

Anne McLaren 1927–2007

This had been a celebratory year for Anne McLaren. In April, her 80th birthday was marked in Cambridge, UK by a special symposium in her honor on germ cells and stem cells, two subjects very close to her heart and the main themes of her research endeavors throughout her career. Many of her colleagues and friends from all over the world gathered to participate in lively scientific sessions, great dinners, and a few speeches in praise of Anne that even she seemed to enjoy. In May, she was awarded, jointly with Janet Rossant, the March of Dimes Prize in Developmental Biology, an accolade in recognition of her outstanding contribution to mouse genetics, embryology, and reproductive biology (see the figure). And then in June, Anne arrived at the Cold Spring Harbor Laboratory as a lecturer for the renowned “Mouse Course” (Course on Molecular Embryology of the Mouse), which she had enthusiastically devoted her time to almost every year since its inception. At the special symposium to commemorate the 25th anniversary of the Mouse Course, Anne talked fondly about her plans for more globetrotting in the coming months, for both science and pleasure. Sadly, all this came to an abrupt halt because of a fatal road accident on July 7th, which took Anne away from us.

Anne’s scientific achievements are truly outstanding. She was able to cut through the chaff to pin down the critical questions, to appreciate the long-term commitment of working on difficult problems, and to recognize the importance of an unexpected result. Through these approaches, whether adopted by herself or encouraged in those around her, Anne had a positive and enduring influence across many topics in biology.

Anne started hitting the headlines in the 1950s with her PhD research conducted at Oxford University on neurotropic viruses and how they gain access to the nervous system. This research was particularly timely given that polio was epidemic in the UK at that time. But it is her subsequent work on mouse genetics and

Mendelian genetics. Together with Donald Michie, she found that extremes of temperature in the animal house could affect litter size and induce variations in the body weight of littermates. This work led to ideas about robustness in growth and development, whereby inbreeding may diminish the ability to compensate for changes in the environment. They also observed that the uterine environment may influence development, for example, the number of vertebrae that are found to vary between inbred mouse strains was in fact determined by the genotype of the mother.

To address the question of uterine effects on embryonic development more rigorously, it was necessary to perform the investigation using embryo transfer techniques. To achieve this, Anne optimized and characterized many of the parameters and technologies in mouse reproductive biology that we take for granted today. Among these was the dramatic demonstration in 1958, with John Biggers, that preimplantation mouse embryos can be removed from the mother’s reproductive tract, grown in vitro for 48 hr, and then transferred to the uterus of a pseudopregnant female, yet still result

in live offspring. In conjunction with the advent of in vitro fertilization, this seminal set of experiments paved the way for today’s technological ability to manipulate the mammalian embryo and to produce transgenic and chimeric animals. The outcome of an extensive series of experiments studying superovulation, embryo culture, and embryo transfer experiments enhanced our understanding of early mammalian embryonic development and catalyzed the application of assisted reproductive technologies to human medicine and agriculture.



Anne McLaren
Photograph courtesy of March of Dimes.

development for which she is now universally recognized and which has had the biggest impact not only on science but also on society.

During the latter part of the 1950s, first in the Zoology Department at University College, London and then in London’s Royal Veterinary College, Anne became interested in the role of the environment in determining phenotypic traits in mice. For example, she looked at variation within inbred strains, which was greater than that seen in F1 hybrids, and between mouse strains, which could not be explained by simple

From London, Anne moved to the Institute of Animal Genetics in Edinburgh in 1959, where she continued research on mammalian fertility including embryo-uterine interactions, hormonal control of implantation, immunological aspects of reproduction, and immunization as a means of contraception. A hallmark of these parallel lines of research is the evident attention to the practical implications of the outcome to human fertility and reproductive medicine. During this time, Anne's research also encompassed elucidation of the genetic basis of certain forms of early embryonic lethality, and she continued to work on parent-related effects on development. Her findings pointed to a strong maternal influence on early development, which we now know is due to maternally inherited factors and the likely activity of epigenetic mechanisms. Anne retained an interest in such phenomena, including genomic imprinting, throughout her career.

Chimeras, animals that comprise genetically distinct cell populations, can be generated experimentally by aggregating two preimplantation embryos. Anne was one of the pioneers in the use of chimeras as a powerful experimental tool to study embryogenesis, lineage allocation, and cell-cell interactions during tissue differentiation. The exciting findings from the chimera work were lucidly summarized in Anne's monograph on "Mammalian Chimeras" written in 1976, soon after she moved back to University College, London to become Director of the Medical Research Council's Mammalian Development Unit (the "MDU"). Her major contributions from this work include discovering that the chimera achieves the ability to regulate its size at the onset of gastrulation, that cells with a different genetic makeup can display self-immune tolerance within the chimera, and that the patch sizes of the genetically different chimeric clones provide an estimate of clone size and the pattern of clonal growth and distribution during organogenesis. These findings brought forth the concept of the allocation of tissue or organ progenitor cells early in development and pointed to the likely existence of pluripotent cell populations in

the embryo. Her chimera studies also informed our understanding of sex determination, notably that germ cell sex (that is, whether germ cells will give rise to oocytes or sperm) is determined by the influence of the gonad's somatic cells and is not set intrinsically by the chromosomal sex of the germ cells.

Germ cell differentiation was one of Anne's passionate research interests both in London and later at the Wellcome Trust/Cancer Research UK Gurdon Institute in Cambridge, to which she "retired" in 1992. Indeed, Anne's contributions to germ cell biology are far-reaching—from her ideas about germline establishment (articulated succinctly in her book *Germ Cells and Soma*, published in 1981) to her work on the origins of germ cells during early gastrulation, the factors affecting their survival and migration to the genital ridges, germ cell sex, and X chromosome reactivation. She continued to explore the role of somatic cells and to identify the molecular players that regulate meiotic differentiation of germ cells and to study the impact of genomic imprinting on the derivation and the developmental potential of embryonic germ (EG) cells (the stem cells that are derived from germ cells). Of course, she did not make all of the critical findings herself, but she always asked the right questions and encouraged others to provide the answers. One of the last questions that she posed to one of us (P.T.) is whether it is possible to track the first instance when a primordial germ cell and a non-germ cell are derived from one epiblast cell of the gastrula-stage mouse embryo. She was convinced that it was the right time to address this question given the advances in real-time cell imaging technology. Anne never stopped thinking and questioning and was always several steps ahead of others in the field.

Anne also worked on sex determination during this period with Liz Simpson. Together they dispelled the H-Y antigen hypothesis, which for many years provided the prevailing candidate for the Y-linked testis-determining activity. Indeed, this theory was so ingrained that it was still appearing in textbooks long after their discovery that particular

mice carrying a variant Y chromosome fragment lacking H-Y transplantation antigens could still be male. It was firm encouragement from Anne that led one of us (R.L.-B.) to enter the field and find the real sex-determination gene. Anne also established methods to explore aspects of gonadal development, such as re-aggregation and organ culture systems, that enabled analysis of how the gonads form. More recently, Anne's lab discovered that prostaglandin D2 could trigger XX male sex reversal in cultured mouse gonadal cells. Although this may not be an essential part of the normal sex-determining process, it is probably an important backup mechanism, adding to the robustness of the initial decision to make a testis rather than an ovary.

While in Cambridge, Anne remained "at the bench" and continued to publish, adding to her impressive list of more than 300 papers. Indeed, her last research article, which came out just a year ago in the *Proceedings of the National Academy of Sciences USA*, combined her three long-standing interests: sex determination, germ cells, and genomic imprinting. Anne was heavily involved in all aspects of this work. She would arrive early in the morning at the MRC's National Institute of Medical Research in London to dissect material from mice held by Paul Burgoyne (who was a former member of Anne's MDU) and then would drive up to Cambridge where she and members of her small lab would continue the experiments.

Anne McLaren was not a scientist living in an ivory tower. She was keenly aware of the responsibility to explain science to the public in an accessible and evidence-based format and the importance of public support for scientific technologies that may raise serious ethical concerns. Anne was a major contributor to the formulation of the legal framework and the implementation of the regulatory policy on human embryo research through her involvement with the Warnock Committee, which advised the UK Parliament and led to the passing of the Human Fertilisation and Embryo Act in 1990. She then served for 10 years on the newly established regulatory body,

the Human Fertilisation and Embryology Authority. Anne also participated tirelessly in the discussion of ethical and scientific issues involved with human embryonic stem cells, therapeutic cloning, and embryo hybrids. Her wise words regarding the ethics as well as the science of reproductive medicine and stem cell research continued to shape general opinion, not just in the UK, but around the world. Her clarity of thought on these issues, outlined so elegantly in a recent Commentary in the inaugural issue of *Cell Stem Cell*, will be sorely missed.

The establishment of the MDU was one of Anne's major accomplishments. The specific goal was to build a cluster of expertise in mouse embryology, reproductive biology, and genetics. Although a small unit, it had a major impact due to Anne's decisive leadership and her innate ability to generate excitement about science. The MDU legacy is clearly visible as many of the Unit's scientific staff, postdoctoral fellows, PhD students, and visiting scientists are now leading scientists in developmental and reproductive biology labs around the world.

Both of us had worked at the MDU and have fond memories of Anne and her style of management. Anne's office was also her personal lab, where she could be found working at her microscope, surrounded, indeed often hidden, by piles of papers, books, and shopping bags each holding the documents of a specific committee. This clutter was not reflected in her mind. She always seemed to be able to instantly locate a desired document in her office. Often, with only a few scribbled notes, Anne would dictate a precisely crafted manuscript, which would need only minor subsequent corrections. This was when comput-

ers and word processors were beginning to replace typewriters, but Anne held out, probably longer than most. Anne guarded her time at the bench, but she would "hold court" at lunchtimes. These occasions, and early evenings in one of the local pubs, were the best time to obtain Anne's views on a problem, whether scientific or not, and were where her formidable fount of knowledge was on display.

Anne received numerous prizes and awards, including the Royal Medal of the Royal Society in 1990 and the Japan Prize in 2002, in addition to this year's March of Dimes Prize in Developmental Biology (see the figure). She was made a Dame of the British Empire in 1993. It has been remarked that some of her professional achievements were "historical" milestones. She was the first woman officer in the 300 year history of the Royal Society of London, the third woman president of the British Association for the Advancement of Science, and the fourth female winner of the March of Dimes Prize in the last 12 years. In her career, Anne was never touched by the stigma of being a woman scientist, rather she lived and worked as "a scientist." However, she was aware of the challenges for female scientists and worked selflessly to promote and support the careers of others.

As Foreign Secretary of the Royal Society from 1991 to 1996, Anne traveled enthusiastically around the globe to stimulate science and scientists. She seemed to be immune to jetlag, delivering talks right after her arrival and yet retaining all of the clarity and sharpness of mind that she was renowned for. One of her great gifts was putting people at ease, and as a result she was extremely popular with graduate students and junior postdocs who were in

awe of her at first. She was always very generous in offering good advice and sharing her ideas. One could visualize the globe crisscrossed with lines where Anne had not only traveled but also laid down a track of benevolent influence.

Anne was a constant inspiration to those who knew her. To her students, Anne was never prescriptive in her approach to supervision, but rather she tried to probe them with questions, allowing them the freedom to explore but making them think. A scientific discussion with her could be both stimulating intellectually, as she would never tolerate sloppy reasoning, and intimidating because of the depth and breadth of her knowledge. She promoted openness in science by discussing not only her published research but also the experiments she was planning to do. She cautioned that one should never rush to publish unless all details were attended to and everything was absolutely correct. However, she always maintained that, despite all the hard work that must go with it, research should be fun, enjoyable, and fulfilling.

With the passing of Anne McLaren, the world has lost an accomplished developmental biologist and geneticist, an iconic figure of scientific integrity, and a strong advocate of social conscience and ethical responsibility in biomedical research. For those of us who were fortunate enough to share moments of our lives with Anne, the only consolation in the face of this tragedy is that we have been exceptionally privileged to have known a warm and sharing person, to have learned about science and life from an incisive mind, and to have been staunchly supported by a skilful mentor throughout our own careers. She is a role model for what we all want to be and wish to achieve.

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