those boys with untreated varicoceles, these parameters decreased over time. He also cited the classic data demonstrating the markedly increased incidence of varicoceles in men with primary vs. secondary infertility.

Finally, Dr. Diamond compared adolescent varicoceles to prenatal hydronephrosis. Often asymptomatic, some benefit from treatment, some don't, and we cannot determine who needs treatment. He is involved in a randomized prospective trial examining the effect of treatment vs. observation in adolescent varicoceles on seminal parameters. Dr. Baskin ended the discussion, proclaiming a draw.

Endocrine Forum
Jay Sandlow, M.D.

Endocrine Forum, moderated by Larry Lipshultz and Abe Mortgentaler, focused on the "Treatment of Patients After Radical Retro pubic Prostatectomy." Dr. Dov Kadmon first presented information regarding the current status of nerve grafts in the patient with non-nerve sparing radical prostatectomy. Sural nerve grafts to reconstruct resected cavernosal nerves performed during radical retropubic prostatectomy can improve erections and allow more men to regain potency and sooner after prostatectomy. The current advances in the therapy of Peyronies disease were the focus of a lecture by Dr. Laurence Levine. The lectures then focused on androgen ablation therapy for advanced prostate cancer. Dr. Chris Logothetis examined the clinical utility of LH-RH and the best patients for this treatment option. Dr. E. David Crawford spoke on whether androgen deficiency should be treated in the patient after radical prostatectomy and/or XRT, a problem of concern for many aging men and

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in particular those after prostate cancer treatment. Finally, Dr. Ian Thompson reviewed the data from the recent New England Journal of Medicine paper on finasteride and prostate cancer and the insights this study provides into the role of androgens in prostate cancer.

Tuesday Morning Poster Session
Robert Oates, M.D.

Although there were 41 fantastic posters in this session, space only allows a brief summary of but a few that were especially outstanding. ***The session was moderated by Robert Oates and Larry Lipshultz.***

#129 Characterization of transcripts expressed during early mouse spermatogenesis: Hayashi et al reported on their subtractive screen study which looked for transcripts expressed differentially during the period of gonadal development in a mouse model. They were able to demonstrate that certain genes, K1 and H21, for example, are highly regulated both temporally and cellularly (somatic or germ) during testis development and beyond.

#1971 Isolation and enrichment of spermatogonial stem cells using rhodamine 123 mitochondrial dye: Lo and colleagues from Baylor described a novel technique to enrich the isolation of murine spermatogonial stem cells by taking advantage of the differential staining of Rho 123 dyes. Proof of their enrichment occurred following stem cell transplantation into sterile Wv mice. Their technique enriches the population 25 fold compared to a non-Rho 123 sorted population. This may one day be applicable for human spermatogonial stem cells as well.

#1221 Sonic Hedgehog in the adult mouse epididymis and preliminary localization in the adult human epididymis: Turner and coworkers from Charlottesville demonstrated the Sonic Hedgehog pathway (including shh – the secreted initiator of shh signaling, ptc – the shh receptor, gli1 – a downstream transcription factor) is expressed in the adult mouse epididymis at both the gene and protein level. They suggested that this pathway may play a role in the maintenance of adult epididymal function. Interestingly they also demonstrated it may be present in the adult human epididymis as well by immunorecognizing shh protein in adult human epididymis.

#3200 Evidence for a testis-vas deferens pump: Banks et al from London demonstrated that rabbit and human testicular capsules exhibit spontaneous smooth muscle contractions as does the human vas, at an approximate rate of 100 per hour. This knowledge may open an avenue for pharmacologic treatment with adrenergic agents in certain conditions. It also is confirmation of what we see clinically when performing vasectomy reversal – the intermittent sudden flow of vasal fluid from the testicular end, no doubt due to a wave of vasal peristalsis initiated by a much more proximal location (is there a pacemaker area?).

#727 Use of whole testis transplantation technology to study the role of GDNF-mediated GFRA1/RET signaling in mouse postnatal spermatogenesis: Naughton and colleagues from St. Louis used an elegant strategy of transplanting testes from mice of three different knockout lines – all involved in the c-RET signaling pathway which is felt to be involved in spermatogenesis. No maturation of germ cells was seen in the Ret, GDNF, and GFRa1- deficient donor testes while the control testes did show maturation of germ cells all the way to spermatozoa. Their conclusion was that postnatal spermatogenesis is indeed dependent upon GDNF-mediated GFRa1/Ret signaling.

#960 Sperm tail flexibility test: a way to select viable immobile spermatozoa for ICSI: Soares and coworkers from Brazil presented their data on a method to select viable, yet immotile spermatozoa, for ICSI when only immotile sperm are available. If the tail moves independently of the head of the sperm, the sperm is most likely viable but when the head and tail move as one (no flexibility) it is most likely not viable. Fertilization and pregnancy rates were detailed and so this appears to be a way far simpler than a micro-HOS assay to select those immotile sperm suitable for oocyte injection.

Wednesday Podium Session: *Infertility Therapy*
Robert Oates, M.D.

Infertility Therapy began with a paper presented by Drs. Schiff and coauthors describing a rat model comparing sutured anastomoses for vasovasotomy or epididymovasostomy with addition of synthetic sealant, biomaterial wrap, or neither. The authors found that for vasovasostomy, sealant led to poorer results, and that biomaterial wrap allowed fewer sutures to be used without sacrificing patency outcomes. Native sutured epididymovasostomy without additional materials provided the best outcomes. Also investigating microsurgical reconstructive techniques, Drs. Chan and coauthors described results of their refinement in the intussusception epididymovasostomy, a 2-stitch longitudinal anastomosis, with an overall patency rate of 95%, and pregnancy rate of 50% for those patients with follow-up exceeding 6 months.

Pertaining to sperm retrieval, Drs. Okada and coauthors observed that successful recovery of sperm from men with Klinefelter's syndrome decreased with age, with a threshold of 35 years old. In a separate paper, these authors noted a decline in serum testosterone in patients with Klinefelter's syndrome undergoing sperm extraction procedures, and recommend that testosterone levels be followed in these patients after sperm acquisition. Drs. Shah and Shah introduced an innovative technique of extracting single seminiferous tubules from multiple puncture sites in the testis. Drs. Zahalsky and coauthors surveyed men regarding post-mortem sperm acquisition, reporting, among other interesting findings, that over 81% of men did not find this activity to be ethically objectionable in any way. Drs. Bakircioglu and coauthors reported outcomes of men with cryptozoospermia and in-vitro fertilization using either ejaculated or testis derived sperm, finding similar results with both.

In the area of varicocelectomy, Drs. O'Brien and coauthors investigated the effect of advanced female age on outcomes of varicocelectomy when surgical or non-surgical approaches coupled with artificial reproductive techniques (ART) are considered. These investigators found improvement in sperm parameters after varicocelectomy, but similar outcomes in pregnancy whether varicocelectomy was performed or not, due to use of ART. The authors observed a higher spontaneous pregnancy rate of 34% in the varicocelectomy group compared with 24% in the nonsurgical group. Drs. Zorba and coauthors reported statistically significant correlations between duration of infertility and total motile sperm count and pregnancy in men undergoing varicocelectomy, supporting the hypothesis of potentially correctable degradation of spermatogenesis over time.

Regarding vasectomy, Drs. Chawla and coauthors observed that 96% of men with rare non-motile sperm after vasectomy eventually become azoospermic. Concerning cryopreservation of sperm obtained via microsurgical epididymal aspiration, testicular sperm extraction or electroejaculation, Drs. Russell and coauthors reported similar IVF outcomes with fresh and frozen sperm in 2039 consecutive cycles. Drs. Grober and coauthors investigated the utility of bench model

simulators in training microsurgery to surgeons early in their training, and found significant and durable improvement in educative parameters in those who had exposure to laboratory-based methods.

Highlights from Moderated Poster Session:
Infertility: Physiology, Pathophysiology & Basic Research
Peter N. Kolettis, M.D.

Lo et el (#1372) successfully transplanted murine spermatogonial stem cells into sterile recipient mice. They were able to enrich the spermatogonial stem cells by as much as 25 fold using the differential property of Rho 123 staining. Schrader et al (#1376) performed real time fluorescence RT-PCR to determine the expression of the genes encoding the catalytic subunit of hTERT and Ccn A1 (both expressed exclusively by haploid germ cells). The combination of expression of both of these genes correctly classified 97% of testicular tissue specimens with and without haploid germ cells. Said et al (#1386) examined the role of some seminal growth factors in varicocele related infertility. They presented data suggesting that TGF-ß1 may play an indirect role in the pathophysiology of varicocele patients, while seminal bFGF and TGF-ß2 levels did not differ between infertile and control groups. Masuda et al (#1391) investigated cyclosporine-induced structural changes of spermatogenic and spermiogenic cells. They demonstrated that cyclosporine directly impairs spemiogenic cell development and impedes Sertoli cell function. Lucon et al (#1403) assessed the relationship between abstinence period and semen quality. Their data suggested that the optimal abstinence time for a semen specimen is three days. This could have important implications for couples undergoing intrauterine inseminations. Paduch et al (#1407) examined USP26, a novel candidate gene for male infertility. Two unreported N-terminal mutations were identified in the protein in infertile men but not in fertile controls. This group's observations may implicate USP26 mutations as a cause for male infertility.

Highlights from Moderated Poster Session:
Infertility: Evaluation and Therapy
Craig Niederberger, M.D.

Desai et al (#1572) devised a computational model that can predict the probability of an endocrinopathy. The investigators have made these models accessible via the Internet. Spaine et al and Carmignani, (#1574 and #1591) presented studies documenting an association between testicular cancer and infertility, which is known by most urologists. These studies confirm the results of previous studies and should be communicated to urologists and nonurologists involved in infertility care. Two studies from the Cleveland Clinic utilized computer generated models to study vasoepididymostomy (VE). The first (#1584) predicted the need for VE by analyzing preoperative and intraoperative variables and the second (#1593) was used to predict outcome. The first model could help urologists decide when to refer a patient to a physician experienced with VE. Timm et al (#1586) presented a study that underscored the need for repeated semen analyses in azoospermic men. In their study, over one third of the patients had some sperm detected on subsequent analyses. All azoospermic samples should be centrifuged and the pellet resuspended and re-examined for sperm. Schiff et al (#1594) performed a randomized study using the Da Vinci robot for vasovasostomy (VV) and VE. They achieved excellent results in both the standard microsurgical and robotic anastomoses. The role of the Da Vinci robot for microsurgical VV and VE in clinical practice remains unclear. Some of the issues to be addressed are the cost of the robot and associated instruments and whether sufficient magnification is provided to perform these anastomoses well. Ezeh et al, (#1596) compared results with standard and invagination VE techniques. As has been demonstrated with previous studies, the invagination procedures may improve patency rates and the time to achieve patency may be shorter. Pregnancy rates were not reported. Abstracts by Russinko et al (#1597) and Cayan et al (#1604), presented studies on adolescent varicocele. Russinko et al demonstrated that subinguinal microsurgical varicocelectomy can be applied in this patient population with a 1.2% recurrence/persistence rate and an overall complication rate of 3.4%. In these authors' view, this approach should be considered the initial surgical approach for adolescent varicocele. Cayan et al demonstrated that varicocele ligation improves semen parameters for adolescents with varicoceles. Their data suggest that the complication rate and recurrence rate were lower with microsurgical technique.

Post-Graduate Course #12IC:
Advances in Male Infertility
Paul Turek, M.D., Course Director

This year, the AUA instructional course entitled "Advances in Male Infertility" was prepared by course faculty Drs. Larry Lipshultz and Paul Turek from Baylor College of Medicine and UCSF, respectively. The first half of the course concentrated on the advances in the diagnosis of male infertility, and the second half dealt with advances in treatment. The course was case-based and wove several interesting male infertility cases throughout the lectures.

Dr. Lipshultz began the course in a talk that emphasized the importance of history-taking in infertility, especially regarding coital timing, and the current issues surrounding mesh herniorraphy. A discussion of clinical varicocele, and hormonal and genetic evaluation followed. A review of tests of sperm function included Kruger morphology, and DNA integrity assessed by sperm chromatin structure and the Comet assay.

Dr. Turek spoke about the current treatment of male infertility, in a talk divided into noon-surgical, surgical and ART treatments. In particular, from experience with men who have partial hypogonadotrophic hypogonadism, he mentioned that there might a "rational" use for clomid in men with low-normal testosterone and LH levels. Data supporting the use of aromatase inhibitors for men with low testosterone/estrogen ratios was also reviewed. Finally, ProXeed, Fertile-One, zinc and folate supplements were discussed. The treatment of various forms of ejaculatory dysfunction including anejaculation, premature ejaculation and retrograde ejaculation were also reviewed. Surgical therapies concentrated mainly on the treatment of obstructive and non-obstructive azoospermia, ejaculatory duct obstruction and varicocele. The value of intrauterine insemination prior to IVF for the male factor treatment was also reiterated. Finally, the (published) world experience with the microdissection, multibiopsy and FNA mapping approaches to sperm retrieval for IVF-ICSI were compared.

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Post-Graduate Course:
Evaluation and Management of the Infertile Male: What's New and Important

Jon L. Pryor, M.D.

The 2004 Post-Graduate course on infertility, held on Sunday, May 9, 2004, was Chaired by Dr. Marc Goldstein and had Drs. Jon L. Pryor and Dominick J. Carbone as faculty members.

The first talk, by Mark Goldstein, asked "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 emphasized that all men from infertile couples need to include 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. The workup of azoospermia includes assessment of potential ejaculatory dysfunction, blockage, or hypogonadism. In all cases one must ensure that a hormone evaluation is obtained. A TRUS is indicated if you suspect ejaculatory duct obstruction (e.g. pain on ejaculation and/or low ejaculatory volume). If the patient has congenital bilateral absence of the vas deferens, it is imperative to have the patient and spouse tested for CFTR gene mutations, including the 5T allele. If the patient has severe oligospermia (less than 5 million sperm/ml) or azoospermia from testicular failure, the physician should order karyotype analysis and microdeletion of the Y chromosome tests. If hypogonadotropic hypogonadism is suspected, an MRI of the pituitary/hypothalamus is indicated.

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 the workup should focus on the female. However, specific problems, like a varicocele, should be treated. If idiopathic infertility is present (minor or moderate), empirical therapy may prove beneficial. If a severe or a non-treatable problem exists, the patients may still achieve a pregnancy with IVF in combination with ICSI, or they should be counseled to adopt or pursue donor IUI.

Specific medical therapy of endocrinopathies, infections, and ejaculatory dysfunction was discussed. 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 is noted, hMG 75IU q MWF should be added. Finally, when treating ejaculatory dysfunction from RPLND or diabetes with sympathomimetics (e.g. imipramine or pseudoephedrine), one should limit administration of these drugs to 10 days to two weeks around ovulation, as they cause tachyphylaxis. In addition, if one drug doesn't work, another sympathomimetic should be tested, as it has been clearly shown that patients may respond to one drug and not another.

Next, surgical therapy of male infertility was discussed. 35-40% of infertile men have varicoceles and 10-20% have obstructions. Therefore, more than 50% of male infertility is 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 results in 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, non-hormonal 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 optimization of sperm quality prior to ART. With regards to the latter, numerous studies demonstrate that varicocele repair prior to ART can improve sperm quality so that lower cost procedures, such as stimulated IUI, may be pursued rather than ICSI. Regarding the former topic, 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.

The basic genetics of infertility 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 prob-

lems, 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, a karyotype and a test for microdeletions of the Y chromosome are indicated. If the patient has CBAVD or idiopathic epididymal obstruction, one must test for CFTR gene mutations.

Sperm acquisition was the next topic. In obstructive azoospermia, microsurgical epididymal sperm aspiration may be the procedure of choice, as it results in a high retrieval rate and allows for cryopreservation. Percutaneous procedures may be utilized if the patient is opposed to open surgery or if only one IVF cycle is anticipated. For patients with non-obstructive azoospermia, microsurgical testicular sperm extraction with tissue preparation in a reproductive center represents the optimal choice.

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. However, it is not advisable to indiscriminately order other tests (e.g. scrotal U.S. or TRUS). All azoospermic males should be biopsied, but this should only be done if you can harvest/freeze sperm at the same time for possible future use in IVF/ICSI. A vasogram should not be done at the time of testicular biopsy. An infertility patient should not be treated with testosterone- it's a contraceptive. Finally, participants were advised to 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. A physician should never use infertility as a diagnostic code. Infertility is a symptom, not a disease. One should 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). The physician should dictate his or her own detailed operative report. If a microscope is used, one should say so and indicate what magnifications were used. It is advisable to 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).

Review of the IC: Vasovasostomy, Epididymovasostomy and Sperm Retrieval Techniques

Christopher G. 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. ◆

Society for the Study of Male Reproduction

Saturday, May 21, 2005
San Antonio, Texas
Program Schedule
1:00 p.m. – 5:30 p.m.

Program Chair: Peter Chan, M.D.

1:00 p.m.	**Introduction**
1:05 p.m.	**Update on the Molecular/ Biological Basis of Spermatotoxicity**
1:35 p.m.	**Update on the Biochemical Basis of Spermatotoxicity**
2:05 p.m.	**Q&A**
2:15 p.m.	**Common Medications and Drugs: How Do They Affect Male Fertility?**
2:35 p.m.	**Impact of Chemotherapy Agents on Male Fertility**
2:50 p.m.	**Impact of Radiation on Male Fertility**
3:05 p.m.	**Q&A**
3:20 p.m.	**Break**
3:35 p.m.	**Impact of Environmental Toxins on Male Fertility**
3:50 p.m.	**Spermatotoxicity of Recreational and Body-building Drugs**
4:05 p.m.	**Q&A**
4:15 p.m.	**Roles of Nutraceuticals and Phytoestrogens in Male Fertility**
4:30 p.m.	**Impact of Heat on Male Fertility**
4:45 p.m.	**Q&A**
5:00 p.m.	**Annual Business Meeting**

SSMR Traveling Fellowship Program 2005

Dear Urology Residency Directors and SSMR Members:

The Society for the Study of Male Reproduction (SSMR) is proud to announce the Fifth Annual SSMR Traveling Fellowship Program, which will take place in conjunction with the 2005 AUA meeting in San Antonio, Texas, this year.

The SSMR is an AUA-affiliated subspecialty society whose mission is to promote the advancement of the science and treatment of male reproduction disorders, through education of practitioners, public education, and informational exchange of research and new advances through meetings. Currently, there are insufficient numbers of male fertility specialists to serve the needs of the population. The SSMR is committed to cultivating interest in male infertility treatment careers in trainees.

Our previous 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 reproduction issues. The Fellowship Program will include attendance at the SSMR educational program and complimentary SSMR banquet participation. Fellows will also attend an AUA post-graduate course in male infertility, 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 reproduction 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 Thursday afternoon until Wednesday evening will be required.

Meeting expenses covered by the program include airfare, hotel accommodations, SSMR meeting and banquet, tuition for the post-graduate course, 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 January 15, 2005. The awards will be announced by February 15, 2005.

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

Sincerely,

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

S S M R

MARK YOUR CALENDARS!

"60 Years of Progress"
60th Annual Meeting of the
American Society for Reproductive Medicine
October 16 – 20, 2004
Pennsylvania Convention Center
Philadelphia, Pennsylvania
Contact: ASRM
Phone: (205) 978-5000
Fax: (205) 978-5005
E-mail: asrm@asrm.org
Website: http://www.asrm.org/Professionals/Meetings/annualmeeting.html

ASA 30th Annual Conference
March 30 – April 5, 2005
Grand Hyatt Seattle
Seattle, Washington
Testis Workshop:
March 30 – April 2, 2005
ASA Annual Meeting:
April 2 – 5, 2005
Andrology Lab Workshop:
April 2, 2005

American Urological Association Annual Meeting
May 19 – 25, 2005
San Antonio, Texas

SSMR Meeting at the AUA Annual Meeting
May 21, 2005
San Antonio, Texas
1:00 p.m. – 5:00 p.m.

Application for the SSMR Traveling Fellowship Program 2005
Thursday, May 19 – Wednesday, May 25, 2005
San Antonio, Texas

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. 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 SSMR Traveling Fellowship functions is expected, as outlined in the attached schedule.

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

Deadline: January 15, 2005

SSMR

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

Address Service Requested