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COMMENTARY

On chilling oocytes and secrets in sperm

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Those of us in the northern climes are anxiously awaiting the first signs of spring after another protracted winter. Imagine, if you will, what it feels like to be a vitrified human oocyte suspended in the hypercooled space of cryoprotectants going though the rude awakening we call "thawing"! Our opening article in this issue revisits the ongoing debate over the reliability and safety of human oocyte cryopreservation as we know it today, and where this field may find itself several years from now. How much longer will we have to wait for the arrival of spring or a consensus on the clinical utility of oocyte cryopreservation? Or, in the parlance of JARG, what new horizons have yet to dawn that will put this debate safely and soundly into the menu of ARTs that our patients will be offered?

The paper by Noyes and colleagues chronicles the field of human oocyte cryopreservation in a scholarly way. It takes us through the days of slow freeze technology and deep into the wonderful world of vitrification, the reigning paradigm that frequents the pages of *JARG* and sister journals, keeping pace with the advances and applications of cryobiology related to human ARTs. Embedded in their treatment of this topic is the question of survivability of gametes and embryos, in addition to the inferences of functionality that are best envisioned as a result of a successful gestation.

I recall being struck by a paper published in *JARG* recently reporting the birth of a boy whose gametes and embryos went through not one, not two, not three, but four "successful" rounds of cryopreservation before a solitary blastocyst was obtained! My interests in this area were also piqued by the realization, as repeatedly indicated from a survey of the literature, that survival rates of 50% are shared not only by oocytes, sperm, and embryos but also by the likes of many commonly used established cell lines—including those that are accessed for the study of human embryonic stem cells. In fact, the wide range of plating and growth efficiencies for human embryonic stem cells indicates that methods currently in use for their long-term or short-term storage have not been optimized and represent an important focus for research in this field. So where does this leave us with regard to the viability and functionality of thawed gametes or embryos? The inescapable conclusion is that new approaches are desperately needed, a conclusion that was reached at the January 2007 NIH advisory meeting convened to set benchmarks for the emerging field of fertility preservation.

Even among the experts in cryobiology, the call for innovative technologies in the area of cell preservation using cooling or desiccating strategies remains high on the priority list for many areas of biomedical research. Thus, as we set the stage for continuing use and application of deep freeze technology for the storage of germ or embryonic "plasms", we should remain mindful that our current approaches will most likely shape a variety of approaches that are now in their infancy. With our readership in mind, in future months we plan to grace the pages of *JARG* with a glimpse of these technologies as they apply to fields of somatic cell preservation, hoping that this will lead to their translation to the wonderful world of gametes and embryos. How this research will proceed within an experimental framework that supersedes the current status of oocyte cryopreservation remains a difficult and somewhat intractable question. Surviving the long and sometimes arduous chronology of the deep freeze of winter may indeed find parallels as we await the dawning of spring, albeit in the

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guise of the biology of thawing and the restoration of metabolism. Human ARTs stand to gain from advances in the field of cryobiology.

A second notable paper in this issue leads the efforts in the field of andrology one step closer to understanding the extragenomic contribution of sperm. While often thought of as merely a device for delivering a male genome to all of the wonders of the oocytes' cytoplasm, sperm have assumed an identity crisis of their own, as the debate has grown over what else they may deposit in the ooplasm.. ICSI success has drawn us to the conclusion that while the acrosome serves an important role in egg investment invasion during natural forms of fertilization, this need not be true for embryos generated by ICSI. Even those remarkable vestiges that power sperm motility through the land mines and physical obstacles that adorn the landscape of the female reproductive tract seem to be vanquished by the oocytes' driving need to eliminate both the axoneme and mitochondria. So the question has often been raised: Exactly what remnants of spermatogenesis and sperm maturation are contributed to the zygote at fertilization? The centriole in humans continues to be well-recognized in this light, and evidence of defects in this structure are being linked to the causes of male infertility in various disease states. And now, the paper in this issue by Garcia-Herrero and colleagues draws attention to another remarkable and likely contributor to the health and well-being of sperm and their donations to the cause of embryogenesis.

Using a gene ontology strategy to characterize the identity and putative properties of sperm-borne RNAs of both the messenger and micro varieties, significant differences are described for human sperm from clinically documented fertile and infertile males. While these studies await further characterization of the RNAs using PCR, the impact of this work will raise eyebrows among andrologists, who have long thought that spermatogenesis was the closing chapter in the transcriptional profiling of the male gamete. This will also be of interest to embryologists who are invested in teasing apart the intricacies of genome remodeling that take place in the newly formed zygote. For example, will these species of RNAs contribute to differential genome remodeling within the fertilized ovum that results in gender-specific markings on mom and dad's chromatin? And could these findings explain the developmental deficits exhibited by digynic pathenogenetic embryos desperately seeking that something else that dad contributed for the ride through and beyond the perils of preimplantation development? Answers to these and other questions will await the material extension of the findings reported here and may create inroads in our understanding of male infertility from a spermocentric perspective. These results also reinforce the role of microRNAs originating not only from the transcriptional repertoire of the oocyte and early embryo but also from the RNA endowment that may have been hidden in the depths of the mature sperm used in natural and artificial conceptions.

What lies within this and upcoming issues of *JARG* is a glimpse of the future of genetics and epigenetics in the field of human ARTs. Perhaps we should be bracing ourselves for departure from the winter doldrums into the changes accompanying the onset of a new season that will be rich in technological advances and insights into the fundamental processes by which we generate offspring. We will continue to highlight the breakthrough work that graces the pages of *JARG* in hopes of stimulating further discussion and discovery in reproductive medicine.