SSMR NEWS

October *Society for the Study of Male Reproduction* 2007

President's Message

Hello to all SSMR members. There are many exciting things happening in our field, and SSMR is at the forefront, leading the way. We had a great annual meeting in Anaheim at the 2007 AUA, which will be highlighted in this issue of SSMR News, and we have even more in the upcoming 2007 American Society of Reproductive Medicine (ASRM) meeting. A huge thanks goes to our outgoing president, Dr. Jon Pryor. Jon is taking the end of his term seriously, as he has not only left office, but he has left medicine altogether, to pursue a career in business consulting. However, we are privileged to still have access to Jon's many talents, as he has agreed to make himself available for SSMR matters. We will miss him tremendously, at every level, but he has left a lasting imprint on our field. I would also like to extend a big welcome to our newly elected officers, Dr. Ajay Nangia (secretary) and Dr. Victor "Trey" Brugh (member-at-large), who will be joining our current officers, Dr. Stan Honig (vice president), Dr. Bob Brannigan (treasurer), and Dr. Peter Chan (member-at-large).

Jay I. Sandlow, MD

The 2007 SSMR meeting was entitled, "Fine Wine or Wrong Time: Infertility in an Older Population Desiring Children" and was organized by Dr. Ray Costabile. Ray put together a great panel of discussants, including Drs. Peter Kolettis, Antoine Makhlouf, Ajay Nangia, Edmund Sabanegh, and Paul Shin. A summary of this meeting follows in this newsletter. Many thanks go to Dr. Brannigan for his efforts that culminated in a great meeting. Our annual SSMR banquet was organized by Aaron Spitz and took place within Downtown Disney. As usual, a great time was had by all.

The upcoming ASRM meeting will be held in Washington DC October 13 – 17, 2007. A schedule of male infertility talks and events at the ASRM are previewed in this newsletter. The 2008 AUA meeting will be held in Orlando, FL from May 17 – 22, 2008. Also, big news regarding our 2008 SSMR meeting. We have successfully lobbied to move the meeting to Tuesday May 20th, thus putting the meeting the day before the infertility scientific sessions. Our program chair, Dr Ajay Nangia from the University of Kansas, has organized a very useful and practical meeting, entitled, "Vasectomy, What is All the Fuss About?" Details regarding this will be outlined by Ajay later in this newsletter. Our annual banquet will be held on Tuesday night and is sure to be a good time.

Another exciting development within the SSMR is the increased collaboration between the SSMR and our foreign counterparts who are members. We have appointed Dr. Ates Kadioglu of Turkey as chair of our International Liaison Committee. We envision the inclusion of our foreign colleagues in the administrative and scientific components of the society and will work to foster a deeper relationship with them. We look forward to their contributions to our society.

Harris M. Nagler, MD, as development chair, has been working with Sue O'Sullivan and Donna Kelly from WJ Weiser and Associates, the group that manages SSMR. They have once again obtained funding to help support all that we do. This is truly remarkable and we are very grateful to Dr. Nagler, Donna and Sue. The SSMR industry partners who contributed to our society include Coast Reproductive, Gyrus/ACMI, and GSK/Schering Plough. Thank you to all these contributors, which allow us to have such a great meeting.

Our Traveling Fellows Program, which continues to be a big success, has undergone a change in leadership. With his election to secretary, Dr. Ajay Nangia has passed the reins to Dr. Ray Costabile. We know that Ray will continue the great tradition and work with the Sexual Medicine Society of North America to move the field of andrology, male infertility, and sexual medicine forward.

Finally, I would once again like to thank Dr. Jon Pryor for all of the hard work that he has done for the society, as well as the Male Infertility/Andrology field in general. I think we all owe Jon a debt of gratitude for the difference that he has made. He will be sorely missed. I look forward to seeing everyone in the near future.⌘

Jay I. Sandlow, MD.
President, SSMR

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2007 ASRM Events of Interest

American Society for Reproductive Medicine
63rd Annual Meeting
October 13 – 17, 2007
Washington Convention Center
Washington, D.C.

SATURDAY, OCTOBER 13, 2007

8:15 a.m. – 5:00 p.m. **Postgraduate Courses**

Course 2 (Two-Day Course)
"Men and ART: The Missing Voice"
Developed in cooperation with the Mental Health Professional Group (MHPG)
Faculty: William D. Petok, PhD, Chair
Peter Chan, MD, CM, MSc
Nanette R. Elster, JD, MPH
Marcia C. Inhorn, PhD, MPH
Mark A. Womack, EdD

Course 11
"Preimplantation Genetic Diagnosis to Improve ART Outcome"
Developed in cooperation with the Preimplantation Genetic Diagnosis Special Interest Group (PGDSIG)
Faculty: Santiago Munné, PhD, Chair
Jacques Cohen, PhD
Ilan Tur-Kaspa, MD

SUNDAY, OCTOBER 14, 2007

8:15 a.m. – 5:00 p.m. **Postgraduate Courses**

Course 15
"No Man is an Island: How the Environment Impacts Male Health Reproduction"
Developed in cooperation with the Society for Male Reproduction and Urology (SMRU).
Faculty: Susan H. Benoff, PhD, Chair
Russ Hauser, M.D., ScD, MPH
Jerrold J. Heindel, PhD
Shanna H. Swan, PhD

Course 21
"Fertility Preservation: Biological Basis, Procedures and Genetic Testing Consequences"
Developed in cooperation with the Fertility Preservation Special Interest Group.
Faculty: Kutluk H. Oktay, MD, FACOG, Chair
David F. Albertini, PhD
Stephan Schlatt, PhD

3:30 p.m. – 5:00p.m. **Reproductive Medicine and Law Workshop**
"Posthumous Reproduction"
Ellen Wright Clayton, MD, JD

"Medical Issues in Posthumous Assisted Reproductive Technologies"
Peter N. Schlegel, MD

"Legal Issues in Posthumous Assisted Reproductive Technologies"
Ronald Chester, JD, MIA; Judith F. Daar, JD

MONDAY, OCTOBER 15, 2007

8:00 a.m. **President's Guest Speaker/TAP Pharmaceutical Endowed Lecture**
"The World of Genomics: What Does it Mean for Medicine?"
John Quackenbush, PhD

8:45 a.m. **Herbert H. Thomas Ortho Women's Health Endowed Lecture**
"Human Pheromones: Effects on Fertility, Sexuality and Emotions"
Martha K. McClintock, PhD

12:15 p.m. – 1:15 p.m. **Menopause Day Roundtables**
M32: "Androgen Replacement After Menopause"
Peter R. Casson, MD

12:15 p.m. – 1:15 p.m. **Interactive Sessions**
"The Role of Directed Genetic Testing in Male Infertility Evaluation and Treatment: Necessity and Advantages"
The Society for Male Reproduction and Urology
Chair: Robert D. Oates, MD
Presenters: Mark Sigman, MD;
Paul J. Turek, MD

2007 ASRM Events of Interest continued

"The Impact of Infertility on Male and Female Sexual Function and Mental Health"
Sexuality Special Interest Group
Chair: Cynthia Ziemer, MDiv, PsyD
Presenters: Carin V. Hopps, MD; Sheryl A. Kingsberg, PhD

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

Assisted Reproductive Technology
"Infertility Treatment and the Risk of Cancer"
Elizabeth S. Ginsburg, MD

Fertility Preservation
"Preservation of Fertility in Men"
Herman Tournaye, MD, PhD

Male Reproduction and Urology
"Varicoceles and Art"
Moshe Wald, MD

"Sperm Retrieval in Non-Obstructive Azoospermia"
Peter N. Schlegel, MD

"Genetic Evaluation of the Infertile Male"
Robert D. Oates, MD

"Preservation of Male Fertility in Cancer Patients"
Daniel H. Williams, MD

"Sperm Processing and Reproductive Options in the Neurologically Impaired Patient"
Nancy L. Brackett, PhD

Menopause
"Androgen Replacement After Menopause"
Peter R. Casson, MD

Surgery
"Surgical Techniques for Acquiring Sperm in Non-Obstructive Patients"
Peter N. Kolettis, MD

"Vas Reversal Techniques"
Edmund S. Sabanegh, Jr., MD

1:30 p.m. **American Urological Association/ Bruce Stewart Memorial Lecture**
"Human Embryonic Stem Cell Differentiation: Toward Making Sperm and Eggs in a Dish"
Renee A. Reijo Pera, PhD

3:00 p.m. – 5:00 p.m. **Male Reproduction and Urology Abstracts; Mini Symposium**

3:00 p.m. – 5:00 p.m. **"Fertiqol: Development and Uses of the International Quality of Life Questionnaire"**

4:30 p.m. – 5:00 p.m. **"Ethical Dilemmas in Male Infertility"**
Anthony J. Thomas, Jr., MD

TUESDAY, OCTOBER 16, 2007

8:45 a.m. **Serona, Inc., Endowed Lecture**
"Everything Conceivable: How Assisted Reproduction is Changing Men, Women and the World"
Liza Mudry

10:15a.m. – 11:00 a.m. **Contraception Day Keynote Speaker**
"The Cochrane Fertility Regulation Group: Synthesizing the Best Evidence About Family Planning"
David A. Grimes, MD

11:00 a.m. – 12:00 p.m. **Contraception Symposium**
"The Politics of Contraception"
Michael A. Thomas, MD

Interactive Session
"From Pronuclear Stage to Blastocyst: How to Select the Best Embroyo for Transfer"
Federacion Latinoamericana de Sociedades de Esterilidad y Fertilidad (FLASEF)
Chair: Carlos E. Sueldo, MD
Presenters: Vanesa Rawe, PhD; Denny Sakkas, PhD

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

Androgen Excess
"Does ART Cause Birth Defects"
Owen K. Davis, MD

Contraception
"Male Contraception"
Kurt T. Barnhert, MD, MSCE

2007 ASRM Events of Interest continued

"Spermicides: Where We Stand 2007"
Susan A. Ballagh, MD

"The Future Contraception"
Carisa R. Garcia, MD

Male Reproduction and Urology
"Effect of Sperm Source on ART Outcomes"
Christopher Schrepferman, MD

"Medications that Impair Male Reproduction"
Robert E. Brannigan, MD

"Semen Retrieval in Patients with Neurogenic Bladder Anejaculation"
Charles M. Lynne, MD

"Sperm Extraction for ICSI Tricks of the Trade"
Peter Chan, MD

Sexuality
"Sexual Health of the Infertile Couple"
John P. Mulhall, MD

"Female Sexual Dysfunction"
Sheryl A. Kingsberg, PhD

"Male Hypogonadism"
Abraham Morgentaler, MD

1:30 p.m. **Plenary Session IV: SRS Ethicon Endo-Surgery, Inc., Endowed Lecture**
"Microsurgery for Male Infertility: Life at the Cutting Edge"
Marc Goldstein, MD

3:00 p.m. – 5:00 p.m. **SMRU Traveling Scholars Abstracts, Mini-Symposium**

3:00 p.m. – 5:00 p.m. **Sexuality SIC Abstracts**

WEDNESDAY, OCTOBER 17, 2007

12:15 p.m. – 1:15 p.m. **Interactive Session**
"Imaging of the Infertile Male — What is Necessary (and What Isn't)"
The Society for Male Reproduction and Urology
Chair: Jay I. Sandlow, MD
Presenters: Robert E. Brannigan, MD; Ajay K. Nangia, MD

12:15 p.m. – 1:45 p.m. **Roundtables**

Male Reproduction and Urology
"Chromosome Microdeletion: How Do They Affect Prognosis"
Victor M. Burgh, III, MD

"Methods for Testing Sperm DNA Integrity"
Mark Sigman, MD

"Use of Strict Sperm Morphology for Male Infertility Evaluation: Assets or Nuisance?"
Amy E.T. Sparks, PhD

Mental Health
"The Male Perspective on Donor Eggs"
William D. Petok, PhD

"Complementary and Alternative Medicine in Infertility: What Should We Tell Our Patients?"
Jacqueline N. Gutmann, MD

Sexuality
"Endocrinology of Female Sexual Desire"
John E. Buster, MD

"Erectile Dysfunction and CV Risk"
Allen D. Seftel, MD

2:30 p.m. – 4:30 p.m. **The Society for Male Reproduction and Urology Abstracts, Mini-Symposium**

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2007 SSMR Annual Meeting at the AUA

4:30 p.m. – 5:00 p.m. Members Meetings: SMRU
"Fine Wine or Wrong Time: Infertility in an Older Population Desiring Children"
Saturday May 19, 2007
Chairman: Raymond A. Costabile, MD

"Changing Patterns in the Age of Parenting in the United States
By Paul R. Shin, MD
Reviewed by Kashif Siddiqi, MD

In the opening lecture for the SSMR, delayed marriages and parenthood was shown not to be a phenomenon isolated to celebrities in Hollywood, as strongly supported by data from the National Survey of Family Growth (NSFG) and other national surveys. In the latest cycle of NSFG, over 60,000 women from ages 15 – 44 were questioned on their family and relationship situations. Results demonstrated that the average maternal age at first birth has increased from 21.4 in 1970 to 25.1 years in 2002. Despite this, the fertility rate, as taken from the NSFG, has unexpectedly decreased from 8.5% to 7.4% during this same period. On the other hand, *impaired fecundity* has increased 12%, and this may be the more accurate data point to follow, based on the fact that its definition is built around an active process of prolonged (36 months) difficulty in achieving pregnancy, as opposed to the constructed measure of *infertility* (that is, no pregnancy in the last 12 months in any otherwise sexually active and unsterilized female).

Other survey data also highlight the state of delayed maternity in the U.S: in 2005, fertility rates in the older age groups of 25 – 29, 30 – 39, and 40+ females are all at all time highs. Unsurprisingly, IVF utility has skyrocketed in the past 6 years, and interestingly are highest in the <35 year age group, with success rates of 30% – 35%. Factors associated with older age at first birth include higher income, higher education, and greater infant wantedness. Despite these trends, U.S. infant mortality rates are stable, a favorable statement of the state of U.S. reproductive health. Broken down, however, a dichotomy of infant mortality rates, as well as use of fertility services and contraceptives in the U.S., appears between higher and lower income, white and non-white populations, a situation that needs to be improved.

"Changes in Reproductive Capability with Aging"
Female by Ajay K. Nangia, MD
Male by Antoine Makhlouf, MD, PhD
Reviewed by Ben Yang, MD

Female: Dr. Nangia stated that the reproductive changes that occur with aging are related to two main factors: ovarian and uterine. Ovarian factors are the primary concern in the decline in female fecundity, and this is primarily due to a loss in oocyte number and oocyte quality. The decline in oocyte count is dramatic, and although 2 million primordial cells are present at the time of delivery, these decline to 1000 by menopause. This loss is physiologic, and is independent of ovulation, pregnancy or oral contraceptives. Moreover, these decreased numbers of oocytes are more likely to have chromosomal, morphologic and functional abnormalities that impair the quality of the remaining oocytes. Uterine abnormalities such as fibroids and polyps also contribute to the decreased fecundity, but the influence of these conditions is less important than the oocyte factors.

Male: Dr. Makhlouf reviewed the literature of the age-related changes in male reproductive physiology. Sperm quality in older men exhibit decreased motility and concentration, although this is not a consistent finding. Testicular changes include a decline in volume, decrease in the number of Leydig and Sertoli cells, a thickening of the seminiferous tubules and in increase in maturation arrest of germ cells. These findings lead to a decline in the efficacy of spermatogenesis. Moreover, changes in testosterone levels (1% – 2% per year) may affect fertility. Also, some studies now suggest that the metabolic syndrome may also cause a decline in reproductive function. These factors all contribute to the perceived decreased fecundity in older men.

"Birth Defects and Genetic Abnormalities in the Offspring of Older Parents"
By Edmund S. Sabanegh, Jr., MD
Reviewed by Josiah Nelson, MD

The discussion on human aging and its relation to birth defects and genetic abnormalities in the offspring of older parents was a fascinating lecture. There were several key points in his address. While I believe that most of us understood that the total # of eggs decreased in the female from birth to menopause, I was interested to learn that the total number of Meiotic errors in those eggs also increased. Another interesting finding in women is that there are microscopic differences in the eggs of older women when compared to younger women. These findings continue to support and help explain the fact that as women age it becomes increasingly difficult to conceive and the number of birth defects increases as well. His lecture also focused on the male factor and how aging affects birth defects. There may be a synergism when both the man and women are older relating to birth defects. This has been reported as it relates to Down's Syndrome. When the mother is over 35 and the father is over 40 there is an increased risk of downs. The most interesting part of the talk related to paternal age and its relation to defects. The increased rate of autism and schizophrenia are especially eye opening. Dr. Sabanegh reported that fathers over 40 are 5.75 times more likely to have offspring with autism than men under 30. In terms of schizophrenia It's been reported that the risk of schizophrenia rises from 1 in 147 births in fathers younger than 25 to 1 in 47 births for fathers 50 years or older. Looking at this data, it does appear that advanced age is associated with fetal abnormalities. This is an interesting area of research that will continue to expand in the next few years.

"Adapting the Evaluation and Treatment of Infertile Couples Based on Parental Age"
By Peter N. Kolettis, MD
Reviewed by John D. Adams, Jr., MD

Dr. Kolettis started the seminar with a discussion of epidemiology, stating that couples are now delaying attempted conception, thus increasing the average maternal age. In 2003, the maternal age was 25.1 years

versus 21.4 in 1971. There has been a decrease in teen births, but women in the 35 – 39 and 40 – 45 age groups are having children at the highest levels in three decades. Paternal age is presumably increasing as well.

Genetic risks and advanced maternal age were discussed. The risk of having a child with genetic disorders such as Down's Syndrome increases significantly as the maternal age increases, e.g. 1 in 1667 births for mothers who were 20 years old versus 1 in 106 births for mothers who were 40 years old. Genetic risks and advanced paternal age were also discussed. Dr. Kolettis reported increased sperm DNA damage and the number of sperm mutations (especially in men over 35 years old), decreased rate of apoptosis, and increased risk of 20 or more disorders such as Apert Syndrome, Achondroplasia, Crouzon Syndrome, and Pfeiffer Syndrome. 2% of children born to fathers over 50 years old have schizophrenia. This is triple the incidence of children born to fathers in their early 20s. Because of these risks, some European countries have an age limit for sperm donation. Advanced paternal age and diminished fertility were linked to decreased semen volume, sperm motility, and morphology. One study suggested time to pregnancy was 4.6 times longer for men over the age of 45 to conceive than men younger than 25 years old, and there is an increased miscarriage rate when the man is older than 40 years old, particularly if the woman is older than 35 years old. Consideration should be given to revising semen reference ranges for older men. There is also increased IVF failure with increased paternal age.

Dr. Kolettis discussed the relationship of advanced maternal age and diminished fertility with regard to diminished ovarian reserve (DOR). DOR can account for decreased pregnancy rates in natural and assisted reproduction cycles and increased miscarriage rates in natural and assisted cycles. DOR reflects follicular depletion and decline in oocyte quality. It is a natural physiological occurrence, usually noted in mid to late thirties, occasionally earlier.

Endocrine changes also have a profound effect. Subtle elevations in FSH may occur in women in their mid thirties. Increased FSH occurs when ovarian reserve decreases. Increased FSH is possibly related to decreased inhibin. There is no change in LH, E2, progesterone, and endometrial biopsy specimens. Reproductive aging primarily of the ovarian origin has also been observed leading to a shortened follicular phase. Other endocrine changes predictive of DOR are increased cycle day three FSH (> 20 mIU/mL), day three inhibin (> 45 pg/mL), and decreased day three inhibin.

The Clomiphene Challenge (CC) test was discussed. In women with normal ovarian reserve, decreases in estradiol and inhibin production by developing follicles should overcome impact of the CC on the HP axis and suppress FSH levels back into normal range by cycle day 10. It is a provocative test that unmasks patients who might not be detected by basal FSH testing alone. The CC was first described in 1987 as a test of ovarian reserve *(Navot et al, Lancet 2: 645-647, 1987)*. It involves measuring day 3 and day 10 FSH, followed by administering 100 mg Clomiphene Citrate on days 5 through 9. An abnormal test is determined by an elevated day 10 FSH level. There is a marked deceased pregnancy rate with abnormal test. The CC test will identify more women with DOR than FSH alone. DOR, confirmed with abnormal CC test, is a cause of infertility independent of age. The results are not easily extrapolated to general infertility population. This test reflects the inability of the developing cohort of follicles (as a whole) to suppress FSH levels into normal range. If a single follicle possesses good reproductive potential then natural recruitment and selection processes could lead to ovulation of highest quality follicle and decreased predictive potential of test. In summary, an abnormal CC test is predictive of poor long-term pregnancy rates in natural cycles, ovulation induction, and IVF. CC is specific with limited sensitivity, but is more sensitive than day 3 FSH test. Screening guidelines include all infertile women >34 (rise in incidence of DOR occurs at this age) and younger women with unexplained infertility.

The chance of conception ending in live birth within 1 year is 75%, 66%, 44% for women ages 30, 35 and 40, respectively. Within 4 years, chance of spontaneous pregnancy is 91%, 84%, 64%, respectively. ART makes up for only 50% of births lost by postponing first attempt at conception from age 30 to 35 and 30% after postponing from 35 to 40 years. Dr. Kolettis discussed the use of IVF in the setting of DOR. The use of GnRH antagonist with gonadotropins prevents premature luteinization/LH surge. Also GnRH antagonist that are given during the follicular phase are not involved in early folliculogenesis. There is also less "over-suppression" of FSH levels and is not directly deleterious to ovary (as agonists may be). Low-dose GnRH agonist suppression administered before gonadotropin stimulation is used for assisting hatching of embryos. Use of estrogen or oral contraceptives in the cycle prior to gonadotropin stimulation is also part of many protocols.

Dr. Kolettis discussed vasectomy reversal in the setting of advanced maternal age. Pregnancy rate/cycle for IVF vs. pregnancy rate/month for intercourse women in their 20s: 50% – 60% vs. 20%, women in their 30s: 40% vs. 10%, and women in their 40s: 20% – 30% vs. 4%. Reproductive span and rate of reproduction among Hutterite women was given to provide an estimate of procreative capacity of women. Vasectomy reversal restores man to normal state. IVF/ICSI cannot really compensate for DOR. Successful reversal allows for other options (e.g., IUI). Dr. Kolettis discussed when to do neither IVF/ICSI or vasectomy reversal in situations such as prohibitive female factors, e.g., 47 year old female with history of 3 surgeries for endometriosis or poor chance for success (e.g., long obstructive interval).

In summary, couples are delaying parenthood making infertility an ever increasing problem. There are small increases in genetic abnormalities with increasing male age and a slight decline in fertility with increasing male age. There is a definite increase in genetic abnormalities with increasing female age and marked decline in female fertility potential in mid thirties. IVF cannot fully compensate for age related decrease in female fertility. Appropriate counseling of couples to address issues related to advanced parental age is imperative.

Course Summaries from the AUA Meeting

"Vasovasostomy, Vasoepididymostomy and Sperm Retrieval Techniques"
By Arnold Belker, MD

During the 2007 instructional course on "Vasovasostomy, vasoepididymostomy and sperm retrieval techniques", Dr. Arnold Belker mentioned the use of modified "infrapubic" incisions placed horizontally to each side of the base of the penis to facilitate access to the ends of the vas when the vasectomy had been performed high in the scrotum

and to enable maximum mobilization of the abdominal end of the vas when an unusually long segment of the vas had been removed at the time of the vasectomy. It is possible to displace the scrotal contents upward through such incisions when vasoepididymostomy might be required. Dr. Belker also emphasized avoidance of any cautery on the transected end of the vas, avoidance of stripping away the blood supply of the vas during mobilization of the vasal ends, and the use of a suture to approximate the perivasal tissue of one end of the vas to the other during vasovasostomy.

The longer the duration of the interval of time from the vasectomy until its reversal, the lower the rates of return of sperm to the semen and of pregnancy postoperatively. The failure to find sperm in the intraoperative vasal fluid bilaterally does not necessarily indicate that bilateral vasovasostomy cannot be successful. The character of the gross appearance of the intraoperative vasal fluid helps intraoperative decision making in such situations; the clearer and more transparent the vasal fluid, the more likely that vasovasostomy will suffice to produce a fertile result in such situations. The importance of intraoperative inspection of the epididymis for evidence of epididymal obstruction when sperm are absent from the intraoperative vasal fluid also was emphasized. If vasoepididymostomy is performed at an epididymal level at which sperm are absent from the epididymal tubular fluid, sperm never will return to the semen postoperatively.

Dr. Belker indicated that the triangular "intussusception" method of vasoepididymostomy, which produces six points of fixation of the vasal mucosa to the edge of the opened epididymal tubule and first was described by Dr. Richard Berger, appears to produce encouraging results. A four-point intussusception method first described by Dr. Joel Marmar and later by Dr. Marc Goldstein also appears to produce satisfactory results of vasoepididymostomy.

"Office Evaluation of the Infertile Male: 2007"
By Larry I. Lipshultz, MD

Although little has changed in the general approach to male infertility in recent years, much has changed in the diagnostic modalities available to the practitioner. A thorough evaluation is still based on a detailed history, physical examination and appropriate laboratory and radiographic tests. Advances in laboratory tests that merit particular attention include the widening application of genetic screening and evaluation of sperm function testing.

Since the cloning of the Y chromosome in the early 1990s, we have been able to identify genetic loci that are responsible for impaired spermatogenesis. Y chromosome microdeletions are found in up to 10% of men with severe oligospermia and 12% of men with non-obstructive azoospermia. Furthermore, men with the AZFb deletion will almost never have sperm on testis biopsy.

Fluorescence In-Situ Hybridization (FISH) has also become more widely used. FISH can be useful in cases of recurrent spontaneous abortions, as well as screening high-risk IVF/ICSI couples prior to initiating a cycle. Our laboratory has recently investigated FISH assays in 29 consecutive men with severe OATS and discovered 93% of these men have abnormal results.

DNA damage has been implicated in impairing post fertilization embryo cleavage. There are three assays in use to assess sperm DNA damage. The Sperm Chromatin Structure Assay (SCSA) is a flow cytometry-based test that measures DNA denaturation. The TUNEL assay relies on flow cytometry or microscopy to measure DNA breaks following fluorescent enzymatic labeling. The Comet assay uses single cell electrophoresis to measure DNA breaks using fluorescent microscopy.

The **SCSA assay** with >30% breaks portends a poor fertility potential. The **TUNEL assay** suggests that >26% breaks is related to poor fertility potential.

A **Comet assay** with >27% damage predicts poor fertility potential.

The rate of idiopathic infertility is usually quoted to be around 25%. With the advent of advanced genetic analysis, it is assumed that this number will decrease. The next era of genetic advances will be to identify and understand specific gene mutations that lead to infertility and develop strategies to treat these abnormalities.

"Male Infertility: How to Treat, Prevent and Collaborate with Gynecologists"
By Marc Goldstein, MD; Cathy Naughton, MD
Reviewed by Joe Feliciano, MD; Peter Chan, MD

Male factor infertility can be diagnosed in about half of the couples presenting with infertility. A thorough fertility evaluation in the male partners of all infertile couples not only can help diagnosing treatable underlying causes of infertility to improve their success in reproduction, but it can also unveil various underlying conditions associated with male infertility that are significant to the general health of the men. These conditions include testis cancer, pituitary tumors and various endocrinological and genetic disorders.

Many of such conditions can be treated to "upgrade" the fertility status of the couples. From medical management for hypogonadism or other endocrinologial disorders, surgical correction for varicoceles and cryptorchidism and reconstruction for obstruction of the excurrent ductal system, the nature and the quality of the management options for men with infertility have indeed improved tremendously in the past decade.

Various lifestyle modifications can help preventing infertility. Simple measures, such as reducing and quitting tobacco consumption, avoiding excessive heat to the gonads, weight and stress management, are useful advice for all couples going through fertility management.

Fertility preservation for cancer patients is gradually recognized as an important cancer survivorship issue. Clinicians should be aware of the current literature on the potential impact of cytotoxic cancer treatment on male reproductive health and the various strategies that can be used to facilitate fertility preservation with sperm cryopreservation.

It is important for reproductive urologists and gynecologists to recognize that their partnership in managing couples facing infertility can allow specific needs of the men and the women to be properly addressed to provide the best care they deserve. Most importantly, even in cases when advanced assisted reproductive technology such as ICSI is required, upgrading the fertility status of the men by proper management can help improving the success of the treatment, making everybody a winner at the end.

"Empiric Treatment of Male Infertility"
By Mark Sigman, MD
Reviewed by Richard Lee, MD; Jay Sandlow, MD

Dr. Mark Sigman covered the broad aspects behind empiric treatments for male factor infertility. First, he emphasized three main concepts: 1) that pregnancy rates are highly dependent on female fecundity, 2) that the specific outcome metrics chosen will influence the results of any assisted reproductive technology (ART) study, and 3) that current studies require improved design, e.g. placebo/control arms. Most empiric therapies for infertility are based on the theory that if a little is good, more is better. Conversely, if a little is bad, less is better.

The first treatments include application of GnRH and hCG. Neither is recommended, as no change in semen parameters was seen after therapy.

FSH (hMG, uFSH, rFSH) treatment in doses of 75 – 150U was examined via a Cochrane review for pregnancy rates. The review states that current studies regarding FSH are underpowered with little interstudy consistency but nevertheless showed an overall increased pregnancy rate; no changes were seen when ICSI was used however. Use of FSH with IVF showed no changes in pregnancy or implantation rate but a questionable impact on fertilization rate. FSH treatment did not change semen parameters; although baseline mixed testicular histology and abnormally increased FSH throw such results into question. Overall, FSH shows no proven efficacy in unselected idiopathic infertile men.

Androgen treatment has been used in low doses to increase epididymal sperm maturation in nine randomized trials, with no change in subsequent pregnancy rates. The use of high dose androgen therapy also does not show any change in pregnancy rates or semen parameters, and may lead to irreversible azoospermia in some instances.

Antiestrogens block feedback by testosterone (T) and estrogen (E) on the hypothalamus and pituitary gland. Examples include clomiphene citrate and tamoxifen. A meta-analysis of antiestrogen therapy showed 1) underpowered studies, 2) mild increases in sperm count and motility, and 3) no significant change in pregnancy rates. These agents are usually relatively safe and inexpensive. Poor responders would include those with increased FSH, severe oligoasthenoteratospermia or azoospermia, or poor testicular histology.

Use of aromatase inhibitors is based on the theory that a decreased T/E ratio adversely impacts sperm production. The only randomized controlled trial with aromatase inhibitors showed no change in seminal parameters or pregnancy rates, leading to the conclusion that no apparent benefit exists with its use in unselected patients.

L carnitine exists at high concentrations in the epididymis. It increases *in vitro* sperm motility and is found in decreased concentrations in the semen of infertile patients. Five randomized trials have been performed with L carnitine; these have yielded conflicting data. It is possible that subgroups with the worst semen parameters may see some improvement.

Control of reactive oxygen species has also been examined. Normal sperm production and maturation requires a small but not excessive amount of reactive oxygen species. Use of antioxidants however has shown inconsistent results in uncontrolled studies. A double-blinded placebo-controlled trial with vitamin C and E, while showing no change in semen parameters, did show a decrease in the level of sperm DNA fragmentation.

Overall, the decision to undergo ART vs. empiric therapy must balance the documented efficacy of ART with its invasive and expensive nature compared to the unproven efficacy but noninvasive and variably expensive characteristics of empiric therapy. If empiric therapy is to be considered, the following regimens are recommended:

1) low count ± motility ? hormonal treatment
2) low motility ± count ? L carnitine
3) poor sperm function ? antioxidants

"The Effects of Urologic Disorders and Treatments on Male Fertility"
By Jay Sandlow, Harris Nagler, Kirk Lo, Mark Goldstein, T. Kolon, C. Wang

A panel of experts from multiple fields discussed various situations seen in male infertility. The panel included Drs. Thomas Kolon, Christina Wang, Jay Sandlow, Kirk Lo, and Marc Goldstein, with Dr Harris Nagler as the moderator, and the topics covered hormonal issues, testicular failure, cryptorchidism, semen cryopreservation, and obstruction. Testosterone is known to increase at two to six months of age. Currently, early orchiopexy (prior to 1 year of age) is recommended, as delayed treatment has been shown to lead to decreased testicular volume and spermatogenesis (patients undergoing orchiopexy at 9 months had superior outcomes compared to those undergoing orchiopexy at 3 years of age).

Unilateral undescended testes have been shown to result in abnormal seminal parameters in 50% of patients, with up to a 2x increased likelihood of inability to conceive. Bilateral undescended testes result in abnormal parameters in 75% of patients, with a 35% additional probability of inability of conceive.

Use of androgen supplementation has been used to help testicular descent. However, one needs to be aware of the impact of supplementation on libido, skin (acne), and epiphyseal closure. Current regimens include either the use of testosterone (IM, patch, or gel) or hCG.

Undescended testes are also 20 times more susceptible to cancer. Currently, little data exists to support the use of serial ultrasounds over testicular self-exam to follow these patients. Patients should be re-evaluated immediately postoperatively after orchiopexy and then six to twelve months afterwards to confirm size, location, and viability of the testis. The patient should also be counseled on and taught how to perform testicular self-exams.

When patients present with a testicular mass that is suspicious for cancer, many are now advocating semen cryopreservation prior to orchiectomy. Studies have demonstrated that semen quality may be better preoperatively, plus the patient does not have to contend with postoperative pain and narcotics, which may inhibit his ability to ejaculate. When patients are not able to ejaculate, several options for sperm acquisition exist, including vibratory stimulation, electroejaculation, and testicular sperm extraction. Each comes with its own set of advantages and disadvantages.

Cancer treatment may also negatively impact male fertility. Alkylating agents, especially, are gonadotoxic and can lead to prolonged azoospermia. The effects of radiation therapy are dose-dependent, with the worst prognosis seen at doses of more than 6Gy. The most effective treat-

ment in these scenarios consists of gamete cryopreservation and an attempt to use less gonadotoxic chemotherapeutic agents.

One should also be cognizant that hernia repair may lead to occult vasal injury. However, success rates following repair are on par with in vitro fertilization pregnancy rates, and strong consideration should be given to repair, particularly when the female partner is young.

The Ramon Guiterras Lecture: "Genetics of Male Infertility"
By Dolores J. Lamb, PhD

The presentation focused on the genetic causes of infertility, current approaches to diagnosis and implications for couples planning to achieve a pregnancy with assisted reproduction.

Defects include chromosomal abnormalities (structural, numerical), accounting for about 6% of all male infertility. Karyotype analysis should be ordered and arguably, all infertile men should be tested (women, as well as together, about 12% of all infertile couples will have an abnormality). In the azoospermic or severely oligospermic male, a Y chromosome microdeletion test should be ordered as about 8% – 12% of these patients will be found to have a microdeletion and deletions of AZFb may aid in prediction of whether sperm will be found on testis biopsy.

There are many well-recognized gene mutation or deletion syndromes causing male infertility including developmental disorders, endocrinopathies and some genetic syndromes. Cystic fibrosis (CFTR) mutations are a particular concern in men with CBAVD. Diagnosis is challenging unless an extensive analysis is performed as over 1300 mutations have been identified. This is not done in the routine clinical genetics lab. Currently, assessment of the female partner for CFTR mutations and the 5T allele is recommended. The couples are at risk of conceiving a child with CBAVD or even cystic fibrosis and should be a genetic counselor.

Finally even in men with a normal karyotype, meiotic abnormalities may result in sperm aneuploidy (wrong numbers of chromosomes in the haploid sperm). This is diagnosed with a sperm FISH analysis. This test should be ordered for men with oligospermia and those with recurrent pregnancy loss (even men with normospermia).

Importantly, in addition to these possible approaches to diagnosis, there are many genetic defects that we cannot diagnose today. Because 80% or more of infertility may have a genetic basis, couples need to undergo counseling to understand that for many infertile men the tools for diagnosis are lacking, but certainly the genetic defects causing the infertility can be transmitted to offspring.

Male Infertility: Evaluation & Therapy

Starting the sessions, Kaplon et al reported the results of an osteopenia screening study. The incidence of osteopenia in the infertile population is approximately 9%, and is 21% in severely oligospermic patients. BMD correlates significantly with low total sperm count and elevated FSH levels, suggesting that these parameters are risk factors for osteopenia. They concluded consideration should be given to screening severely oligospermic patients for osteopenia.

Alukal et al described an analysis of chromosomal aneuploidy in patients with oligoasthenoteratozospermia (OAT) using fluorescent insitu hybridization (FISH). 29 patients with OAT were identified in there database. Of these, 27 (or 93%) had an abnormal result. Significantly higher frequencies of germ cell aneuploidy were identified in the OAT group. They concluded that patients with OAT should be offered FISH before undergoing IVF/ICSI

Walters reported an interesting sperm morphology study comprising 2 groups of men Group 1 consisted of men with a history of natural paternity presenting for elective vasectomy. Group 2 consisted of a computer generated random sample (n = 100) of age-matched men with sperm concentrations > 20 million/ml. presenting for infertility evaluation. Men with proven fertility have a high frequency (56%) of abnormal SM according to Kruger's criteria that is not significantly different from infertile males. Strict morphology likely represents a heterogeneous and non-specific surrogate marker of abnormal sperm fertilization capacity. Accordingly, couples should be counseled with caution to pursue assisted reproductive technologies based solely on SM.

Smith et al detailed an investigation of 12 men undergoing TRUS Prostate Biopsy. All men submitted semen analysis approximately one week prior to (first specimen), one week after (second specimen), and 2 – 4 months following biopsy (third specimen) to assess for changes to semen parameters. Total motile sperm counts decreased (average 35%) in 7 out of 12 patients. Of the 7 men that provided a third specimen, 3 had total motile sperm counts that remained decreased (average 43%) from their pre-biopsy specimen. Overall this study was an interesting observation requiring further study.

Khera et al described the findings of 26 men had a persistently elevated serum prolactin level (>22 ng/ml) and underwent a head MRI. They found there was no significant difference between prolactin values among patients with and without a pituitary microadenoma. However, the average testosterone values for men with and without pituitary microadenomas were significantly different ($p = 0.02$). Lower testosterone values in patients with hyperprolactinemia increased the probability that the patient will have a pituitary microadenoma.

Casteren et al assessed the total number of patients who used their banked semen and evaluated ART outcome during 20 years of follow-up. During follow-up 91 patients (14.3%) died due to their underlying illness. A total number of 42 patients out of 466 (9.0%) requested the use of the banked sperm after a mean time of 4.7 years. 43% were clinically pregnant with the use of cryopreserved semen and other were still trying or lost to follow up. Overall, almost 1 out of 10 patients will use the cryopreserved semen and in almost half of them this will result in a clinical pregnancy

Rosenberg et al provide consecutive new patients/partners coming to a single urologist were given questionnaires prior to initial consultation. Patients have a very limited understanding of urologic abnormalities associated with male infertility. IVF is most familiar to patients and are perceived as moderately successful. Varicocele repair was identified as a major factor by only 13% of patients prior to consultation. Further public health awareness of the treatable, reversible causes of male infertility is necessary to educate the public regarding the urologic causes and treatments of male infertility.

Lee et al demonstrated a decision analysis of treatments for obstructive azoospermia secondary to a vasectomy. A Markov decision analysis model was created to simulate initial therapy with vasectomy reversal, MESA, or TESE with IVF/ICSI. Vasectomy reversal appeared to be more cost-effective than both percutaneous TESE with IVF/ICSI and MESA for the treatment of obstructive azoospermia.

Bakircioglu et al followed 95 azoospermic men who diagnosed nonmosaic Klinefelter's syndrome (KS). All patients were underwent microdissection testicular sperm extraction (micro TESE) and ICSI was performed when sperm were successfully recovered. Sperm was successfully recovered in 48 micro TESE attempts of 95 (50.5%). 22 pregnancies were achieved in 46 cycles (45.2%). Four pregnancies resulted with abortion and three pregnancies are ongoing. In 15 pregnancies resulted with delivery of 9 boys and 10 girls, total of 19 chromosomally normal babies.

Okada et al investigated the outcome of salvage microdissection TESE in patients in whom first TESE in other institutions had failed. The sperm retrieval rate (SRR) of salvage microdissection TESE was 57% and 6% in patients who had undergone conventional and microdissection TESE, respectively (p=0012). The SSR of microdissection TESE as a first attempt was 56%. Therefore salvage microdissection TESE is not useful for patients who had failed in the same procedure and concluded salvage microdissection TESE should be recommended to patients who had undergone conventional TESE as a first attempt.

Morris et al performed diagnostic and therapeutic fine needle testicular aspirations were on 95 azoospermic men, including 51 obstructive (OA) and 44 non-obstructive (NOA) cases. The number of non-motile and motile sperm per 20 high-powered fields were assessed at initial collection and following incubation at 24h and 48h in either primary media (PM) or Ham's F10 + protein (F10). Incubation in PM or F10 media improved sperm motility with significant improvement noted between 24 and 48h for OA cases. F10 media may provide extra benefit for cases of NOA. These results suggest the ideal timing of oocyte retrieval for ICSI may correlate with 48h sperm incubation for OA cases and 24h for NOA.

Davis et al attempted Optical Coherence Tomography (OCT) is a novel real-time imaging modality that uses near-infrared light to visualize the microstructure of biotissues. This preliminary study suggests that OCT technology has a level of resolution that approaches that of underlying normal testicular histology. Further research will be needed to determine whether OCT can be clinically used to help identify areas of spermatogenesis in men undergoing TESE for non-obstructive azoospermia.

"Infertility: Physiology, Pathophysiology, Basic Research" Reviewed by Bobby B. Najari

"Machado-Joseph Microsatellite Expansion in Patients with Azoospermia
By Bobby B. Najari*, Francesca Gordon, Larry I. Lipshultz, Dolores J. Lamb

The authors examined microsatellite instability in the MJD gene of azoospermic men compared to a control population. They quantified the length of the triplet repeat region in this gene in 392 azoospermic men and 367 men representative of the general population. They did this by amplifying the triplet repeat region by PCR and quantifying the fragment length with a DNA sequencer. The azoospermic cohort had close to twice the incidence of alleles that were longer than two standard deviations above the population mean (4.8% vs. 2.6%). The azoospermic group had two patients with allele lengths large enough to present with Machado-Joseph disease, whereas the control group had no such alleles. The authors expressed a concern that the fact that unstable triplet repeat regions undergo further germline expansion may result in longer alleles in offspring conceived through ART. Lastly, the authors suggested that their findings, in combination with similar results in the *AR, SCA1,* and *DMPK* genes, may be indicative of an impaired DNA repair mechanism in patients with severe infertility.

A Testicular Isoform of RUNX2 Protein is Translated Differentially from Its Bone Isoform, and Colocalizes with Î³-H2AX-Containing Nuclear Foci in the Spermatogenic Cells
By Satoru Kanto*, Yoichi Arai, Masanobu Satake

The authors described and characterized a unique testicular isoform of the Runx2 protein, which was previously only thought to be expressed in bone. They used ten-week-old C57BL/6J strain mice to harvest testicular tissue and performed Northern blot analysis, immunoblot analysis, immunohistochemistry, and immunofluorescent staining on the samples. They found that the testicular isoform shared the amino-terminal 87 amino acids with the bone isoform, but was shorter and lacked a Runt domain. Additionally, the testicular isoform used the Met1 initiation codon, whereas the bone isoform uses the Met69 initiation codon. The protein localized to spermatogenic cells, specifically outside heterochromatin regions in the nuclei of these cells. The localization was specific to meiotic prophase I until late pachytene, and colocalized with gamma-H2AX, a marker of DNA repair. In summary, the authors described a unique isoform of Runx2 specific to the testes that plays a role in transcriptionally active DNA regions during prophase I.

Isolation and Culture of Human Spermatogonial Stem Cells (SSCS) from Testicular Tissues
By Hideyuki Kobayashi*, Koichi Nagao, Kazuyoshi Kataoka, Fumito Yamabe, Koichi Nakajima, Masato Nagata, Keiichiro Takasugi, Tadashi Ohira, Minoru Kurita, Hiroshi Hara, Kazukiyo Miura, Nobuhisa Ishii

The authors described a new method for isolating spermatogonial stem cells from testicular tissue using Thy-1 surface antigen expressed by these stem cells in the testis. They used magnetic-activated cells sorting (MACS) with magnetic microbeads conjugated to anti-Thy-1 antibodies to enrich spermatogonial stem cells from human testis cell suspensions. The cells were cultured in serum-free media with non-dividing STO cell feeders and GDNF, BFGF, and GFRalpha-1 growth factors. A limitation of the study was the lack of any comparison of the efficacy of this enrichment technique to other enrichment techniques utilizing other spermatogonial stem cell markers.

No Evidence of Germline Transmission by Adenovirusmediated Gene Transfer to Mouse Testes

By Yoshiyuki Kojima*, Yutaro Hayashi, Akihiro Nakane, Satoshi Kurokawa, Kentaro
Mizuno, Kenjiro Kohri

The authors examined whether adenovirus gene therapy transmits DNA to the germ cells or offspring in a mouse model. An adenovirus vector containing the *LacZ* gene was injected into both the interstitial space and seminiferous tubules of mouse testis. The authors used both PCR and histology to detect the presence of the gene in epididymal sperm and fetuses 3, 17, 14, and 28 days after injection. PCR of the genomic DNA isolated from the sperm failed to demonstrate presence of the gene. This was also true using RT-PCR on 1297 fetuses. Histologic X-gal staining demonstrated bet-gal activity in the Leydig and Sertoli cells of the testis, but not in germ cells or fetuses. The authors concluded that their findings demonstrate that gene therapy with adenovirus can be used for male infertility without affecting potential offspring.

Production of Functional Spermatids from Mouse Germline Stem Cells in Ectopically Reconstituted Seminiferou Tubules

By Kita Kaoru*

The authors recapitulated spermatogenesis ectopically *in vitro* in the mouse model. They established two lines of germline stem cells (GFP+ and haspin+) from the testes of embryonic and neonatal nude mice. The suspension was mixed with MATRIGEL matrix and injected subcutaneously into the dorsal region of the mice. At 4-10 weeks, microscopic observation showed tubular structures in the area and histologic observation revealed germ cells in these tubules. GFP+ spermatids were injected into wild-type oocytes, producing 4 pups that were GFP+. However, the mechanism by which germline stem cells induce the formation of tubular structures in the surrounding tissue remains unclear.

Characterization of Two Novel Isoforms of the Male Germ Cell-Specific Transcription Factor Crem

By Klaus Steger*, Saskia Jaspers, Birgit Gellersen, Rita Kempf, Annemarie Samalecos,
Wolfgang Weidner. Giessen, Germany and Hamburg, Germany.

The authors characterized two isoforms, è2-F-G-H-Ib and è2-G-H-Ib, of the cAMP-responsive element modulator (CREM) protein that are present in male germ cells. Western blot analyses *in vitro* and *in vivo* demonstrated the expression of two proteins with a molecular weight of 28 and 22.1 kd, indicating a novel upstream open reading frame. Electrophoretic mobility shift assay showed that these proteins bound to DNA in a sequence specific manner, consistent with their function as transcription factors. This work expands our knowledge of transcription and translation in male germ cells.

The Histone Deycetylase Inhibitor Ichostatin-A Arrests Meiosis in Male Mice

By Klaus Steger*, Irina Fenic, Hamid M Hossain, Violetta Sonnack, Svetlin Tchatalbachev, Johannes Trapp, Klaus Failing, Martin Bergmann, Manfred Jung, Trinad Chakraborty, Wolfgang Weidner. Giessen, Germany and Freiburg, Germany.

The authors described the effect of the histone deacetylase (HDAC) inhibitor trichostatin-A (TSA) on male Balb-c mouse meiosis. They treated the mice with TSA and sacrificed them at various time points afterwards. ELISA demonstrated decreased HDAC activity and Western blot showed increased histone H3/H4 acetylation. Histology showed a loss of pachytene spermatocytes due to apoptosis. Genome-wide expression analysis showed 507 genes that were significantly regulated. These changes occurred as early as 2.5 hours after exposure, however the effects were reversible upon removal of the drug. These findings may be clinically useful in the counseling of patients treated with HDAC inhibitors.

Generation of Fluorescent Sperm by Use of In Vivo Gene Transfer to Hamster Testes

By Hiroki Kubota*, Kevin Coward, Olivia Hibbitt, Nilendran Prathalingam, William Holt, Kenjiro Kohri, John Parrington. Nagoya, Japan, Oxford, United Kingdom, London, United Kingdom.

The authors described the transfer of a gene into the germ cells of male Golden Syrian hamsters using electroporation. They used a vector designed to produce enhanced yellow fluorescent protein containing a mitochondrial localization signal peptide. The vector was injected into the right testis of adult male hamsters and an electrical current was applied to it, while the left testis was used as control. The protein was expressed in the spermatocytes and spermatids at 20 days after the procedure, and epididymal sperm examined at 40 days also expressed the protein. This protein expression did not impact sperm motility or the proportion of spermatogenic cells in the testis. This technique could be applied to other genes for the creation of transgenic mice.

Involvement of Growth Factors in the Process of Postvasectomy Micro-Recanalization

By Brandon C Stahl*, Timothy L Ratliff, Barry R De Young, Moshe Wald. Iowa City, IA.

The authors characterized the expression of various growth factors after vasectomy. They performed unilateral vasectomy in 18 rats with a sham surgery on the contralateral side and sacrificed the mice at 2, 8, and 12 weeks. Real-time PCR and ELISA were used to identify and quantify the expression of the growth factors in vas specimens from the surgical sites. They found significantly higher degrees of expression platelet-derived growth factor beta (PDGF-â), PDGF-á, and transforming growth factor beta (TGF-â) after vasectomy. The testicular end of the vas expressed significantly higher levels of PDFG-â. While microcanalization was present in some post-vasectomy samples, the authors did not compare the degree of growth factor expression in these samples to the expression in sample without microcanalization.

Predictors of Success of Testicular Sperm Extraction (TESE) in Non-Obstructive Azoospermia
By Sakr A Mostafa*, Aly M Abdel-Karim, Magdy El-Pordiny. Alexandria, Egypt.

The authors conducted a retrospective study on 138 patents with non-obstructive azoospermia (NOA) comparing parameters that were associated with ease of retrieving sperm on testicular sperm extraction (TESE). They compared 65 patients in whom motile sperm was retrieved with one or two samples to 73 patients in whom more than two biopsies were done. Only 26 of these 73 patients had sperm in any specimens. Serum inhibin>80 pg/mL, the presence of at least one spermatid in the semen, and the presence of Y-chromosome microdeletions were all correlated with the presence of sperm after TESE, whereas testicular size, FSH, and testicular histopathology were not predictive of sperm retrieval. This study is helpful in using patient characteristics to counsel patients on the success of a planned TESE.

Interleukin-1B Signals Through a Cjun-N-Termianl Kinase (JNK)-Dependent Inducible Nitric Oxide Synthase and Nitric Oxide Production Pathway in Sertoli Epithelial Cells
By Tomomoto Ishikawa*, Masato Fujisawa, Patricia L Morris. Kobe, Japan and New York, NY.

The authors evaluated interleukin-1â and its effect on inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production in Sertoli cells. They cultured Sertoli cell from rat testes and treated them with IL-1â. They also were cultured with cyclooxygenase-2 (COX-2) and cJUN NH2-terminal kinase (JNK) as these regulate IL-1â expression. RT-PCR and Western analysis were used to evaluate NOS mRNA and NOS protein expression. Culture with IL-1â increased iNOS mRNA and protein expression. IL-1â induced NO production in a time dependent manner, but reactive oxygen species (ROS) were not altered. The presence of JNK, but not COX-2, influences iNOS expression and NO production. The findings suggest the Sertoli cell's role in monitoring and responding to cytokines present in the testis.

Expression of Leptin and Leptin Receptor in the Testis of Fertile and Infertile Patients
By Tomomoto Ishikawa*, Hitoshi Fujioka, Takeshi Ishimura, Atsushi Takenaka, Masato Fujisawa. Kobe, Japan.

The authors characterized the expression of leptin and leptin receptor in 46 human testes with immunohistochemistry. These patients included 8 with obstructive azoospermia due to vasectomy, 6 patients with Sertoli cell only syndrome, and 32 oligospermic patients with grade II or III varicocele. They found that leptin is primarily expressed by spermatocytes and leptin receptor is primarily expressed by Leydig cells. The ratio of germ cells expressing leptin to the total number of germ cells was inversely correlated with serum testosterone level. Leptin receptor expression was also inversely correlated with testosterone. Their work suggests that leptin may play a feedback role in Leydig cell testosterone secretion.

Mono-(2-Ethylhexyl) Phthalate Rapidly Decreases Claudin-11 in Sertoli Cells
By Yutaka Kondo*, Tomomoto Ishikawa, Kohei Yamaguchi, Yuichi Sakamoto, Takeshi Ooba, Masato Fujisawa. Kobe city, Japan.

The authors examined the effect of a phthalate, mono-(2-etylhexyl) phthalate (MEHP), on Sertoli cell expression of a tight-junction protein, claudin-11. Sertoli cells were isolated from rat testes and cultured with varying concentrations of MEHP or control media. Using RT-PCR, they demonstrated that MEHP significantly decreased claudin-11 mRNA in a time and dose dependent manner. Western blot analysis also showed that MEHP induced the phosphorylation of p44/42 and protein kinase C. Their work suggests that environmental contaminants like phthalates may have an effect on spermatogenesis, although they did not compare the dosages used in the experiment to those found in the environment.

Protamine as Prognostic Parameter for Testicular Sperm Extraction (TESE) and Possibly Intracytoplasmic Sperm Injection (ICSI)
By Klaus Steger*, Klaus Failing, Thorsten Diemer, Martin Bergmann, Wolfgang Weidner. Giessen, Germany.

The authors examined the ratio of protamine-1 (P1) to protamine-2 (P2) and its association with spermatogenesis and ICSI outcomes. They examined the testicular biopsies of 47 men with non-obstructive azoospermia (NOA) using in-situ hybridization and RT-PCR and compared them to testicular biopsies of 8 men with obstructive azoospermia after vasectomy. They scored the efficiency of spermatogenesis in these tissues by the percent of seminiferous tubules containing elongated spermatids. They found a positive correlation between the efficiency score and percent of protamine positive round spermatids in both groups. The NOA group had significantly lower levels of protamine positive cells. Additionally successful fertilization was correlated with the P1:P2 ratio. This work provides a prognostic marker for successful ICSI fertilization.

Isolation of Germ Cells from Leukemia and Lymphoma Cells in a Human In Vitro Model: Potential Clinical Application For Restoring Human Fertility after AntiCancer Therapy
By Kazutoshi Fujita*, Akira Tsujimura, Yasushi Miyagawa, Hiroshi Kiuchi, Yasuhiro Matsuoka, Tetsuya Takao, Shingo Takada, Norio Nonomura, Akihiko Okuyama. Suita, Osaka, Japan.

The authors described a technique for isolating human germ cells from malignant cells in five leukemia cell lines and three lymphoma cell lines. They used fluorescence-activated cell-sorting (FACS) based on antibodies against major histocompatibility complex (MHC) class I and CD45. This technique successfully separated human germ cells from malignant cells in 7 out of the 8 cell lines. In the remaining cell line, treatment with interferon gamma induced MHC class I expression in the malignant cells, enabling isolation with this technique. The need for immunophenotyping each patient and the possible further requirement of surface marker induction limit the clinical applicability of this technique.

DNA Fragmentation Rates in Ejaculate and Testicular Sperm
By Rohan Shahani*, Sergey I Moskovtsev, Brendan Mullen, Bryce Weber, Kenneth Cadesky, Thomas Hannam, Keith Jarvi, Kirk C Lo. Toronto, ON, Canada.

The authors examined sperm DNA damage in testicular and ejaculated sperm collected on the same day from ten patients. These men had persistently elevated (>30%) sperm DNA fragmentation on TUNEL assay after 3 months of therapy with multi-vitamins and anti-oxidants. They found that TUNEL positivity was significantly lower in the testicular sperm (21.4%) compared to ejaculated sperm (37.5%). The study supports the idea that sperm DNA damage is progressive through the reproductive tract. However, the small sample size limits the ability to make decisions about the use of testicular versus ejaculated sperm for ICSI in men with elevated sperm DNA damage.

Nuclear Magnetic Resonance Based Metabonomic Investigation of Seman, Urine and Plasma Metabolite Profiles in Healthy Volunteers and Men with Spinal Cord Injury
By Prasad Patki*, Michael Craggs, Julian Shah, Anthony Maher, John Lindon, Elaine Holmes, Olivier Cloarec, Jeremy Nicholson. Stanmore, United Kingdom and London, United Kingdom.

The authors used nuclear magnetic resonance (NMR) spectroscopy to compare metabolite profiles of semen, urine, and plasma between 11 men with spinal cord injury and 9 healthy, fertile controls. The technology found differences in all biofluids, with semen samples showing decreased uridine, altered amino acid distribution, and increased signals from acetyl groups of glycoproteins. This study illustrates a non-destructive manner to evaluate seminal fluid, however further works needs to be done to elucidate the significance of the differences described here.

Success of Repeated Testicular Sperm Aspiration in Azoospermic Patients
By Edson Borges, Jr, Daniela P A F Braga, Tatiana C S Bonetti, Assumpto Iaconelli, Jr, Fabio F Pasqualotto*. Sao Paulo, Brazil and Caxias do Sul, Brazil.

The authors described their outcomes with testicular sperm aspiration (TESA) using a buttery needle under local anesthesia instead of testicular sperm extraction (TESE). Out of 189 men with obstructive azoospermia (OA) or non-obstructive azoospermia (NOA), 143 had sperm found during the first attempt. 50% of patients who failed their first attempt had sperm on the 2nd attempt, and 40% of those who failed their 2nd attempt had sperm found on the 3rd. These authors have described impressive success rates with a minimally invasive technique.

Ghrelin Expression in Human Testis and Serum Testosterone Level
By Tomomoto Ishikawa*, Hitoshi Fujioka, Takeshi Ishimura, Atsushi Takenaka, Masato Fujisawa. Kobe, Japan.

The authors characterized the expression of ghrelin in the testis and its relationship to testosterone. They collected tissue samples from 5 fertile patients, 8 patients with obstructive azoospermia, and 36 oligospermic patients with varicocele. They used immunohistochemistry to characterize the location of ghrelin expression and used beta-hydroxysteroid dehydrogenase to label Leydig cells. Ghrelin was expressed in the interstitium, the Leydig cells, in the seminiferous tubules, and in Sertoli cells. The ratio of Leydig cells expressing ghrelin to total Leydig cells was negatively correlated with serum testosterone. This work, along with the work on the hormone leptin by this group, helps establish that these hormones are involved in steroid production in the testis.

Screening for Y Chromosome Microdeletions in Idiopathic and Nonidiopathic Infertile Men with Varicocele and Cryptor Chidism
By Song Ninghong*. Nanjing,,jiangsu province, China.

Poster not presented.

"Infertility: Evaluation and Therapy" Moderated Poster Session
By Tullika Garg, MD, Harris M. Nagler, MD

The final moderated poster session of the meeting consisted of twenty papers pertaining to evaluation and treatment of male infertility. The prize winning paper was abstract number 1929, "Pre-Chemotherapy Sperm Procurement in Teenagers: Analysis of Outcomes and Predictors of Sperm Retrieval." Below is a series of brief take-home points from each paper in the session.

Abstract 1926: Males with hypogonadism can develop osteopenia and osteoporosis. Bone mineral density monitoring with DEXA scans is recommended regardless of age.

Abstract 1927: Positive serum antisperm antibodies are highly predictive of obstructive azoospermia and may obviate the need for testis biopsy prior to reconstruction or sperm retrieval.

Abstract 1928: One-third of vasectomy patients never return for follow-up. Providing the patient with a follow-up appointment at the time of vasectomy improves patient compliance with post-vasectomy semen analysis.

Abstract 1929: Procuring sperm in teenage boys prior to chemotherapy is successful with TESE. Positive predictors of success include prior history of ejaculation. Negative predictors include low FSH levels, low Tanner stage and castrate testosterone levels.

Abstract 1930: Two-thirds of childhood cancer survivors have low inhibin B levels. ow inhibin B levels have a strong correlation with decreased spermatogenesis and may be a marker for post-chemotherapy gonadal function.

Abstract 1931: Older males have increased low-level mosaicism. This may be associated with increased infertility with increasing age.

Abstract 1932: The age of a patient with varicocele has no impact on semen parameters before and after ligation.

Abstract 1933: Routine semen parameters do not predict the quality of chromatin in sperm.

Abstract 1934: Exposure to petrochemicals decreases acrosome and cytoplasmic residues, therefore, decreasing overall sperm motility.

Abstract 1935: Post-vasectomy patients may be cleared with one azoospermic semen analysis at sixteen weeks.

Abstract 1936: Comparison of automated sperm FISH versus reading by certified personnel showed increased aneuploidy detection and accuracy with the automated system.

Abstract 1937: A case report showed that recurrently pregnancy loss can result from paternal gonadal mosaicism.

Abstract 1938: A comparison of two groups of testicular torsion patients showed that patients who underwent orchidopexy had poor semen quality than patients who underwent orchiectomy.

Abstract 1939: Patients with maturation arrest on testis biopsy, normal FSH levels have increased chromosomal abnormalities and Y chromosome microdeletions and therefore, lower ICSI pregnancy rates and successful TESE.

Abstract 1940: Serum inhibin B levels decrease after varicocelectomy.

Abstract 1941: Patients who undergo varicocelectomy prior to ICSI have higher pregnancy rates than patients who undergo ICSI without varicocelectomy.

Abstract 1942: A learning curve exists for microdissection TESE. This may impact sperm retrieval rates.

Abstract 1943: Low FSH levels are predictive of successful sperm recovery with TESE in patients with nonobstructive azoospermia.

Abstract 1944: The sperm of spinal cord injured patients has a high DNA fragmentation index and processing the semen for dead sperm does not affect the index. Therefore, both motile and nonmotile sperm have high DFI.

Abstract 1945: Paternal age has a negative effect on ICSI pregnancy outcomes using epididymal sperm. ⌘

Mark Your Calendars!

ASRM Annual Meeting
October 13 – 17, 2007
Washington, DC

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

ASA Andrology Lab Workshop
April 12, 2008

ASA Special Symposium
April 12, 2008

AUA 2008 Annual Meeting
May 17 – 22, 2008
Orlando, FL

NEW DAY!
SSMR Annual Meeting
at the AUA Annual Meeting
Tuesday, May 20, 2008
Orlando, FL

7th Annual SSMR/SMSNA Traveling Fellowship Program

The 7th annual traveling fellowship program took place in conjunction with the AUA in Anaheim, California and was a great success. This year was the third combined fellowship with the Sexual Medicine Society of North America (SMSNA).

The SSMR would like to express our gratitude to the SMSNA for their academic and financial support of the fellowship. These awards are designed to expose young urology residents to the field of sexual medicine, including male infertility and erectile dysfunction, and allow them to participate in many of the events at the AUA.

Men's Health Fellowship Winners

John Adams	University of Mississippi
Joseph Feliciano	SUNY Downstate
Tullika Garg	Medical College of Wisconsin
Richard Lee	Cornell University
Bobby Najari	Baylor College of Medicine
Josiah Nelson	University of Wisconsin
Kashif Siddiqi	Medical College of Georgia
Bryce Weber	University of Toronto
Benjamin Yang	Duke University

Allied Health Fellowship Winners

Yolanda Cockerham	Tulane Department of Urology
Paula Laureanno	Brown University
Teresa Rodriguez	University of Miami
Leia Spencer	Mount Sanai, Ontario ⌘

2008 SSMR Program

"Vasectomy – What is All the Fuss About"
Ajay K. Nangia, MD

Vasectomy is one of the "bread and butter" minor surgeries for most urologists, with over 520,000 being performed each year in the U.S. The National Survey for Family Growth reported that vasectomy accounted for 6% of the contraceptive methods used in 2002. Recently a connection between a form of Alzheimer's and vasectomy was published and resulted in a statement being made to address this by the AUA. The AUA is also looking at creating guidelines on vasectomy at the moment. So how is it that such a "minor" operation can cause so much fuss? Why do so many of us get compulsive about the vasectomy — consult to technique to post op instructions and semen analyses? What is the evidence for what we say and do? Is there any evidence? This has led to the topic of the 2008 SSMR Subspecialty Society meeting held at the AUA annual meeting in Orlando. Program Chair, Ajay K. Nangia MD has gathered an enthusiastic and broad faculty, eager to discuss this relevant and common topic. They will cover a myriad of issues including vasectomy technique — evidence for one over another; post op complications and associations, or lack of — to legal ramifications and whether this is what all the fuss is about. The final panel will be a group of leaders from our field that will review the future direction by the AUA to develop guidelines. We hope that the information the faculty provides will help the audience have more evidence to support their current practices or provide new evidence that can help them adapt.

Surely, everyone will have their own opinions and hopefully, will encourage fruitful and lively debate during the question and answer sessions. We invite all members of the Society as well as all attending the 2008 AUA annual meeting to attend this topical presentation, which has wide appeal, as well as significant coverage in the lay media. ⌘

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

SSMR Board of Directors

Men's Health Traveling Fellowship Program 2008

Dear Urology Residency Directors, SSMR and SMSNA Members:

The Society for the Study of Male Reproduction (SSMR) and the Society for Sexual Medicine of North America (SMSNA) are proud to announce the Seventh Annual Traveling Fellowship Program with the SSMR and the third combined award for the two societies. This will take place in conjunction with the 2008 AUA meeting in Orlando, Florida.

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

Our goal is to present residents in training with the opportunity, while attending the AUA meeting, to have a more intensive exposure to male infertility and sexual medicine issues. The Fellowship Program will include mandatory attendance at the SSMR and SMSNA educational programs and complimentary SSMR banquet participation and SMSNA lunch. Fellows will also attend AUA post-graduate courses in male infertility, erectile dysfunction and the infertility podium and poster sessions, as well as a symposium with fellowship directors and faculty members on how to prepare for a future successful career as an andrology 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 Sunday through Tuesday will be required.

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

An application is 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, 2008.** The awards will be announced by February 15, 2008.

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

Sincerely,

Raymond A. Costabile, MD
Jay Y. Gillenwater Professor of Urology and Vice Chairman
Urology Department
University of Virginia School of Medicine
Charlottesville, VA, 22908 ⌘

Application for the Men's Health Traveling Fellowship Program 2008

Sunday, May 18 – Tuesday, May 20, 2008
Orlando, Florida

Please print or type.

Name:_____Degree(s):_____

Work Address:_____

City:_____State:_____Zip:_____

Home Address:_____

City:_____State:_____Zip:_____

Work Phone:_____Home Phone:_____Fax:_____

E-mail:_____

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

Institution/Department:_____

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

Signature of applicant: _____

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

Signature of department chairman:_____

Send completed applications to:
Raymond A. Costabile, MD
Jay Y. Gillenwater Professor of Urology and Vice Chairman
Urology Department
University of Virginia School of Medicine
Charlottesville, VA, 22908

Deadline: January 15, 2008

Mark Your Calendars!

From February 15 – April 15, 2008, you will be able to vote for the 2008 – 2009 open SSMR leadership positions on line at www.ssmr.org.

Exercise your RIGHT TO VOTE!

Thank you once again to our to our 2007 educational grant providers

Coast Reproductive
Gyrus/ACMI
GSK/Schering Plough

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SSMR

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