On the matter of Krogh's principle

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Published online: 13 January 2011
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The New Year brings with it an opportunity for change. What may be “new” is often cast in the shadows of what came in the prior year, or even many years in the past. So upon welcoming 2011, *JARG* builds upon a proven tradition in the biomedical enterprise known as *Krogh's Principle*, with this and subsequent issues.

The Danish physiologist, August Krogh, pioneered the field of gas exchange and respiration by presciently recognizing that the data he so much desired in hand would only be accessible from certain types of organisms. For this work, he received the Nobel Prize in Physiology or Medicine, in 1920. His search and productive adoption of what might be referred today as the “experimentally tractable organism” led him to pronounce, in 1929, the following: “*For a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied.*” Some years later, Krebs accorded to this statement the status of a principle.

My first encounter with the “principle” happened to be day one of my PhD studies. My mentor, Everett Anderson, shared the 1970s version that went something like, “for every question in biology, there is an organism(s) uniquely suited to provide an answer.” It was patently obvious at that time that securing and sustaining funding from the NIH for basic research in the field of reproductive biology meant embracing the “principle,” in studying what were then the model systems for fertilization and embryogenesis. Notable among these was the sea urchin. It would be an understatement to suggest that current foundations for the physiology of fertilization—the cortical reaction; the block to poly-

spermy; egg activation—did not take their origins in this and other species of marine invertebrates. Material was plentiful, gametes were homogeneous and fully trained to produce thousands of healthy embryos in a matter of hours, and the timing of sperm entry and embryonic sequelae could be manipulated with exquisite precision! Does this not sound like the dream come true for those of us challenged to solve fundamental problems in human ARTs? Wishful thinking at best!

By the time my generation of scientists was ready to compete for NIH funding, around the late 1970s, things had drastically changed. Model organisms were no longer considered relevant to the study of human disease and development, and emphasis was rapidly redirected to the use of rodents or primates (hence the timing for establishing Primate Centers throughout the US). This trend held on until the 1980s, when the real model systems emerged: soil worms; fruit flies; yeast; African toads, and of course, *Mus musculus*, the flag bearer of mammalian physiology. Adoption of these models, and the recognition by funding agencies that herein the mysteries of human biology would be uncovered, was prompted by two advances:

First, the decade of the genome brought with it genetic tractability! Genes could be discovered, manipulated, and their products (proteins) could be made to perform feats of extraordinary proportions. To wit, the evolution of recombinant proteins, expression vectors of various kinds, and the ability to generate myriad forms of organisms whose properties ranged from the molecular to behavioral were all now well within the reach of most biomedical scientists. A powerful outcome from these years was the realization that genes from model organisms were highly conserved and thus served as templates or sentinels for unraveling the secrets of the human genome. As recent history shows, the gap between genetics and epigenetics may be wider than

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originally anticipated—especially given the genetic heterogeneity of *Homo sapiens*, as it corresponds to our model systems' relatively homogeneous and inbred genomes.

The second major advance was the realization that basic biochemical mechanisms for fundamental processes such as cell division, shared an uncanny sense of parity, whether this be in yeast or humans. Unveiling the cell cycle in all its glory was perhaps the most significant of these advances. Consider that the Nobel Prize in Physiology or Medicine in 2001 was awarded to a yeast geneticist (Leland Hartwell), a fruit fly developmental biologist (Sir Paul Nurse) and a marine invertebrate cell biologist (Tim Hunt), for demonstrating the commonality of M-phase promoting factor (MPF) in driving the cell cycle in mitotic and meiotic processes. Bear also in mind that these discoveries now form the basis for a deeper understanding of human cancer and the development of therapeutic strategies to prevent or cure this and other disease states attributable to uncontrolled cell proliferation. *JARG* has drawn attention to the importance of the cell cycle machinery in attaining genetically balanced human embryos (*Supercilious cell cycles in the human embryo*, June 2010 27:263) and such examples of the Krogh Principle in action should continue to impact the field of human ARTs; the question is “How?”

We are witnessing changes in the practice of human ARTs; changes that encourage lower dose COH, improved methods of cryopreservation for gametes and embryos, and validation of procedures such as gonadal transplantation and oocyte in vitro maturation for couples with special needs in seeking resolution of their infertility. While the Krogh Principle may imply that organisms somewhere in our biosphere are ready to lend a hand to the next decade of research in these areas, the truth of the matter is that we are, as a species, rather unique

when it comes to our reproductive strategy. For this reason, perhaps, we should finally recognize—as Krogh did 82 years ago—that we sometimes simply cannot identify organisms that reliably fulfill the criteria needed to extrapolate data from an animal model and apply them to the human (a good example is in the area of cryopreservation, where the biophysical properties of human gametes bear little resemblance to those of most all of the tractable animal models at hand); furthermore, in the end, such work will require forms of funding from private and governmental sources that, in parallel, see not only the advantages of working with “relevant” materials, but the necessity for this, if true solutions to the management of infertility are to become a reality.

All hope is not lost, however, when one considers a recent imperative issued by the NICHD over the past months. A “Dual Purpose” program will fund research on reproductive fitness by bringing together the very best of rigorous science in the agricultural area with the potential for translation to human biology. Animal science has been a robust and productive research enterprise, bearing most directly on health and fecundity in species such as the cow, pig, horse and sheep. The novel NICHD program intends to provide funding for initiatives that, in the best of worlds, will recognize the value of the Krogh Principle and foster delivery of technical advances with immediate and long-lasting influence in the field of human reproductive medicine. *JARG*, too, recognizes the importance of research on large animal models and will continue to support the publication of high-quality papers that bring insights from these organisms closer to the realities of human ARTs. In this vein, look for a new series of papers called *Krogh's Corner*, where experts in animal models will reveal the potential for human translation.

Happy New Year!