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EDITOR'S COMMENTARY

Telegraphing your telomere length to the next generation

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"Whatever the truth may turn out to be, it is now certain that senescence is part of the natural order of things. It is not one that should be interfered with without the utmost of care and circumspection."

P.B. Medawar and J.S. Medawar, 1977, The Life Science: Current Ideas of Biology. Wildwood House Ltd., London (ISBN 0-7045-0243-7)

Even 40 years ago, the problem of aging was capturing the attention of many in recognizing that as long as medicine could extend our health far beyond the limits of our reproductive lifespans, the caretakers of quality lifestyles would continue to foot the bill during our gradual somatic demise. At least that is what the Medawars imagined in concluding that "Ageing as it occurs in an individual is accompanied by slow, orderly deterioration of all the faculties." But that was well before telomeres and their length came to be known as central players in the senescence landscape, and something worthy of exploitation if it could prevent or reverse the certainty that it will happen, like it or not!

Our preoccupation with aging today exceeds the boundaries scientific curiosity back when the "natural order of things" was viewed as a means for population control in societies facing food shortages, disease, and lifespans inconsistent with prospects for controlling the inevitable. Rather, the telomere stands firm as a sentinel of longevity capping the ends of our chromosomes, as failure to do so sets into action many of those diseases that compromise both the quality and quantity of life that can be expected [1]. And to no surprise, telomere lengthening or shortening has figured prominently in the fields of reproductive biology and medicine in an atmosphere of flexible life cycles oscillating between, and in sequence from generation to generation with, the nascent interchangeability of gametes and stem cells and the hopes for immortalization resulting from somatic cell nuclear transfer technology [2].

If we dissect the telomere issue along gender lines, then it is worth noting that the tale of aging in males has taken on an interesting twist of late regarding current laboratory practices in human ARTs. Specifically, the *longer-is-better* notion was tested in a study by Yang and colleagues in which a positive association was reported between sperm telomere length (STL) and age, sperm count/ejaculate, and embryo quality in IVF cycles, despite the fact that clinical pregnancy rates were not significantly correlated with longer telomeres [3]. While this study is provocative in its clinical implications and sets the stage for more extensive studies, how much TL is determined by factors intrinsic to germ cells as they differentiate or in response to the microenvironment established by Sertoli cells of the seminiferous epithelium remains to be established. More recently, Ioannou and collaborators explored the three-dimensional architecture of telomeres and centromeres in sperm from 10 normospermic individuals ranging in age from 29 to 48 [4]. Their findings illustrate a remarkable degree of segmental ordering of telomeres and centromeres that was postulated to represent a novel property of male genome organization of potential clinical importance in chromatin remodeling following fertilization. Stay tuned as the telomere saga unfolds with respect to the impact of aging on male reproductive health.

But matters of telomere length and reproductive aging have also attracted attention in female reproductive physiology, with the historical focus being aimed at oocytes and preimplantation embryos [5]. As noted above for male gametes, the somatic cells surrounding the oocytes have long been

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suspected of influencing the final quality of oocytes that would contribute to the next generation some degree of genomic stability, and performance, as drawn upon following fertilization. It is in this context that we draw our readership's attention to two papers this month querying the assessment of telomere length in granulosa cells and the possible relationship between TL and PCOS.

Granulosa cells (GCs) are an interesting subject for studies of telomeres given their developmental legacy from protector of the female germ line in the primordial follicle (see cover this month), through to their final destiny as progesterone secreting cells in the *corpus luteum*. In the first of these studies, Li and colleagues focused their attention on both the levels of the telomere lengthening catalyst telomerase using an ELISA assay (TA), and the more conventional use of RT-PCR for determination of TL (*Telomere length is short in PCOS and oral contraceptive does not affect the telomerase activity in granulosa cells of patients with PCOS. 10.1007/s10815-017-0929)*. Surveying these parameters in GCs collected from 163 infertile women, they compared patients grouped according to whether or not they had PCOS and whether or not they had been taking oral contraceptives for treatment of PCOS. Their findings indicate that (a) TL was shorter in PCOS patients, (b) TA levels showed little variation between all groups examined, and (c) although a tendency towards TL shortening was observed in patients exhibiting early onset infertility, there was no prognostic value identified with respect to embryo quality assessment on day 3, nor was there a correlation between TL and clinical pregnancy rates.

Quite the opposite finding is reported by the group of Cuilan Zhang *(Significantly lengthened telomere in granulosa cells from women with polycystic ovarian syndrome (PCOS) 10.1007/s10815-017-0945)*. In this study, TL evaluation was made in both the patients' peripheral blood leukocytes (WBCs) and GCs from 75 PCOS patients and 81 patients undergoing ART treatment for obstructed fallopian tubes. The conventional qPCR assay was used for both cell types that clearly indicated no difference in TL for WBCs in either of the groups. However, an increase in TL was evident in GCs from the PCOS group relative to the controls, which in this study was comprised of a more homogeneous group for which the cause of infertility was well characterized. Among the many plausible explanations for the discrepancy in findings are inconsistencies in study design, patient populations, and how DNA samples were prepared for the seemingly identical methods for TL assessment. While the jury remains out as to the role of TL measurements in evaluating the pathophysiology of ovarian function, as seen here for PCOS, should a TL increase be confirmed and extended, several interesting implications arise that may have bearing on the etiology of PCOS, and more importantly on the physiology of the ovarian follicle.

It was some years ago now that the classical studies of Hardy and Franks first hinted at the unusual behavior and organization of GCs in early antral follicles of PCOS patients, suggesting that something about this microenvironment was impacting cell cycle progression and/or apoptosis [6]. Subsequent studies from this group showed a clear relationship with the regulation of GC proliferation [7] such that local hyperandrogenic conditions may favor a tempered climate eliciting the arrested phenotype recognized clinically. As a lead to an upcoming issue of JARG, it is noteworthy to point out that recent studies have implicated the existence of dual interactions between local androgens and cell cycle modifiers from the TGF beta family of growth factors that among other things seem to regulate follicle responsiveness to FSH [8].

In closing, we would like to acknowledge the generous contributions of our editorial board members and reviewers and give special thanks to Dr. Richard Anderson of Edinburgh who has served JARG as an Associate Editor for the past 8 years. We also with this issue would like to recognize our newest board members who once again bring an ever expanding base of expertise that will enrich and extend JARG well into the future. We extend a warm welcome to Lusy Aghajanova, Jemma Evans, Emily Jungheim, Yves Menezo, Gianpiero Palermo, Nigel Perreira, Rusty Pool, and Alexander Quass.

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