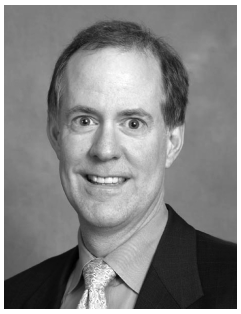
SSMR NEWS

February *Society for the Study of Male Reproduction* 2007

President's Message

It seems fitting that I bid my fellow SSMR members a WARM welcome at the end of an icy, cold winter. I hope everyone is having a good year and looking forward to joining us in Anaheim in May for the AUA meeting. A few months ago the ASRM meeting was held in New Orleans. For those who have not had a chance to see the destruction from Katrina, it was beyond what pictures or words could describe, and the saddest part was it did not appear like a lot of reconstruction was occurring. My hat goes off to the ASRM, which wanted to help New Orleans by holding the meeting there. The highlights from that meeting are summarized in this issue of SSMR News.



Jon L. Pryor, MD, PhD

This year's SSMR meeting at the AUA will be held on Saturday, May 19th, 2007, from noon to 4:30 p.m. The Program Director, Raymond Costabile, MD, put together a spectacular program that is both different and very practical for the clinician and is entitled: "Fine Wine or Wrong Time: Infertility in an Older Population Desiring Children." Paul Shin, MD will look at epidemiological aspects of parenthood in the United States. Drs. Ajay Nangia and Antoine Makhlouf will lead a panel on the changes in reproductive function with aging. Dr. Edmund Sabanegh will then describe what genetic and birth defects are associated with the older parent. Dr. Peter Kolettis will then discuss how to adapt your evaluation and treatment of the older couple. Dr. Costabile and the faculty will finish the meeting with case discussions and a question and answer period. At 4:00 p.m. we will conduct the business meeting. The local arrangements chair Aaron Spitz, MD in conjunction with Wendy Weiser and Associates are arranging a wonderful dinner. We look forward to seeing you there for "fine wine and a good time."

There is a lot going on behind the scenes on the business aspects of SSMR (that was a hint: if you want to get involved, please let any Board member know and we will put your expertise to work for the Society). As a reminder, we now have only three membership categories: active, candidate, and senior. We also decided to drop membership in the AUA as a requirement for membership in the SSMR. The chair of the membership committee, Dr. Stan Honig, is using Androlog, contacting previous traveling fellows, and soliciting members from other international andrology societies to increase our membership. Please encourage your colleagues, residents, or allied personnel who have a sincere interest in male infertility, to join the SSMR. Applications for the SSMR can be obtained on line at www.ssmr.org. Speaking of international societies, we are not letting globalization pass us by- we are going to start an ad hoc international liaison committee and ask the chair of that committee to sit on the Board of Directors of SSMR as a non-voting member. We hope this will both increase our membership as well as get a better global perspective of reproductive issues in other countries. Thanks to Dr. Harris Nagler who chairs the Development Committee, we have identified funding for an **allied** traveling fellows award for nurses, nurse practitioners, and P.A.s. This new award will be under the direction of Dr. Ajay Nangia, who is also in charge of the Traveling Fellowship Award for residents and fellows. We are in discussions with the Society for Sexual Medicine Society of North America (SMSNA) to see if they want to co-sponsors the allied traveling fellowship, as they do for the resident/fellow traveling fellowship. So if you have a resident/fellow or allied personnel who are interested in male infertility and sexual dysfunction, please have them contact Dr. Nangia at ajay.k.nangia@hitchcock.org for details of the award; the Men's Health Traveling Fellow application deadline was February 1; the Allied Traveling Fellow application deadline is March 1, 2007.

We continue to wrestle with how to allow members to link their websites to the SSMR website and are suggesting that SSMR and/or the AUA works on a set of vasectomy guidelines. So again, if you want to get involved in any of these issues, please do. In the meantime, stay warm and I look forward to seeing all of you soon in Anaheim. ⌘

Jon L. Pryor, MD
President, SSMR

CONTENTS

Review of the ASRM 2006

Contributions by: Robert Brannigan, MD; Russ Hauser, MD, MPH; Margaret Hollingsworth-Kressin, MD; Stanton Honig, MD; Tony Makhlouf, MD; Harris Nagler, MD; Craig Niederberger, MD; Jay Sandlow, MD; and Mark Sigman, MD.

MONDAY, OCTOBER 23, 2006

INTERACTIVE SESSION

The Fetal Basis of Male and Female Reproductive Dysfunction
Chair: Susan Benoff, PhD
Speakers: Gail Prins, PhD, Hugh S. Taylor, MD
Summarized by Tony Makhlouf, MD

Xenoestrogens are environmental contaminants with estrogenic activity. Reports of declining sperm counts over the last decades have fueled interest in these "endocrine disruptors" as possible culprits. The effects of in-utero and perinatal exposure of male fetuses to these compounds was the focus of a presentation by Dr. Prins, with an emphasis on prostate development and carcinogenesis.

Dr. Prins started by reviewing the embryonic origin of the prostate. Unlike the seminal vesicles and vasa deferentia, which develop from the mesodermal Wolffian duct, the prosate has an endodermal origin. In mammals, it develops from the urogenital sinus, and its female homologous structures are the vagina and lower portion of the cervix and/or uterus in most species. In humans, testosterone produced by the fetal testis at the 12th week of gestation triggers prostate development. Most structural development of the human prostate occurs in the second trimester, with some maturation continuing in the the 3rd trimester. The prostate then remains quiescent during the low-testosterone period of childhood until puberty. It is during the prenatal period of development that the prostate may be most susceptible to the effect of exogenous estrogens.

The neonatal rat is a convenient model for studying xenoestrogen effects on the prostate because rodent prostate morphogenesis occurs post-natally, corresponding to the changes seen in humans in the second and third trimesters. The model described by Dr. Prins involved exposure of neonatal rats to various xenostrogens, and then later following the development of the exposed animals.

Bisphenol-A (BPA) is a synthetic aromatic compound with weak estrogen activity. It is used as an additive in polycarbonate plastics, dental sealants and tin-can linings. It has been shown to accumulate in placental tissues and milk, and could leach out of baby-bottles during heating, raising concerns about human fetal and neonatal exposure. In the rat model, exposure of neonatal rats to environmentally relevant doses of BPA did not trigger the development of prostatic tumors in adulthood. However, if the exposed rats were later treated with high dose estrogens, prostatic intra-epithelial neoplasia (PIN) is seen. In contrast, control rats not exposed neonatally to BPA did not develop PIN in response to estrogen later in life. This demonstrated that BPA could have a lasting effect on prostatic tissue. How does the prostate retain a "memory" of this exposure is the focus of intense research. One likely mechanism is through the epigenetic mechanism of DNA methylation. Dr. Prins and collaborators demonstrated that BPA exposure altered the methylation pattern of at least 30 genes. To confirm that methylation changes were transcriptionally relevant, they focused their attention on phosphodiesterase-4 (PDE4) whose promoter was found to be hypo-methylated in response to BPA exposure. They showed that adult transcription of PDE4 was significantly higher in the BPA treated rats compared to controls. Whether this particular gene plays a role in the induction of carcinogenesis remains to be seen.

In summary, Dr. Prins presented exciting work that outlines a plausible mechanism to explain how early exposure of reproductive tissues to endocrine disruptors could lead to a lasting effect. This concept should certainly be kept in mind when interpreting and designing epidemiological studies of the effect of xenoestrogens on male reproduction.

Plenary Session American Urological Association Bruce Stewart Memorial Lecture: "The Future of Reproductive Medicine: Genetics, Economics, Politics"
Speaker: Lawrence S. Ross, MD
Summarized by Craig Niederberger, MD

Dr. Lawrence Ross, President of the American Urological Association, gave the Bruce Stewart Lecture on "The Future of Reproductive Medicine: Genetics, Economics, Politics." Beginning with a history of the discovery of the male gamete, and evolving to the great leaps of in-vitro fertilization and intracytoplasmic sperm injection, Dr. Ross then developed a series of issues into categories of "Good," "Bad" and "Ugly." As an overview, the "Good" included reproductive possibilities for couples who would never have been able to conceive and stimulation of research and scientific advancement. Dr. Ross gave as an example of reproductive possibilities the area of gamete cryopreservation, noting the state-of-the-art, the difficulties and the promises of cryopreserving for future use sperm, ova, embryos and whole organ tissue of testis and ovary. Dr. Ross also described advances in techniques yielding tissue for cryopreservation, including testis mapping and microsurgical testicular sperm extraction.

Dr. Ross then described as in the "Good" advances in the understanding of molecular genetics and reproduction, and areas of investigation in female reproductive medicine in ovulation stimulation, fertilization failure and the relationship between reproductive potential and obesity. Mirroring the promises of molecular genetics, Dr. Ross also noted the dangers of artificial reproductive technology in the "Bad," including genetic risks of in-vitro fertilization, pointing out the still limited duration of studies correlating birth defects and modern artificial reproductive techniques.

Dr. Ross described the therapeutic promises of somatic cell nuclear transfer, or "cloning," but also noted the danger of using the technique for reproduction, and cited the recent highly public debacle stemming from scientific misconduct of a South Korean investigator. However, Dr. Ross pointed out that the current political climate so hostile to investigation into somatic cell nuclear transfer in the United States is driving investigators to international locations to conduct research.

Exploring the exploding costs of medical care, Dr. Ross noted that in 2004, total United States health expenditures rose nearly 8%, three times the rate of inflation. Totaling nearly two trillion dollars, this cost represented 16% of the gross domestic product of the United States.

Interestingly and tragically, Dr. Ross observed that the most common

cause of bankruptcy in the United States is major illness. With such economic and social cost, increasing regulation of health care is inevitable. Dr. Ross described regulation to be directed toward increased accountability, including steps to insure continued provider skills in maintenance of certification, but also the more concerning drive toward remuneration based on patient outcomes. The clear message that emerged was that if we as physicians don't regulate ourselves, that political bodies who do not have the depth of medical understanding that physicians do will feel compelled to regulate us, and that motion is already underway.

Dr. Ross concluded with a rallying appeal for experts in both male and female reproductive medicine and biology to work together to build the promises of modern science such as molecular genetics in our field, while containing cost and controlling political efforts that would thwart our humanitarian efforts. In all, Dr. Ross' 2006 Bruce Stewart lecture was interesting and stirring.

CONCURRENT SESSIONS

The Society for Male Reproduction and Urology Abstracts
SSMR Newsletter Summary Monday p.m. Podium Sessions
Summarized by Stanton Honig, MD

Vascular Endothelial Growth Factor (VEGF) Gene:Therapy Using a Non viral Gene Delivery System Improves Erectile Function in a Diabetic Rat Model
Mills et al Denver CO

The authors report their data in the injection of DNA encoded with VEGF in a non viral gene delivery system. The VEGF injected diabetic rats were studied and data compared to diabetic control rats and sham injected diabetic rats. Maximal intracavernosal pressures were normal in the control rats, slightly diminished in the VEGF treated diabetic rats, but were of low levels in the diabetic rats. In addition, Western blot analysis confirmed expression of the VEGF fusion protein and mRNA transcript within the cavernosal tissue of the VEGF treated diabetic rats. The authors concluded that they able to successfully perform in vivo transfection of VEGF into rat corpus cavernosum using a non viral gene delivery system and were able to restore some degree of erectile function.

Use of Two Vibrators vs. one Vibrator salvages Ejaculatory Failures in men with Spinal Cord Injury.
Ibrahim et al Miami FL, Ioannina Greece

The authors report their success with using two vibrators in cases of ejaculatory dysfunction in patients with spinal cord injury. All patients underwent at least two vibratory stimulations using the high amplitude Ferticare vibrator. 47% of all patients, and 57% of patients with a level above T10, had success. In failures, 22% were salvaged using two vibrators at the same time, one usually dorsally and one ventrally. This was suggested as an option in treatment of these patients prior to proceeding to EEJ or testis sperm extraction.

Defective Recombination: The Role of MLH3 in Infertile Men.
Margreiter M et al New York, NY

The authors evaluate the presence of mutations in the MLH3 mismatch repair protein in patients with non obstructive azoospermia. Previous work in their lab suggests that MLH1 may play a role in male infertility. In this study, they reported no difference in the frequency of MLH3 mutations in fertile and patients with NOA. Although a negative study, further studies like this are a necessary prerequisite to identification of genes and proteins important in spermatogenesis.

The Kinetics Of The Return Of Motile Sperm To The Ejaculate After Vasectomy Reversal.
Yang et al San Fransisco, CA

The authors report on the return of sperm to the ejaculate after vasectomy reversal. They divide groups by whether V-V or E-V was performed and whether motile sperm was identified in the vasal fluid. The authors concluded that if there was motile sperm seen in the vasal fluid, then 95% had motile sperm by 6 months, whereas only 76% had sperm by six months if only non motile sperm was seen. Interestingly, only 31% of patients who had an E-V performed had motile sperm in the ejaculate by 6 months. A plea was made in the Q/A session to report successes based on at least 10 million motile in the ejaculate to better assess likelihood of success without ART. Pregnancy rates were not reported in this study. This data is very valuable to the practitioner who is counseling patients regarding early ART in these patients. This data was very similar to data reported by Marmar and Goldstein about 15 years ago.

Antidepressant Associated Changes in Semen parameters
C Tanrkut et al New York, NY

The authors present the data in two patients with depression of semen parameters that coincided with starting and stopping serotonin reuptake inhibitors. These data points are certainly food for thought regarding the use of these drugs by young men of reproductive age. Further data that formally evaluate these drugs with regards to semen parameters will be important to determine if these case reports are isolated, unrelated events or a pattern that needs further study. Comments from the audience discussed the importance of the FDA evaluating the effects of all new drugs on semen parameters. Wayne Hellstrom commented that there were no sperm studies done on dapoxetine, the SSMI undergoing clinical trials for premature ejaculation.

Propagation and Maturation of Male Gonocytes in Vitro.
Neri Q et al New York, NY

This study evaluated the ability of spermatogonial stem cells to propagate and immortalize in vitro in media with different growth factors including GDNF, bFGF, FSH, LIF in mice. The study suggested that GDNF and BFGF supplemented with LIF was most suitable to support the germ cell population and after administration of FSH and LH, it became possible to identify post meiotic cells. Without the growth factors, the spermatogonial stem cells proliferated for only a few days. However, when these growth factors were added, proliferation and propagation of the germ cells continued for an extended period of time. The authors concluded that the maintenance of these spermatogonial

stem cells in culture could be used to repopulate the testes of patients with Sertoli cell only syndrome or provide a direct source of haploid male germ cells.

SMRU Mini-Symposia "Exposure to Endocrine Disruptors on the Etiology of Male Infertility"

Special Lecture: Effects of Endocrine Disruptors on Male Infertility
Russ Hauser MD, MPH
Harvard School of Public Health
Summarized by Russ Hauser, MD, MPH

Dr. Hauser gave an excellent overview on issues related to endocrine disruptors. There is a series of industrial chemicals, pesticides and chemicals that are present in consumer products. These chemical substances may be responsible for the release of endocrine factors that subsequently may be responsible for a drop in spermatogenesis. There clearly appears to be geographical variability with respect to sperm concentrations in the general population. The mechanism of how endocrine disruptors effect spermatogenesis is unclear, however possible mechanisms include steroid receptor binding, inhibition of certain steroids and/or changes in the level of endocrine binding proteins.

Specifically, phthalates may be responsible for some of these changes. There is widespread human exposure to these chemicals. The Wall Street Journal in October 2005 reported data on these chemicals. They are present in IV bags, PVC piping which is softened by phthalates, food packaging, adhesives, and coating of some medications.

Dr. Hauser summarized his report by stating that these phthalates are ubiquitous and may be responsible for population based drops in semen quality in certain geographic areas.

TUESDAY, OCTOBER 24, 2006

INTERACTIVE SESSIONS

Surgical Therapy of Male Infertility: Indications and Outcomes (Varicocele, Vasectomy Reversal, Sperm Retrieval)

The Society of Reproductive Surgeons
Chair: Peter N. Schlegel, MD
Speakers: Marc Goldstein, MD, Larry I. Lipshultz, MD
Summarized by Jay Sandlow, MD

Two cases were presented, vasectomy reversal and varicocele-related infertility. The first case presented the scenario of a patient presenting for possible vasectomy reversal with an older female partner. The participants discussed possible pre-operative historical factors that would influence decision-making, such as prior hernia repairs, epididymitis, previous paternity, and obstructive interval. One of the basic points is that with advanced maternal age, factors other than patency are important in achieving a successful pregnancy, and couples must be aware of the amount of time it may take for adequate seminal parameters to be achieved, as well as the increased miscarriage rate in older women. Ovarian reserve testing, such as a clomiphene challenge test, may be useful in identifying women where time is a major consideration. On physical exam, important factors include testicular size and consistency, epididymal fullness vs. induration, testicular vasal remnant length, and distance of vasal gap. In cases of small, soft testes or no prior paternity, FSH testing may be helpful. Finally, the presence of sperm in a preoperative semen analysis means that at least one side will be a vasovasostomy, which aids in the decision-making process, although the absence of sperm does not preclude VV.

Another point discussed was the repair of a varicocele at the same time of the reversal. Although there is literature to suggest that this is not contraindicated, most feel that unless there is an absolute indication for repair, the varicocele should be left alone until the outcome of the reversal has been determined. The discussion then turned to intraoperative factors, with the presence or absence of sperm in the vasal fluid, as well as the gross quality of the fluid (thick and creamy vs. thin and water-soluble) being important predictors of postoperative success. Finally, discussion turned to postoperative factors that may increase success, including the use of NSAID's and steroids to decrease scarring, sperm cryopreservation in the event of secondary scarring, and some outcomes data. One study was cited that demonstrated a lower natural pregnancy rate in men who were >15 yrs out from their vasectomy, even with a VV, compared to men <15 yrs out. The bottom line is that adequate counseling of these couples is extremely important, as they must understand the pros and cons of surgical reversal vs. sperm aspiration/IVF.

The second case examined primary infertility in the setting of a varicocele. Discussion centered around what preoperative testing was important, as well as what had been done previously. For instance, in a couple who had already failed IVF x2, DNA fragmentation testing may be useful in counseling couples regarding intervention vs. another try of IVF. Preoperative hormonal evaluation, as well as the grade of the varicocele has been shown to predict postoperative response and most participants will check this. Some surgical techniques were discussed, and most agree that the use of a micro-Doppler aids in the identification of the testicular artery, and it is important to save this, as well as the collateral supply, such as the cremasteric and vasal arteries. Magnification with either surgical loupes or an operating microscope is essential and most use the microscope. This allows for the identification of lymphatics, as well as the artery and helps with the dissection of the small veins that surround the artery and lymphatics. Finally, the discussion turned to the effect of varix ligation on non-seminal parameters, such as DNA fragmentation. Although the semen analysis is a rough indicator of success, many have had success without significant improvement in these parameters, and it is thought that other factors that are not measured by the semen analysis, such as sperm function, DNA integrity, and even unidentified factors, may be affected by the varicocele, and repair may help.

In summary, although everyone has their own biases and techniques, most male infertility experts perform similar procedures with similar outcomes.

Tuesday, October 24, 2006

CONCURRENT SESSIONS

Male Reproduction and Urology Abstracts

The Society for Male Reproduction and Urology
Moderators: Mark Goldstein, MD
Jay I. Sandlow, MD
Summarized by Robert Brannigan, MD

DOES THE SIDE MATTER? FINDING SPERM IN NON-OBSTRUCTIVE AZOOSPERMIA WITH VARICOCELE

S. Shefi, K. Danziger, P. J. Turek, University of California San Francisco, San Francisco, CA

O-112: The objectives of this retrospective cohort study were to determine in cases of nonobstructive azoospermia (NOA) with associated varicocele which testis is more likely, if either, to harbor sperm on

retrieval. The authors postulated that sperm production in the testis ipsilateral to the varicocele would be more profoundly affected, and they used cytologic techniques and clinical data from fine needle aspiration (FNA) mapping to assess this theory. A total of 31 varicocele patients were evaluated by FNA mapping. The authors found that 20 patients (65%) had sperm detected by FNA in at least one testis. Based on the percent of FNA sites showing sperm in each testis, most men had equal proportions of sites positive for sperm in both testes, whereas 23% had more sperm on the right than left testis. Far fewer men (3%) had more sperm on the left than right side. There were statistically fewer sperm-positive sites on the left (118/313) than right sides (149/321) among study subjects (p=0.002, Chi square test). Of note, sperm lateralization patterns in patients with genetic infertility appeared similar to that of the cohort as a whole. The authors concluded that most men with NOA and varicocele who require sperm retrieval for ICSI will be found to have equal proportions of sperm in both testes. In those cases where sperm production differs between sides, the right side is much more likely to have sperm than the left.

GHRELIN AND LEPTIN INTERPLAY IN PROPER GONADAL FUNCTION

D. J. Lamb, S. Whirledge, R. G. Smith, Baylor College of Medicine, Houston, TX

O-113: The authors provided background on their work noting that the reproductive role of ghrelin (the endogenous ligand of the growth hormone secretagogue receptor (GHSR) and leptin (an adipose secreted hormone) remains largely unknown. Dr. Lamb explained that in the testis, ghrelin and the leptin receptor are expressed by Leydig cells and the ghrelin receptor is present in both Sertoli and Leydig cells. Furthermore, ghrelin suppresses luteinizing hormone (LH) secretion, and while mice lacking ghrelin are fertile, mice lacking functional leptin (*ob/ob*) are obese, infertile, and exhibit impaired spermatogenesis. The authors hypothesized that leptin and ghrelin act to regulate spermatogenesis locally in the testis, as well as centrally in the CNS. The investigators used mice with a deletion of the ghrelin receptor (*ghsr -/-*) or a targeted disruption of ghrelin which were crossed to the leptin-deficient background (*ob/ob*). Wild-type, *ob/ob, ghrelin -/-,* and *ob/ob//ghrelin -/-* mice were then examined for testicular morphology, semen analysis, and apoptosis. Testicular histology, DNA Fragmentation, and Flow cytometry were used to assess the testes and tissue from these organisms. The authors found that testes sections from *ghrelin -/-* and *ghsr-/-* mice displayed slightly altered morphology. When compared to wild-type mice, Leydig cells appeared fewer in number and less well-developed, and some tubules displayed no germ cells. They noted that seminiferous tubule lumens in *ob/ob* mice exhibited an empty appearance with markedly reduced spermatogenesis and atrophied interstitial Leydig cells. Interestingly, elimination of both ghrelin and leptin rescues the phenotype. In stained testis sections of *ob/ob//ghrelin -/-* mice, seminiferous tubules abundant with mature sperm and Leydig and Sertoli cells displaying normal cell associations and morphology were found. Regarding flow cytometry results, testes from *ob/ob* mice have reduced apoptosis compared to wild-type mice. Furthermore, levels of apoptosis in *ob/ob* mice were restored to wild-type levels when *ob/ob* mice were bred onto the *ghrelin -/-* or *ghsr -/-* background. The authors concluded that breeding *ghrelin -/-* mice onto the *ob/ob* strain rescues defective spermatogenesis and restores normal levels of apoptosis in the testis. They suggested that ghrelin is essential for spermatogenesis, and that ghrelin signaling is balanced by the expression of leptin. This supports the notion of a delicate interplay of ghrelin and leptin not only in the hypothalamus, but also within the testis, a novel and important assertion.

ALTERATIONS IN LEYDIG CELL NUMBER AND MORPHOLOGY AMONG INFERTILE MEN WITH VARICOCELES

S. H. Benoff, I. R. Hurley, H. Xu, J. L. Marmar. The Feinstein Institute for Medical Research, Manhasset, NY; Robert Wood Johnson Medical School at Camden, Camden, NJ

O-114: The objective of this study was determine whether changes in Leydig Cell (LC) number and/or size were present in testicular biopsies of men with varicoceles, and to assess how these changes contribute to the underlying mechanisms that produce the infertile state. (Testis biopsies were assessed for LC count, morphology and function (which was based on evidence of cytochrome P450 side chain cleavage enzyme [SCC] and neuronal nitric oxide synthase [nNOS] within LC). The investigators also examined the relationship between these parameters and apoptosis, Fas expression, cadmium (Cd) levels, inducible NOS (iNOS) and endothelial (eNOS). The testes were biopsied by ultrasonically-guided percutaneous aspiration at the time of varicocelectomy (left varicocele [LV, n = 18]; bilateral varicoceles [BLV, n = 45]) or at sperm retrieval for ICSI (w/ prior vasectomy and normal spermatogenesis; controls [C], n = 9) and fixed in formalin. The authors assess Cd levels by atomic absorption. Apoptosis was determined by TUNEL in paraffin-embedded testis biopsy sections and nNOS, iNOS, eNOS, SCC and Fas expression assessed by indirect immunocytochemistry. The authors graded antibody staining intensity on a scale of 0 (absent) to 4 (maximum) by two blinded observers. LC were identified by location, morphology and expression of SCC and counted per unit area using a microscope ocular grid. The authors found that LC number per unit area was markedly decreased in varicoceles as compared to controls. Hypertrophic LC (?1/3 larger than normal) represented only 10% of LC in control biopsies but were >50% with varicoceles ($p<0.008$). nNOS was observed primarily in LC while iNOS and eNOS were predominantly observed within the seminiferous epithelium. Interestingly, expression levels for NOS with varicocele were eNOS>nNOS>>>iNOS (ANOVA, $p<0.001$). The authors reported that apoptosis was detected in germ cells but not LC. Furthermore, LC hypertrophy was positively correlated with SCC, nNOS, Fas, eNOS and germ cell apoptosis but was not related to iNOS or testicular Cd. They found that eNOS was highly correlated with apoptosis. (The authors concluded that a decrease in LC count/unit area was observed among infertile men with varicoceles along with compensatory hypertrophy of these cells. Expression of nNOS and SCC was elevated in hypertrophic cells. Hypertrophy was also positively correlated with elevations in eNOS, Fas expression, and apoptosis. They suggested that these changes may represent the activity of oxidative stress. The authors also stated that these findings may support the selective use of antioxidants as an adjuvant to surgical treatment.

BENEFICIAL EFFECTS OF DIETARY INTAKE OF PLANT PHYTOESTROGENS ON SEMEN PARAMETERS AND SPERM DNA INTEGRITY IN INFERTILE MEN

G. Song, L. Kochman, E. Andolina, R. C. Herko, K. J. Brewer, V. Lewis. University of Rochester Medical Center, Rochester, NY

O-115: The objective of this observational pilot study was to investigate the correlation between dietary phytoestrogens and semen parameters, seminal total antioxidant capacity and sperm DNA integrity. The authors recruited 48 men with abnormal semen parameters whose partners had been trying to conceive for at least one year. Controls consisted of 10 men with normal semen analyses who had fathered a pregnancy within the previous year. DNA integrity was measured using sperm chromatin structure assay (SCSA) and total antioxidant capacity (TAC) of seminal plasma was assessed using colorimetric TAC assay. Block food frequency questionnaires (NutritionQuest) were used to estimate the dietary intake of isoflavones (genistein and daidzein) of each patient. Higher mean levels of genistein and daidzein were observed in fertile control men compared to infertile men (genistein, 527 ± 183 ug/day in infertile men vs. 1722 ± 714 ug/day in fertile controls; daidzein, 241 ± 84 ug/day vs. 788 ± 327 ug/day, $p<0.05$). Of note, the levels of daidzein and genistein were higher in men with better sperm DNA integrity (DNA fragmentation index, DFI < 30%) compared to men with poor sperm DNA integrity (DFI = 30%, p=0.08). Interestingly, the authors performed regression analysis which revealed significant correlation ($P<0.05$) between dietary intake of genistein and semen parameters including sperm count (r=0.448), motility (r=0.311), progressive motility (r=0.424) and sperm DNA fragmentation index (r= - 0.325). Furthermore, similar correlations were found between daidzein and semen parameters. The investigators did not observe the correlation between dietary intake of isoflavones and seminal total antioxidant capacity (r=0.138 with genistein, r= 0.141 with daidzein, $p>0.05$). In conclusion, the authors noted that they observed an association between dietary phytoestrogens and semen parameters including sperm DNA integrity. They suggested that a larger population study and basic research should be performed to confirm these findings and to clarify the mechanism of the effects of isoflavones on sperm physiology.

INVOLVEMENT OF GROWTH FACTORS IN THE PROCESS OF POST-VASECTOMY MICRO-RECANALIZATION

B. C. Stahl, T. L. Ratliff, B. R. De Young, M. Wald, University of Iowa, Iowa City, IA

O-116: The authors studied a rat model that involved real-time PCR, enzyme-linked immunosorbent assay (ELISA), and histopathological analyses of the vasectomy sites and controls at different time points to investigate the role of growth factors in the process of post-vasectomy micro-recanalization.. Unilateral vasectomies were performed in 18 male Sprague-Dawley rats with a sham surgery on the contralateral side. Animals were sacrificed at 2, 8, and 12 weeks. Segments of the vas deferens, including the previous vasectomy site on the surgical side and a segment of vas of similar length from the sham-operated sides were taken for mRNA and protein isolation and pathological examination. The investigators used real-time PCR to assess the relative expression of transcripts of 7 common growth factors and 3 receptors. Additionally, ELISA was performed for growth factors with positive PCR findings to determine if increased transcription resulted in increased translation. (The authors found that histological examination revealed the presence of microcanals in 2 of 18 rat specimens, one from the abdominal and one from the testicular end. Interestingly, real-time PCR of all animals demonstrated a 12-fold increase of platelet-derived growth factor beta (PDGF-ß) mRNA, 6-fold increase of PDGF-ß receptor, 11-fold increase of PDGF-alpha (á), 7-fold increase of PDGF-á receptor, and a 9-fold increase of transforming growth factor (TGF)-ß. All of these increases were statistically significant ($p<0.05$), and all of these elevations were seen at all time points. Smaller increases of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) were also seen. Insulin-like growth factor-1 (IGF-1) was unchanged in this study. A modest decrease of fibroblast growth factor (FGF) and the EGF receptor was noted. Upon closer evaluation, the testicular ends of the vas demonstrated trends toward higher levels of growth factor expression compared to the abdominal ends with only PDGF-ß reaching statistical significance, and protein analysis revealed a statistically significant increased expression of PDGF-ß protein by ELISA. (The authors concluded that the rat vasectomy model shows microcanal formation analogous to that reported in humans. The sustained, local upregulation of TGF-ß and PDGF-á and -ß at the surgical site is significant, and this increase is greatest on the testicular side of the vas deferens. This work provides new understanding regarding the mechanisms that may lead to vasectomy failure. The authors also noted that a possible role for treatment with PDGF and/or TGF may exist here to increase the success rate of vasectomy reversals.

DOES VARICOCELE SIZE EXERT D

R. P. Bertolla, M. M. Mori, D. M. Spaine, E. G. Lo Turco, A. P. Cedenho, V. Ortiz. Sao Paulo Federal University, Sao Paulo, Brazil

O-117: The aim of this prospective study was to determine if varicocele size exerts deleterious effects on testicular function in adolescents. (The study included 360 consecutive adolescents aged 14-18 years. All adolescents were examined by the lead author. Physical examination findings and testicular volume (measure using a Prader orchiometer) were recorded, and semen was collected after 3-5 days of ejaculatory abstinence and analyzed according to the WHO guidelines, morphology by Kruger's strict criteria. All adolescents included in this study had already initiated masturbation. Informed consent was signed by the patients and their parents or legal guardians. (The authors found that 27.8% of the adolescents presented with varicocele grades II and III, and 7.8% (95% confidence interval: [5.0; 10.6]) with a grade III varicocele. The investigators noted a high prevalence of testicular asymmetry in adolescents with left grade II varicocele (41.7%) and with left grade III varicocele (51.9%). In contrast, adolescents without varicocele showed very low testicular asymmetry (11.0%). Patients with a Grade III left varicocele showed a lower total progressive motile sperm count (29.39x10) than adolescents without varicocele (122.07x10^6) ($p<0.01$), while grade II left varicocele (78x10^6) did not differ from either group ($p>0.05$). (The authors concluded that adolescents with grade II or III varicoceles had ipsilateral testicular growth retardation, and this is associated with decreased testicular function as it is demonstrated by the lower sperm concentration and total motile sperm count. Additionally, testicular asymmetry was also noted in adolescents with varicocele grade II or III, when compared to adolescents without varicocele. In summary, the presence of varicocele leads to alteration in testicular volume, but only the presence of a grade III varicocele leads to decreased semen quality, which in turn suggests that size of varicocele may determine the importance of lesion to the seminiferous epithelium.

Mini-Symposia "Testing for Sperm DNA Integrity"
by Mark Sigman, MD
Summarized by Mark Sigman, MD

Both physicians and patients are commonly requesting DNA integrity testing. However, there is no agreement on what exactly the tests measure, what are normal thresholds, what do normal results imply and what do abnormal results imply. While normal sperm DNA is compacted, nicking and ligating are normal physiologic processes. Abnormalities of chromatin may involve direct DNA fragmentation, defects in nuclear proteins, or defects in the tertiary structural arrangement of chromatin. Residual DNA breaks may persist because of dysfunction of the normal nicking and ligating process, or because of increased rates of fragmentation due to insults such as reactive oxygen species.

Many conditions have been associated with impaired chromatin integrity, including cancer, systemic diseases, varicoceles, chemotherapy, smoking as well as many other conditions. There are a variety of tests available to measure DNA and chromatin integrity. The TUNEL assay, the comet assay inside to nick translation and sperm nuclear matrix stability assay all directly detect DNA breaks. Other assays determine the susceptibility to DNA denaturation. These include the acrodin orange flow cytometric assay (SCSA-type assay), the comet under alkaline conditions, the sperm chromatin dispersion assay, chromomycin dye binding and DNA breakage detection FISH. For a majority of tests there is limited clinical data which rules out routine use. Data has been published correlating SCSA-type assays and TUNEL assays with pregnancy outcomes. What has become clear is that even with abnormal DNA fragmentation pregnancies may occur by intercourse, IUI, IVF, and ICSI. What remains debatable is whether abnormal results lead to decreased pregnancy rates. Current studies suggest lower pregnancy rates by intercourse with increasing percent of fragmented DNA. However, this data is based on relatively few patients with abnormal DNA integrity. Similarly, when examining IUI and DNA integrity, data suggests decreased pregnancy rates with increased fragmentation rates. However, there are few studies examining this relationship. The relationship between DNA integrity and IVF pregnancies remains quite unclear with some studies suggesting a moderate relationship while other studies demonstrating no relationship. A majority of studies currently suggest pregnancy by ICSI does not correlate with DNA fragmentation. It is likely that not all DNA fragmentation is pathologic and current tests do not differentiate between physiologically important damage and physiologically unimportant damage. Hopefully future studies will allow us to further define the role of DNA integrity testing.

WEDNESDAY, OCTOBER 25, 2006

INTERACTIVE SESSIONS

Controversies in the Treatment of Male Infertility: When to Treat and When to Send for ART
Society for Male Reproduction and Urology
Chair: Harris M. Nagler, MD
Speakers: Robert D. Oates, MD, Richard J. Paulson, MD
Summarized by Harris Nagler, MD

"Controversies in the treatment of Male Infertility: When to treat and when to send to ART," was the title of a lively interactive session chaired by Harris M. Nagler, MD, Chair, Sol and Margaret Berger Department of Urology, Beth Israel Medical Center. The participants in this session were Robert Oates, Professor of Urology at Boston University School of Medicine and Dr. Richard Paulson, Director of USC Fertility, Professor of Obstetrics and Gynecology and Chief of the Division of Reproductive Endocrinology and Infertility at the University of Southern California Keck School of Medicine.

The goals of this session were to:

- Understand importance of evaluating the infertile male
- Understand opportunities of urologists to improve sperm production
- Understand the opportunities of ART
- Understand the opportunity for collaborative approach to the infertile couple

The approach was:

- Present Background Positions of:
  - Urologists
  - Reproductive Endocrinologists
- Case Presentations
  - Highlighting areas of controversy and or consensus
  - Invite discussion and questions

The concern outlined was the

- Increased Use of IVF/ICSI
- Increased Costs of Treatment
- Hidden Costs of
  - Higher order gestations
  - The unresolved issues of increased birth defects
- Failure to diagnose significant medical conditions

Dr. Oates presented his views of the Team Approach to Care of the infertile couple and emphasized his belief that All males of infertile couples need to be evaluated at the onset of treatment because he may be able to:

- Improve their chances naturally
- Improve their chances with IUI
- Improve their chances with ICSI
- Improve his overall health
- Improve the health of the offspring
- Improve their chances for future conception

He then highlighted some of the issues that may be discovered by urologic evaluation such as:

- Gonadotoxins
- Smoking
- Obesity and sperm density
- Marijuana
- Anabolic steroid use

The importance of a urologic examination for the early detection of testes cancer and it increased incidence in the infertile male and the detection of varicoceles which are diagnosed by physical examination and not semen analyses or hormonal studies. Dr. Oates stated that varicocelectomy

- Increase chances of natural pregnancy
- Now and in future
- Increase chances of IUI, not IVF
- Increase chances of sperm in ejaculate in NOA (nonobstructive azoospermic patients)

ASRM Guidelines, in fact,

- Recommend male evaluation
- Recommend varicocele repair
- Dr. Oates then emphasized the importance of Genetic evaluation (including karyotype, microdeletion studies, CF mutation analysis and counseling for men with severe oligospermia or nonobtructive azoospermia. He also alerted the audience about the potential importance of increased

Paternal age leading to:

- Progeria
- APKD
- Schizophrenia
- Achondroplasia (> 50yrs 7.8x 25-29yrs)
- Apert syndrome
- MEN2
- Autism

Benefits of reconstruction as outlined by Dr Oates included

- Opportunity for natural conception
- Opportunity for more children - later on
- Opportunity for pregnancy each month
- Avoids ICSI
- Decreased Costs
- Decreased Morbidity to the female partner

The presentation then went on to review the benfits of Vasectomy Reversal / Reconstruction compared to testicular sperm acquisition followed by IVF/ICSI. Dr. Oates presented his view that reconstruction was

- Quite successful
- More cost-effective than aspiration/ICSI
- Gives couples multiple opportunities
- Each and every month till menopause
- Better for the older woman
- Chances of conception per month/ICSI less
- Provides her with multiple opportunities

Dr. Paulson then responded with the views of the reproductive endocrinologist. He framed his discussion with a historical perspective outlining the time frame of the major innovations which form the foundation of the debate.

- 1970's Microsurgical vasovasostomy
- 1978 Louise Joy Brown, first IVF baby in the world
- 1981 Elizabeth Carr, first IVF baby in USA
- 1985 First birth from cryopreserved embryo
- 1988 First attempts at ICSI
- 1992 First human birth after ICSI
- 1990's Surgical sperm retrieval and ICSI
- 2000's Sequential culture media
  + soft transfer catheters = - IVF success

He reviewed the available data of ART results from the 2003 SART data base. He acknowledged concerns or questions that have been associated with IVF including multiple gestations, decreasing success with increasing age, low birth rate and increased chromosomal abnormalities and imprinting disorders. Dr. Paulson highlighted the serious flaw that exists when comparing IVF results and reconstructive data. The result of reconstruction that are generally quoted are from published "master surgeons" and series and that these results may not be generalizable. Whereas, IVF data is reported and available on a program basis. He also introduced the concept of fecundibility indicating that the conception rate per cycle does not decrease with additional cycles. Additionally, he contended that the time to conception with TESE and ART was shorter than after reconstruction and this was an important consideration for older couples. He analyzed reported data and extrapolated funcidibility rates 2.3% per cycle as compared to higher fecundibility rates of ART.

After the presentations cases scenarios were presented and debated. A consensus evolved that couples deserved and needed a coordinated approach to the management of infertility which provided couples with appropriate information so that they may fully understand all options including risks, benefits and alternatives.

CONCURRENT SESSIONS

Male Reproduction and Urology Abstracts

Summarized by Margaret Hollingsworth-Kressin, MD

The last SMRU concurrent session was moderated by Dr. Nancy Brackett and Dr. Natan Bar-Chama.

The first paper was from University of Michigan, Dr. Morris et al. Their group looked at the ideal culture time and buffer to improve sperm motility from testicular aspirates of azoospermic men. Their recommendations were 1) 24 -hour incubation for men with obstructive azoospermia (OA) and 48 hours for men with non-obstructive azoospermia (NOA); 2) Nerve-injured patients (spinal cord injured or post-RPLND) behaved like NOA; and 3) There may be a slight advantage with F10 (Ham's F10 + albumin; Irvine Scientific) buffer compared to PM buffer (PM=human tubal fluid + HEPES buffer + gentamicin + human serum albumin; Irvine Scientific).

The second presentation by Li, et al, from the University of Virginia was on the involvement of calcium-binding tyrosine phosphorylation-regulated protein (CABYR) in the fibrous sheath protein involved in capacitation. They found that one of the six CABYR variants containing predominantly coding region A (CRA) form heterodimers and trimers and complex with roporrin (an RII-like domain containing protein) and coimmunoprecipitated with AKAP3 (a scaffolding protein) to form the fibrous sheath. This was the first demonstration that CABYR binds with another RII-like domain containing protein and a confirmation that different CABYR variants participate in the assembly of supermolecular structure by oligomerization to form the fibrous sheath.

Dr. Honig presented the third paper which looked at outcomes, complication, as well as timing of repeat TESE. They found good results in the second, third, and even fourth TESE procedure. In select patients perhaps—patients who have larger number of sperm in the testes—the patient can have a repeat procedure in less than 6 months. There were no changes in TESE success rates at early (2-6 months), intermediate (6 months) or late procedure.

Next, the presentation from Dr. Tanaka looked at the risk of ICSI from Klinefelter Syndrome patients. One of the things they looked at was how to identify the different cells from spermatogonia to round cells. They also analyzed 5 sperm and also found that XY/XXY mosaics did not enter meiosis thus concluding that injection of the sperm or spermatid posed lower risk than previously accepted. Dr. Peter Schlegel pointed out Cozzi's experiment with a much larger sample size (543) that says 47, XXY cells can undergo meiosis and form spermatozoa.

The fifth presentation was by Dr. Benoff. Her group looked at induction of heat shock proteins as a protective effect in men with varicoceles. Reflux from varicoceles is believed to raise testes temperature, increase nitric oxide levels and oxidative stress. It's been shown that Cadmium (Cd) and Fas ligand (FasL) are also involved in germ cell apoptosis, and CD elevates nitric oxide (NOS). Heat shcok proteins (HSP70-1) mRNA was assessed by RT-PCR from testes biopsied by percutaneous aspiration at varicocelectomy or at sperm retrieval during ICSI. Expression of iNOS, eNOS, FasL and SCC (side chain cleavage enzyme) were assessed by scoring of antibody staining. Cd was measured by atomic absorption. They found that induction of HSP70-1 protects against germ cell apoptosis in pathways that involve FasL, eNOS and Cd. HSP70-1 positive biopsies showed decreased FasL and increased sperm density in spite of higher eNOS and decreased SCC. HSP70-1 therefore may be an important marker in testis tissue which that may point us towards potential treatment regimen.

The final presentation was from Dr. Neri et al, and they showed that the combination of BMP's (bone morphogenetic protein) increased the amount of primordial germ cells (PGC) present as it does in early embryos. PGS were shown to be able to proliferate and enter meiosis. PGC's also need supporting cells and specific growth factors. Somatic cell support during embryonic stem cell differentiation may be used as possible treatment for men with germ cell aplasia. ⌘

SSMR Elections

This year, the Society for the Study of Male Reproduction will be entering the 21st Century and begin holding elections on-line. In the past,we have held these elections during the Business Meeting of the SSMR at the AUA. The ballot will be placed in the Member's Only section of the website (www.ssmr.org). All voting members will be able to vote from March 15 - May 1, 2007.

The positions open for election this year are Secretary and Member-At-Large. We encourage all voting members to participate in this process. To log in to the Members Only section you will need your Username (which is your last name) as well as your password (which is your member number). You can request your password at the sign-in if you do not have that information available. We hope that this will make it easier to stay involved in our society and make your voice heard. ⌘

SSMR once again thanks our 2006 Industry Partners and invites their continued support.

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Silver

Surgical Specialties Corporation

Needs and Objectives for the 2007 SSMR AUA Program Anaheim, CA

Needs:

What the Urologist needs to know about the effects of changing patterns of parenting in the United States.

1) Epidemiological aspects of parenthood in the United States
2) Changes in reproductive function in men and women with aging
3) The increase in genetic abnormalities, birth defects and other syndromes associated with the "older" parent.
4) How to adapt the evaluation and treatment of the "older" couple presenting with infertility

Objectives:

At the conclusion of the session the participant will:

1) Understand the changing pattern of couples waiting until a more advanced age to parent and the implications for infertility.
2) Look at this trend and its effect on infant mortality, birth defects as well as the increase in infertility.
3) Understand what is known about changes in reproductive function in males and females and the subsequent decrease in fertility that occurs with aging.
4) Examine the myths and realities surrounding the concept that advanced maternal and paternal age leads to an increase in birth defects and autism.
5) Realize that changing patterns of parenting will initiate changes in the evaluation and treatment of infertile couples.

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

Agenda for SSMR at the 2007 AUA

Saturday, May 19, 2007
12:00 p.m. – 4:00 pm
Annual Business Meeting will be held from 4:00 p.m. – 4:30 p.m.
Anaheim, California
Location: Marquis Ballroom Northeast – Anaheim Marriott

"Fine Wine or Wrong Time," Infertility in an Older Population Desiring Children"
Program Chair: Raymond A. Costabile, MD

12:00 p.m. - 12:15 p.m.	**Introduction:** *Raymond A. Costabile, MD* - Statement and definition of problem - Case illustrations - Objectives and introduction of faculty
12:15 p.m. - 1:00 p.m.	**Changing Patterns in the Age of Parenting in the United States:** *Paul R. Shin, MD* - Epidemiology of parental age in U.S. - Changes in parenting patterns - Trends in infertility - Infant mortality trends - Birth defects – autism - Comparison with other countries
1:00 p.m. - 2:00 p.m.	**Changes in Reproductive Capability With Aging: Panel Discussion** • **Female:** *Ajay K. Nangia, MD* • **Male:** *Antoine Makhlouf, MD, PhD* - Changes in sperm production and physiology with aging - Endocrine changes affecting reproduction - Changes in sexual function with aging
2:00 p.m. - 2:15 p.m.	**Break**
2:15 p.m. - 3:00 p.m.	**Birth Defects and Genetic Abnormalities in the Offspring of Older Parents – True, True or Unrelated?** *Edmund S. Sabanegh, MD* - Panel discussion or Point/Counterpoint - Changing indications for fetal/intrauterine testing
3:00 p.m. - 3:45 p.m.	**Adapting the Evaluation and Treatment of Infertile Couples Based on Parental Age** *Peter N. Kolettis, MD* - Vasectomy reversal in the "older male" vs. ART - Laboratory tests in the "older" couple -Tailoring ART for the "older" couple
3:45 p.m. - 4:00 p.m.	**Case Discussion and Questions** *Raymond A. Costabile, MD and Faculty*
4:00 p.m. - 4:30 p.m.	**SSMR Business Meeting**

You are invited to attend the 2007 SSMR Annual Banquet!

Saturday, May 19, 2007

Naples Ristorante e Pizzeria

1550 Disneyland Dr.
Anaheim, CA 92803

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

Naples is a dynamic dining establishment in the Downtown Disney District. The menu features the aromas and flavors of Southern Italy- from Mount Vesuvius to the Amalfi Coast.

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 19, 2007.

Casual attire is appropriate.

# of people attending _____ x $65.00 per person = $ _____ (on and before April 19, 2007)

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Please return this form to the SSMR office no later than April 19, 2007.

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Mark Your Calendars!

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

XIX North American Testis Workshop
April 18 - 21, 2007

Andrology Lab Workshop
April 21, 2007

ASA Special Symposium
April 21, 2007

American Urological Association Annual Meeting
May 17 – 24, 2007
Anaheim, CA

ASA 33rd Annual Conference
April 12 - 15, 2008
Hyatt Regency Albuquerque
Albuquerque, NM

Andrology Lab Workshop
April 12, 2008

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