

## Synopsis: 2003 Annual Meeting of the American Society of Andrology

The 28th Annual Meeting of the American Society of Andrology took place in Phoenix, Ariz, March 29–April 1, 2003. It was a great success, with over 150 abstracts submitted, although we missed many of our international colleagues who were unable to attend due to security issues associated with the war in Iraq. The meeting began with the annual Postgraduate Course, organized by Arthur Burnett, MD (Johns Hopkins University), featuring 8 talks on “Erectile Dysfunction and Androgens.” The course proceedings will be published in the *Journal of Andrology*.

**Victor D. Vacquier**, PhD (Scripps Institute of Oceanography, University of California), opened the ASA meeting with the Sero Lecture on “The Evolution of Gamete Recognition Proteins.” Sperm chemoattractants have arisen independently many times in evolution, and evidence for their existence in mammals has recently come to light. Dr Vacquier explained how gamete recognition proteins evolve very fast by a process called “positive selection” and gave examples of proteins that show a high level of interspecies differences due to this rapid evolution, including TP2, ZP2, P15, acrosin, P2, and ZP3. Furthermore, the genes for these proteins typically vary at the site that is critical for their biological activity while the rest of the gene is conserved. Examples for this feature include the well-studied sperm genes for zona adhesion, fertilin alpha and beta, PH20, acrosin, SAM 1, and SP17. Rapid evolution is thought to be important to create barriers for cross-species fertilization; this would be particularly important for marine species such as sea urchins and abalones, which shed their gametes into the ocean in close proximity to those of other species.

The 2003 AUA speaker was **George J. Bosl**, MD, from Memorial Sloan-Kettering Cancer Center in New York, who spoke about “Germ Cell Cancer: Etiology, Detection, and Cure: 2003.” About 90% of germ cell tumors originate in the testis and 5% in the mediastinum. These tumors are 30–50 times more common in Caucasians than in African Americans and are curable in over 90% of patients. About 7500 new patients with germ cell tumors will be seen in this country during 2003, an incidence of 9.9 per 100 000 men in the 15- to 34-year-old age group. Germ cell tumors generally are categorized as either seminoma or nonseminomatous. Patients with seminoma are grouped into either “good” or “intermediate” risk cate-

gories because there is no “poor” risk category for this group. In contrast, non-germ-cell-tumor patients may have “good,” “intermediate,” or “poor” risk potential. Serum markers of germ cell tumors are alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG), and lactic dehydrogenase (LDH). Current chemotherapy that includes Bleomycin, Etoposide, and cis-platin achieves a 94% cure rate in good-risk patients. Unresponsive or relapsed germ cell tumors still are curable in up to 70% of patients with new chemotherapeutic regimens, and lack of relapse within 2 years is considered a cure. A promising cytogenetic marker of germ cell tumors is i(12p), and such markers may play a significant role in the diagnosis and perhaps treatment of germ cell tumors in the future.

In a lecture entitled “Regulation of Segmented Function in the Epididymis,” **Terry Turner**, PhD (University of Virginia), showed us the latest evidence that specific genes, particularly those involved in segmentation of embryos, such as Hox and Sonic Hedgehog genes, are differentially expressed in the discrete segments of the epididymis where they may help account for segment-specific organ function. The use of gene expression arrays is helping his lab and others to better characterize patterns of gene expression in the epididymis and reveal embryonic genes that continue to play roles in adult function.

**Barry Zirkin**, PhD (Johns Hopkins University in Maryland), and **Bernard Robaire**, PhD (McGill University in Montreal, Canada), teamed up to provide insights on “Male Reproductive Aging: Mechanisms and Consequences.” They study Brown Norway rats, a strain that ages gracefully without getting fat or developing tumors. Barry showed that Leydig cells (LC) from old rats produce less testosterone than those from young rats. Through a clever series of experiments in which LCs were reversibly suppressing for extended periods of time, he could keep LCs young in old testes! He concludes that LC age is due to intrinsic factors likely related to damage from reactive oxygen species. Bernard then showed novel evidence that sperm from old rats are also less healthy as evidenced by altered motion characteristics, increased susceptibility to oxidative stress, increased incidence of sperm aneuploidy and chromatin instability, and other markers of genomic integrity such as DNA methylation. Such changes have implications for reproductive success in older men.

A Memorial Symposium honored the late Lonnie Russell for his major contributions to the study of spermatogenesis. **Rex Hess**, PhD (University of Illinois), spoke on "Complexity of the Testis Made Simple and Fun," a theme based on Lonnie's unique talent for tackling complex subjects and simplifying them for the rest of us, as exemplified by his book, *Molecular Biology Made Simple and Fun*. Speaking in a joyful and free-spirited manner to remind us of Lonnie's fun-loving and insightful personality, Rex reviewed a method for evaluating spermatogenesis that uses a decision tree to simplify the identification of stages in the cycle of the seminiferous epithelium. The highlight was a Quick-time movie entitled *Symphony of Stages* and dedicated to Lonnie. This movie shows the stages in time-lapse, with cells dividing and germ cells moving into and out of the epithelium in sequence, all to the tune of a Russian dance in the classical music of *The Nutcracker*. **Wayne Vogl**, PhD (University of British Columbia), focused his talk on the role of ectoplasmic specializations and tubulobulbar complexes in sperm release and junction turnover. Ectoplasmic specializations, named by Dr Russell, are unique actin-containing adhesion junctions found in Sertoli cells at sites of intercellular contact. Recent studies indicate that the gelsolin-phosphoinositide pathway may be involved with actin filament disassembly in these structures during junction turnover. Preliminary immunolocalization results are consistent with the idea that tubulobulbar complexes may be involved with the internalization and degradation of adhesion components from sites previously occupied by ectoplasmic specializations. Tubulobulbar complexes were discovered by Dr Russell, who also suggested that they may play a role in junction turnover. Finally, **Kim Boekelheide**, MD, PhD (Brown University), discussed "Sertoli Cell Microtubules: From Morphology to Function." On the basis of the thesis of his student Shawna Fleming, Kim described a novel molecular tool, adenoviral coexpression of gamma-tubulin and green fluorescent protein, which they used to specifically disrupt Sertoli cell microtubules in vivo. The resulting Sertoli cell dysfunction markedly altered the seminiferous epithelium, causing inhibition of spermatid translocation, spermatid release, and residual body phagocytosis, while increasing germ cell apoptosis. The presentation illustrated the power of combining morphological assessment and molecular tools with the in vivo dissection of complex cellular processes such as Sertoli cell microtubule-dependent functions.

**Luiz Renata de Franca**, PhD, from the Federal University of Minas Gerais in Brazil, was the ASA International Lecturer. His talk, "New Insights on Sertoli Cell Proliferation and Efficiency," nicely complemented the Spermatogenesis Symposium. Using pigs and fish as diverse animal models, Luiz showed that the regulation of

Sertoli cell proliferation and hence testis size by thyroid hormone (T3) is more complex than predicted based on evidence in the rat model. Bridging nutrition and male reproductive function, he also explained how leptin plays important roles in testis development. For example, leptin knockout mice are infertile (with decreased testis and epididymal weight and decreased gonadotropins), but the condition can be reversed by giving back leptin.

Symposium II brought us up to date on prostate cancer. **Nancy Weigel**, PhD (Baylor College of Medicine), discussed her research on "Vitamin D and Prostate Cancer Growth," providing evidence that vitamin D inhibits the growth of prostate cancer cells in vitro. Interestingly, the extent of inhibition and recovery varies by cell line and is related to the presence of functional p53. Thus, vitamin D or an analog may have potential as a future chemotherapeutic or chemopreventive agent. **Ronald K. Ross**, MD (University of Southern California's Norris Comprehensive Cancer Center), discussed the "Epidemiology of Hormonal Effects on Prostate Cancer," starting with the 3 major risk factors: age, family history, and race. Prostate cancer is an androgen-dependent disease, and increased risks by race are associated with higher average serum testosterone levels that are also race-dependent. Genetic predisposition for prostate cancer is associated with polymorphisms in BRC 1 and 2, androgen receptor, and 5 alpha-reductase among others. Future genetic tests should allow high throughput screening for susceptible genotypes. Finally, **Colleen C. Nelson**, PhD (University of British Columbia), explained how gene arrays are being used to characterize "Aberrant Gene Expression in Prostate Cancer Progression." Her central hypothesis is that drift in gene expression occurs in tumors because it is adaptive in allowing tumors to survive. Initially, androgen-dependent tumors are treatable by androgen ablation, but they become resistant to this approach when they become androgen-independent with time. Her work shows that genotoxic stress leads to changes in gene expression such as YB-1 transcription factor entering the nucleus and turning on a gene cascade related to repair of damaged DNA. She is tracking changes in gene expression by tumors over time to determine specific genes and expression patterns associated with the transition to androgen-independence.

Symposium III centered on "Androgen Action in Human Health and Disease." **Christina Wang**, MD (Harbor-UCLA Medical Center in Torrance), provided an "Update on Androgen Replacement Therapy," summarizing the advantages and disadvantages of currently available therapies: injectable esters, transdermal patches, transdermal gels, and implantable pellets. New testosterone delivery modalities on the commercial horizon include buccal (through adhesion to the gum), sublingual, long acting injectable esters (months duration per injection).

tion), and 7 $\alpha$ -methyl-19-nortestosterone (MENT). MENT is somewhat more selective than testosterone in that it can be aromatized but is not available for 5 $\alpha$ -reduction; this potentially would result in the compound being less active in the prostate. At the current time, MENT is delivered as a subcutaneous implant, but in the future it is hoped that a transdermal method may be developed for its delivery. Other selective androgen receptor modulators (SARMs) are also under active development. **Randall Urban**, MD (University of Texas Medical Branch), spoke about the clinical problems of sarcopenia or loss of muscle, which can occur with HIV wasting, severe burns or trauma, during space travel, with prolonged bed rest, or with normal aging. Anabolic androgens can help prevent muscle loss in many of these conditions, apparently by promoting synthesis of new muscle and increasing intramuscular IGF-1 levels. His recent studies in older men and women suggest that androgen action in muscle may be less effective with prolonged use. Therefore, his group is beginning to explore the potential benefits of cyclic androgen therapy. **Monique Cherrier**, PhD (University of Washington in Seattle), conducts research on "Androgen Effects on Cognitive Function in Humans." She reviewed animal studies on effects of gonadectomy on axon density, synapse number, neurotransmitters, and metabolic activity in specific areas of the brain. Male rats made hypogonadal show increased dopamine in the prefrontal cortex, decreased synapses in the hippocampus, decreased ability to learn appropriate avoidance in a T-maze learning task, and increased anxiety. With testosterone replacement, these changes normalized, even in older animals. Her studies in older men show that compared to placebo treatment, testosterone can improve spatial memory and verbal memory (story recall).

Symposium IV, on "Environmental Influences on Human Semen Quality," began with a talk on "Pesticides and Semen Quality: Evidence of a Link From the Study for Future Families," by **Shanna H. Swan**, PhD (University of Missouri). Since 1998, Shanna has led a multicenter team of scientists examining semen quality from 4 areas of the United States. On the basis of the observation that sperm counts and total motile sperm counts were lower in men from Missouri (rural) compared with men from Minneapolis (urban), she hypothesized that pesticide exposure might account for this difference. After obtaining internal measures of exposure to a number of pesticides, she was able to show an association between exposure to certain pesticides and increased risk of having poor semen quality. Such data provide fertile ground for future studies linking exposure to effect. **Steve Schrader**, PhD (National Institute of Occupational Safety and Health), discussed "Occupational Exposures and Altered Semen Quality: What Are the Risk Factors?" Using examples from human studies at NIOSH and elsewhere, he

provided useful insights on how governmental agencies estimate risk and regulate chemicals and allowable exposures accordingly. Resources on this topic are available at <http://www.cdc.gov/niosh/homepage.htm>, and a pocket guide to hazardous chemicals is available in CD format from NIOSH upon request (Publication No. 2002-140, June 2002). Finally, **Gary Klinefelter**, PhD (US Environmental Protection Agency) relayed the "Saga of a Novel Sperm Biomarker: Discovery to Proof of Concept." The sperm protein SP-22, which Gary found to be diminished in sperm from rats treated with a variety of epididymal and testicular toxicants, localizes to the sperm head. Antibodies to SP-22 and recombinant SP-22 inhibit fertilization in vitro and in vivo and cross-react with sperm of many species. Efforts are under way to explore the association between SP-22 in human sperm and infertility, which could lead to improved fertility assays applicable to the diagnosis of infertility, and to toxicology testing.

**Mary M. Lee**, MD (Duke University), gave the ASA Women in Andrology Lecture on "Mullerian Inhibiting Substance: Role in Sexual Differentiation and Gonadal Development." One of the first proteins expressed in testis development, Mullerian Inhibiting Substance (MIS) is necessary for normal development of the male but not the female tract (knockout mice have retained Mullerian ducts, foci of Leydig cell hyperplasia, focal tubule atrophy, and infertility) whereas overexpression in adults is detrimental in both sexes. Using EDS to kill Leydig cells, she then showed that MIS can inhibit Leydig cell regeneration and down-regulate steroidogenesis. Using microarray analysis, she is studying MIS-regulated genes in Leydig cells and other reproductive cell types. Clinically, she is using MIS to help diagnose gonadal disorders, especially in cryptorchid newborns and virilized girls, and as a tumor marker.

**Laura Schieve**, PhD (Centers for Disease Control and Prevention), updated us on "Risks for Adverse Birth Outcomes After Assisted Reproductive Technologies." On the basis of data for 2001, births from assisted reproductive technologies (ART) are expected to exceed 1% of live births in the United States, so there are sufficient data to begin to explore risk factors. Her analyses of data from 383 clinics reporting in 2000 provide demographics of women using all types of ART procedures and respective success rates. Risks for multiple births (about 35% of ART pregnancies) include the type of ART, patient's age, number of embryos transferred, and number of embryos available for transfer. ART also poses risks for low birth weight and preterm infants even after controlling for other factors thought to predispose for low birth weight or prematurity. Risks for chromosome aberrations are increased for ICSI cases, as is risk for hypospadias, although in

these cases it is not clear whether the risk stems from the ART treatments or is related to the underlying infertility. On the other hand, the good news is that risks for childhood cancer and other developmental problems do not appear to be associated with ART.

The Andrology Laboratory Workshop was held after the meeting. Organized by Greg Kopf, PhD, Pasquale Pa-

trizio, MD, and Charles Muller, PhD, the workshop expanded on the theme “Partnerships in the Andrology Laboratory: Integration of Clinical Andrology, Basic Science, and the Pharmaceutical Industry.”

**Sally Perreault (Program Chair), Arnold Belker, Rex Hess, and Lisa Tenover**