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Sydney Brenner: The birth of a model organism and the worm's connection to reproductive biology

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A giant of science, Sydney Brenner, recently died at the age of 92. He was a pioneer in molecular biology and helped decipher the fundamentals of the genetic code. In 2002 he shared in the Nobel prize for biological and medical advances gained from pioneering work to establish the nematode worm *Caenorhabditis elegans* as a model organism. There are now hundreds of worm labs around the world. Just about every *C. elegans* paper cites Brenner's 1974 introduction to the worm simply titled "The genetics of *Caenorhabditis elegans*" [1]. The classic molecular genetic tools Brenner established and that were built upon by the ever-expanding worm community of researchers are an amazing legacy. The areas of basic biological research that the worm has impacted are far too numerous to list here. However, for myself and hopefully the readers of *Molecular Reproduction and Development*, Brenner's biggest impact is the worm's emergence as an important model for understanding reproductive biology and its diverse molecular mechanisms.

Although Brenner wanted to understand the "mind of the worm", two of his postdoctoral trainees, Judith Kimble and Sam Ward, helped establish the worm to study reproductive biology. Their 1988 review on germ-line development and fertilization [2] was a key summation of the rapid growth in the understanding of worm reproductive biology. Early studies were informed by work on other nematode species and opened up many important questions. How and when is the germ-line specified? How is germ-line stem cell proliferation regulated? What pathways does the worm use to coordinate events like meiotic maturation, ovulation, sperm migratory behavior, fertilization, and egg activation?

In my opinion, Brenner's true genius was in recognizing the power of genetics foreshadowed in the title of his 1974 paper. Kimble and Ward along with coworkers isolated hundreds of mutations that impacted germ-line biology and gametogenesis. Molecular and mechanistic insights soon followed. My own lab utilizes both forward and reverse genetic approaches to identify genes required for gamete activation and fertilization. *C. elegans* (and all nematodes) have amoeboid sperm that crawl rather than swim towards oocytes and the site of fertilization in the reproductive tract [3]. These sperm do not have an acrosome but do fuse membranous organelles to the plasma membrane during sperm activation. The fusion of these vesicles is required for sperm to function properly. Despite not swimming, *C. elegans* sperm ultimately face the same universal challenges sperm from all species face during their voyage towards and interactions with the egg. In a few short decades, backed up with modern genomics, bioinformatics, transgenic technologies, and more recently, genome editing tools, we now have a growing understanding of the molecular underpinnings of

worm fertilization that rivals any of the other more traditional model systems [4]. This exhilarating and ongoing wave of gene discovery in the worm is opening up many new questions for our community to address long into the future.

I was lucky enough to see Sydney Brenner's last International *C. elegans* Meeting address to the community of his intellectual offspring. He said that he was best at getting things started early. I would argue that his legacy goes much deeper than this modest statement. I am grateful for the fertile ground (pardon the pun) from which the field of *C. elegans* reproductive biology has grown while remembering that this is just a small fraction of Brenner's overall impact on the life sciences.

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