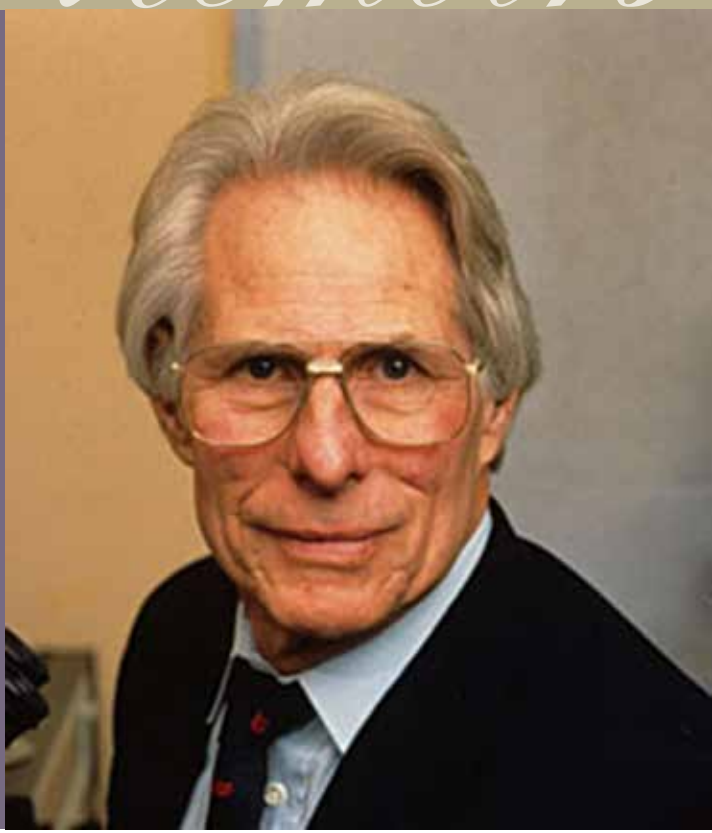
Neal L. First

1930–2014

BIOGRAPHICAL *Memoirs*



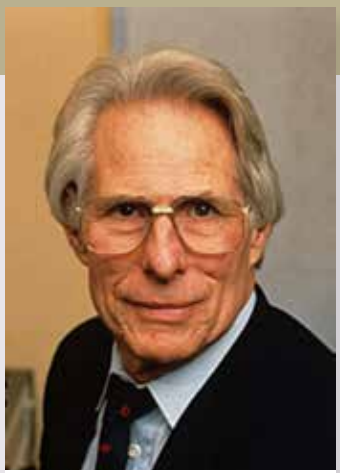
A Biographical Memoir by
R. Michael Roberts
and John J. Parrish

NATIONAL ACADEMY OF SCIENCES

NEAL LLOYD **FIRST**

October 8, 1930–November 20, 2014

Elected to the NAS, 1989



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By R. Michael Roberts and John J. Parrish

Neal Lloyd First was a charismatic and influential leader as a researcher and policymaker in the fields of agriculture and genetics. He made major contributions to advances in mammalian *in vitro* fertilization, embryo development, embryo cloning of cattle, and nuclear transplantation in embryos. He received numerous awards for his research, including the Morrison Award for animal science, the Von Humboldt award, the Upjohn research award, and the Wolf Prize, which is often called the Nobel Prize for agriculture. In 1989, he was inducted as a member of the National Academy of Sciences.

First received his bachelor's, master's, and Ph.D. degrees from Michigan State University and spent almost his entire career as a faculty member at the University of Wisconsin-Madison.

Neal Lloyd First was the son of Glenn and Irma First and was brought up with two younger brothers, John and Richard, on a farm in Orange Township, Ionia, Michigan. The farm is presently owned by Josh First, Neal's grandnephew and grandson of his brother John. Although this fifth-generation family farm is now predominantly focused on dairy cattle, it was smaller and much more diversified during Neal's boyhood and probably contributed to his lifelong affection for animals, especially his beloved horses.

Neal graduated from Ionia High School in 1948, where he had been class secretary of Future Farmers of America. He entered Michigan State College to study animal husbandry and obtained his B.S. degree in 1952 before being drafted into the Army, where he served as a fixed-radio signal operator during the Korean War. After completing his military service Neal returned to Michigan State College (soon to be renamed Michigan State University), where he completed an M.S. (1957) and a Ph.D. (1959) in animal sciences. He subsequently served as an instructor (1956-1960) at the university, before joining the Department of Meat and Animal Sciences of the University of

Wisconsin-Madison as an assistant professor in 1960. He became an associate Professor in 1964 and professor in 1968. He was awarded the L. E. Casida Chair of Reproductive Biology and Biotechnology in 1989 and remained in Wisconsin's Department of Animal Sciences and as a member of the Endocrinology-Reproductive Physiology Program until his retirement in 2006, at which time he accepted an appointment as Distinguished Research Professor in the Department of Biological Sciences at Mississippi State University.

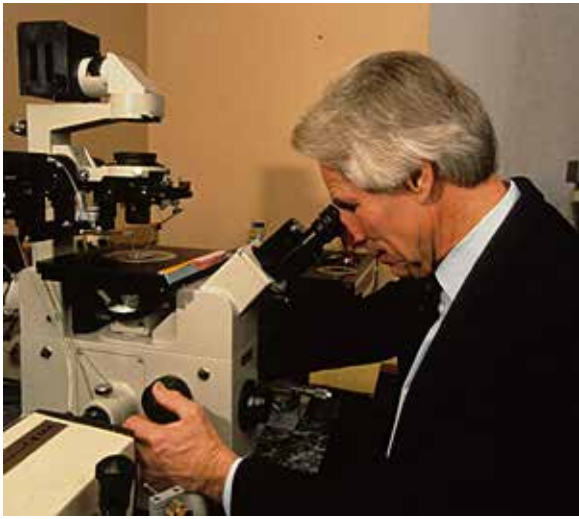
Neal was confident in both his person and his science, and there is little evidence that he was ever subservient to his more senior peers. Instead, from the start he worked with them on an equal footing. He certainly benefited from an ability to seek out and work harmoniously and productively with a surprisingly large number of faculty colleagues at Wisconsin.

Neal died in Nashville, Tennessee, on November 20, 2014, at the age of 84, from complications of cancer. He is survived by his former wife, Edith Kerstetter First and their four children: Douglas, Eric, Phillip, and Patricia; his eight grandchildren and one great-grandchild; his wife, Marijo Kent-First, and their two children: Patrick and Nicholas.

Neal's accomplishments in the fields of agriculture and genetics were astonishingly broad. He published more than 250 refereed papers and reviews that contributed to advances in sperm cryopreservation, sperm metabolism, activation, motility and fertilization ability, oocyte maturation, mammalian *in vitro* fertilization, embryo development, nuclear transplantation and cloning, as well as reproductive endocrinology, an area that first won him renown as an animal scientist. Even in Neal's earliest publications from his M.S. and Ph.D. research he was involved in topics as disparate as semen freezing in sheep and ovarian function in swine. This range of interests, intellectual restlessness, and desire to contribute useful discoveries to animal agriculture persisted throughout his life.

As his career took off at the University of Wisconsin he formed productive collaborations with two renowned scientists, the reproductive endocrinologist L. E. Casida and the biochemist H. A. Lardy. With Casida he published extensively on the endocrine link between the pituitary gland and the ovary in swine and how diet and exogenously supplied hormones intervened in normal estrous cyclicity and fertility, studies all aimed at improving reproductive efficiency on the farm. Although he co-authored over 30 papers with Casida, the one most-cited paper from that period, on the effect of exog-

enous progesterone on estrous cycle length in gilts—intact young female pigs—was without his senior collaborator (1). (Neal was confident in both his person and his science, and there is little evidence that he was ever subservient to his more senior peers. Instead, from the start he worked with them on an equal footing. He certainly benefited from an ability to seek out and work harmoniously and productively with a surprisingly large number of faculty colleagues at Wisconsin.)



Neal First at the Microscope.
(Courtesy University of Wisconsin Archives.)

Neal's partnership with Lardy began a little later, in the early 1970s, and melded the latter's interests in developing technologies to assess biochemical changes in small samples of tissue with Neal's own interest in sperm research and improving methods for *in vitro* fertilization in cattle. Collaborating with them was David Garbers, another ex-farm boy, who began research as an undergraduate on a work-study project in Neil's laboratory. After subsequently completing his Ph.D., Garbers went on to an illustrious career as a reproductive biologist and to membership in the NAS. In a period of just three years, Garbers, Lardy, Neal, and colleagues published six widely cited papers on sperm respiration and motility and the crucial role played by protein kinases and cyclic adenosine monophosphate (cAMP); two of these papers are referenced here (2, 3). This period of productive research illustrated another of Neal's great gifts, a knack of recognizing homegrown talent and fostering it. As Garber told an interviewer, "By the time I finished my degree, I had no doubts that I wanted to pursue scientific research as my major endeavor in life" (http://www.hhmi.org/news/david-garbers-hhmi-investigator-1944-2006). Neal was an inspiring mentor.

Although Neal's work on parturition and numerous other aspects of endocrinology continued, it was clear that by 1980 his attention was increasingly being drawn to artificial reproductive technologies. In a period of just a few years his laboratory published a series of groundbreaking papers on sperm capacitation (4, 5) and the subsequent acrosome reaction in bovine sperm (6), conditions for the *in vitro* maturation of oocytes derived from ovaries

obtained at the slaughterhouse (7), *in vitro* fertilization of the matured oocytes (8), and improving media that could promote the optimal development of the ensuing zygotes to the blastocyst stage (9, 10).

He also began experiments on nuclear transplantation into oocytes, initially in mice and subsequently in cattle and pigs. His team produced pioneering papers on the roles of proteoglycans in controlling sperm activation and the subsequent acrosome reaction (a process that essentially uncaps spermatozoa prior to their contact with the oocyte) (11), on the *in vitro* fertilization of bovine oocytes with frozen-thawed semen (an essential step in being able to conduct *in vitro* fertilization routinely in the laboratory) (12), figuring out when transcription from the embryonic genome begins in bovine embryos (13, 14), and cloning by nuclear transfer from the early cleavage stages of bovine (15, 16) and porcine embryos (17). His laboratory worked with that of Nobel laureate Howard Temin to develop bovine leukemia virus as a vector for gene transfer (18). Although this latter endeavor never really "took off," it illustrated Neal's ability immediately to sense the direction that the science was going, seize opportunities as they arose, and adapt procedures used in more optimized model systems, particularly the mouse, to agriculturally relevant species such as cattle and pigs. Neal also steered his team into animal cloning, venturing into the role played by the cytoplasm in reprogramming nuclei from somatic cells. His group showed, for example, that the cytoplasm from bovine oocytes supports embryo development in other species (19). He collaborated with scientists at the University of Pennsylvania to demonstrate that genome-wide epigenetic alterations accompany the nuclear transfer procedure in cattle and possibly account for the developmental aberrations that often accompany cloning (20). His work and writing on biotechnology and animal genetics continued until shortly before his death.

In perusing Neal's published papers, one is struck not just by the diversity of subject matter and the range of collaborations that underpinned his work but also by the large number of animal models he and his students employed. There are papers on the classical agricultural species—sheep, cattle, and pigs—but also many others on horses, rabbits, and rodents. To understand why it is necessary to work on such a diversity of animal subjects, the general reader should be aware that the molecular processes, anatomical features, and behavioral strategies that support reproduction in mammals have evolved and diverged at spectacular rates, such that one animal rarely serves as an adequate model for another. One cannot gain full insight into the reproductive physiology of the pig by working solely on cattle, and vice-versa, any more than one can draw firm conclusions about the human from experiments performed only on the mouse. Neal understood the importance of comparative studies and how one species can be valuable for one set of experiments but not necessarily for all. Finally,

working with costly, large, sometimes dangerous animals—which mature late, have pregnancies that last months rather than days, require more than a cage in which to survive, and necessitate a team whenever surgery is contemplated— was a challenge that Neal and his students took on and relished.

Professional activism and recognition

Neal was an effective figure in guiding policies at the national level for the large part of his career. He did extensive duty on several influential national committees, beginning while still a junior faculty member, when he became a member of the National Research Council (NRC) Panel on Education in Agriculture in 1968. He visited Indonesia several times as an advisor working with the U.S. Agency for International Development and China as part of the 1979 NAS Delegation on Agriculture. He was a member of the NIH Reproductive Biology Study Section from 1980 to 1984, and a program manager in 1985-86 with the newly initiated U.S. Department of Agriculture (USDA) Competitive Grants Program, when the USDA, for the first time, provided competitive funding for animal agriculture. From 1994 to 1998 he served on the National Advisory Board on Ethics in Reproduction, from 1997 to 2001 on the NAS Commission on Life Sciences, and from 2000 to 2004 on the NRC Standing Committee on Biotechnology, Food & Fiber Production, and the Environment. He was a member of the 1997-98 NRC committees that made recommendations on the retirement of chimpanzees that were being held in various research facilities throughout the country, and he chaired the important 2000 Cold Spring Harbor/Banbury workshop on cloning animals.

Neal received numerous awards for his research, including the Animal Physiology and Endocrinology Award from the American Society of Animal Sciences in 1977, the Alexander von Humboldt Award for Outstanding Research in Animal Agriculture in 1987, election to the National Academy of Sciences in 1989, the SSR Research Award in 1991, the American Society of Animal Sciences Morrison Award in 1993, and the Wolf Prize for Agriculture (often called the Nobel prize for agriculture) in 1997. Most of these later awards recognized Neal's groundbreaking research in embryo cloning, sperm activation, *in vitro* fertilization, and ovum and embryo development as representing major advances for genetic improvement in livestock. Nor were his contributions to the University of Wisconsin-Madison limited to research; he was also an accomplished teacher. He was the recipient of the university's Outstanding Teacher Award, College of Agricultural and Life Sciences, in 1971 and Excellence in Teaching Award in 1978.

Mentorship and graduate and postdoctoral trainees

During his years on the Wisconsin faculty Neal mentored 14 M.S. and 25 Ph.D. students and 17 postdoctoral fellows, as well as numerous visiting scholars. Many of these have themselves gone on to illustrious careers. Neal was generous in providing help that enabled many of these trainees to get a good start in their careers, as illustrated by this comment from Professor Randall Prather of the University of Missouri, who completed his Ph.D. in Neal's laboratory in 1987:

> *When I was a graduate student about to finish up, Neal walked into our laboratory meeting and announced that the USDA was soliciting research proposals and he wanted to know who had ideas. After some deliberation I raised my hand and said that I could write one. Over the next weeks I formed a first draft of what I thought was a great idea. I gave it to Neal in the morning; by late that afternoon, he had returned it and agreed that it was probably a fundable idea, but that the format needed a lot of work. I took it home that night and dutifully complied with his format requirements and returned the edited version the next morning. Needless to say I had not performed the formatting exactly as he wanted. So, that afternoon he gave it back to me, and I worked on it and returned it the next morning. I was a slow learner and it took me several more days to realize that he would not accept less than perfect and that his rigid format was the only way to write a 'grant' (grants are funded, proposals are ideas). Since I was a student, the proposal was submitted in his name and the funding was subsequently awarded. Just after the funding arrived, I–now a postdoc–found a faculty position and was poised to leave. Neal told me that if I finished the first year of the grant at Wisconsin, that [sic] I could take the rest of the money with me! That was a real shot in the arm to a new assistant professor. I learned a lot from Neal about how to write a 'grant', and how to be generous.*

James Thomson, D.V.M, Ph.D., a colleague at Wisconsin, had similar recollections.

> *I first met Neal when I came to the University of Wisconsin as a postdoctoral fellow in 1991. Although I was working in John Hearn's lab at the Wisconsin National Primate Research Center, Neal took a personal interest in my work, provided with me access to his own lab's resources, and was there to help me at key events in my early career. When I derived*

> *primate embryonic stem cells in 1995, Neal communicated the work to PNAS. When Neal received the Wolf Prize in Agriculture in 1996, he arranged for me to travel to Israel with him to give a talk on primate ES [embryonic stem] cells. While there, he introduced me to his friend Joseph Itskovitz, who contributed to the work that led to the isolation of human ES cells. Neal and his wife, Marijo, made me and my family feel very welcome in Madison, always including us at Christmas gatherings at their home. Neil was both a mentor and a friend, and he will be missed.*

These two quotes are from a short memorial essay written for *Biology of Reproduction* about Neal (21), but they epitomize the manner in which he helped guide those who came under his influence to productive independent careers.

One of the two authors of this essay (Roberts) became acquainted with Neal when he visited the University of Florida sometime around 1980.

> *The content of his seminar, given to the interdisciplinary group in reproductive biology, remains vague [in my memory] but the impression he made on me was strong. He lectured well, and I was captured by his enthusiasm and enjoyment for the subject and his charm. When I was awarded the Alexander von Humboldt award for agriculture in 1996, Neal was invited down to the Missouri campus to introduce me at the ceremony. He chose to travel in a small chartered plane and, after the event was over and with considerable aplomb and a big smile, presented the bill to the Dean of Agriculture and then immediately departed for Madison. Roger Mitchell, my dean and a complete gentleman, accepted the charge with equal aplomb. The occasion epitomized both men. I have a number of other fond memories of Neal. He was sometimes incautious but immeasurably kind, and a loyal friend whom I greatly miss.*

Co-author Parrish, also a Wisconsin professor, was professionally much closer to Neal:

> *Neal First was a major figure in the field of reproductive physiology with major contributions to process of parturition, impacts of heat on male sperm production, in vitro fertilization in the bovine, cloning and genetic manipulation of livestock. His most enduring impact however was as a mentor for his many undergraduate, graduate and post-doctoral students*

as well as the vast numbers of visiting scientists. Dr. First was always giving individuals the tools to excel and move on to the next level with success. The consequences of that kind of mentoring is that Neal's students now occupy leadership roles in agriculture, veterinary and human medicine, academia, industry and government service in the U.S. and world-wide. I am humbled and feel it a privilege to have had Neal First as a mentor and follow him as a professor at the University of Wisconsin-Madison. Neal, not a day goes by that I do not think of you. We miss you." (John Parrish, Ph.D. Professor, University of Wisconsin-Madison.)

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