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From Embryo to Ethics: a career in science and social responsibility

An interview with Anne McLaren

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Much of this interview took place during two days of the June 2000 "Experimental Embryology of the Mouse" Course at Cold Spring Harbor. Anne has been participating in the course almost since it began in 1983, and relishes the opportunity to interact with the students and to pass on to them her extraordinary knowledge and love of mammalian reproduction and developmental genetics. On their part, the students deeply appreciate Anne's genuine interest in them, and her gentle encouragement as they struggle for the first time to flush oviducts and find genital ridges. In this setting anyone who knows Anne will appreciate the challenge I had in deflecting her attention away from the lab to talk about herself. Even while answering my questions she had one eye out for the course activities - the student that needed help, the mouse eating the note on top of its cage, the demonstration about to begin.

Anticipating Anne's reluctance to be interviewed I had submitted questions beforehand, to which she had courteously replied, in longhand. These responses are quoted without change. To my verbal questions Anne responded with characteristic graciousness, and was always succinct, wryly humorous, and modest about her own achievements while being very generous about others. Now and then, I was treated to glimpses of the side of Anne that is often hidden, but is at the core of her success and leadership as a scientist; her formidable and razor sharp analytic intellect and her single-minded determination. It came as no surprise to learn that Anne had once thought of being a lawyer, but there are generations of scientists who are very glad that she did not! For in her career, Anne has had a profound and radical influence on the fields of mammalian reproduction and embryonic development. This is not only through her innovative and rigorous research, but also by her ability to inspire others, her generous and tolerant mentorship, and her social action. This volume of the *Int. J. Dev. Biol.* is a tribute to her continuing achievements in all of these areas.

Anne is notoriously reticent about her background and early life, and I leave the future exploration of this fascinating topic to a biographer. Her undergraduate education was at Oxford University, 1945 -1949, where she graduated with a 1st class Honours degree in Zoology.

Abbreviations used in this paper: ARC, Agricultural Research Council; MDU, "Mammalian Development Unit"; MRC, Medical Research Council; p.a., per annum.

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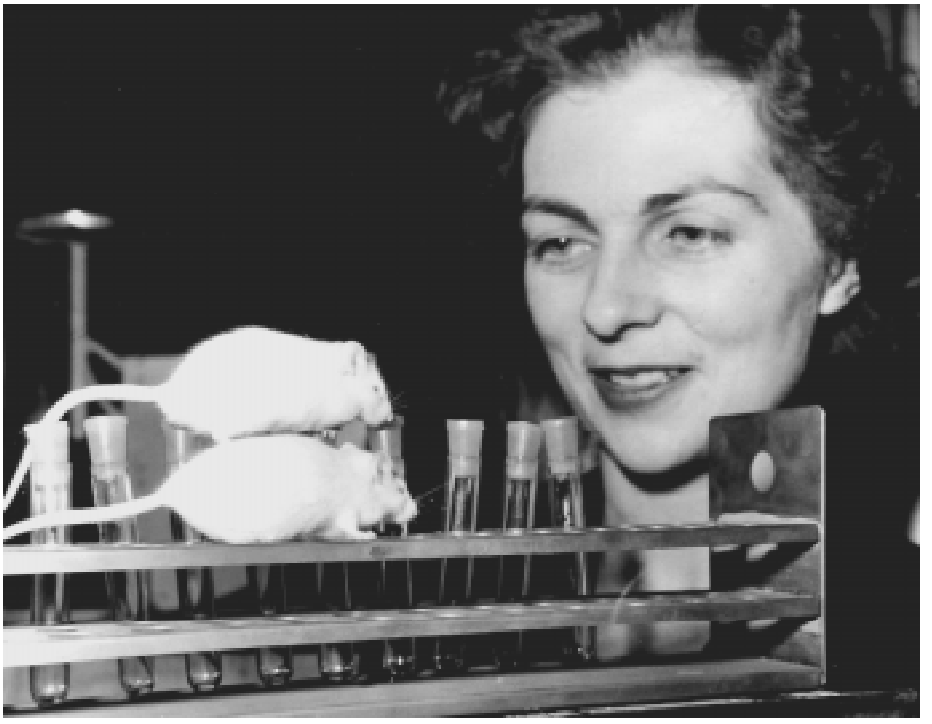

Anne McLaren in her laboratory in 1959. *Photo kindly provided by John Biggers.*

"When did you become interested in science and how was this interest kindled? Did you consider other careers besides that of research scientist?"

"Like all children I was interested in a general sort of way in science and didn't have it educated out of me. But, I had no specific interest in science till I went to University - at that time Biology seemed to be the easiest subject to swat up for an Oxford scholarship.

Before going to university I considered other careers - as a child, I wanted to be a ballet dancer, and later I considered journalism and law (I would have made a good lawyer, but I'm glad I didn't become one), but after a year or so at Oxford I was hooked on biological research."

After graduating, Anne stayed on at Oxford for her Ph.D. She studied neurotropic viruses in mice - a topic of relevance to poliomyelitis, a major medical problem at the time. In 1952 she was awarded an Agriculture Research Council (ARC) fellowship to work in Peter Medawar's Department of Zoology in University College London. Here, she published her first influential studies on mouse development, in collaboration with her partner, Donald Michie. One of their initial achievements was to uncover an intriguing maternal effect on embryo development. They found that almost all mice of the C57BL strain have six lumbar vertebrae, while most C3H mice have five. They traced this difference back to the uterine environment since most C57BL embryos transferred into C3H foster mothers developed five lumbar vertebrae. This research was influential in two ways. First, the outcome was quite unexpected and its molecular basis is still not known, although one can speculate about such factors as strain-specific differences in the levels of maternal retinoids. Second, the need to exchange large numbers of embryos between females of different strains led Anne to optimize the techniques of superovulation and embryo transfer. These two procedures are, of course, crucial for today's high throughput production of transgenic and knockout mutant mice.

Anne's early work also shed new light on several key problems in mammalian reproductive biology, including implantation and the reciprocal interactions between the uterus and embryo, ovarian function, and the control of fetal and placental growth. Many of these topics are only just beginning to be explored at the molecular level, which is greatly encouraging given their clear relevance to clinical problems in pregnancy and fetal development. Perhaps one of the most influential contributions of Anne and Donald Michie at this time was to apply rigorous analytical and statistical standards to problems in mammalian reproduction, a field that had previously been somewhat confused by "fuzzy" experimental design. Their work also generated important data about the interactions between environmental stress and genotype in producing phenotypic variation. Anyone who has read Anne's wonderful commentary entitled "Too Late for the Midwife Toad" (McLaren, 1999), will know that this problem, and her early experiments with Donald Mitchie, are still highly relevant today.

"Who influenced you most as a scientist?"

"My then colleague and partner Donald Michie. Having as a very young man been one of the leading cryptographers and computer scientists at Bletchley Park during the Second World War, he had a highly developed sense of experimental design and scientific rigor, and an unparalleled understanding of statistics." [1]

The work at University College was so successful and prolific that, then, as now, mouse cage space became a limiting factor and the operation moved to the so-called "Canine Block" of the Royal Veterinary College in Camden Town, London. The move fortuitously lead to a most important and fruitful collaboration with John Biggers, who was at the time studying the development of chick leg bones, using culture techniques. He and Anne combined their skills of *in vitro* culture and embryo transfer to show for the first time that mouse embryos grown outside the mother could be returned to the uterus and develop to term. The events leading up to the birth of these famous "Brave New Mice" is beautifully described in Dr Biggers' article "Research in the Canine Block" in this volume (pp. 469-476). The technique of embryo transfer is, of course, now a cornerstone of the genetic manipulation of the mouse, and also of assisted reproduction in humans.

In 1959, Anne moved to the University of Edinburgh, where an ARC Unit of Animal Genetics had been founded by Conrad

[1]Note: for readers who do not know the fascinating history of Bletchley Park, go to http:// www.bletchleypark.org.uk

The "Ford Hut". *University of Edinburgh in 1998. (Courtesy of Maggie and Annie Hargrave).*

Waddington. According to Anne, the facilities here were "state of the art", having been established with a generous grant from the Ford Foundation, and she recounted this period to me with great relish and later said, "Science was such fun, then". The ARC Unit clearly provided a most productive and stimulating environment, since Waddington was very successful in obtaining finance for groups studying the genetics of a range of different organisms. Notwithstanding the Ford Foundation grant, some conditions seem to have been quite Spartan. British readers will probably identify with the fact that Anne's lab was in a prefabricated "Ford hut" heated with electric fires, and that embryos had to be carried through the snow to the main building for transfer into recipients! Don't try whining to Anne about your physical work environment!

"There are rumors that you lived in a commune in Edinburgh! Is this so?"

"No. I wish I had. When Waddington set up the Institute of Animal Genetics in Edinburgh after the war, bringing many of his wartime team with him, there was little available accommodation in the city. He bought a stately home just outside Edinburgh, and many of the staff (complete with wives, husbands, children) moved in. Moreton Hall was still functioning as a sort of commune in about 1950. Donald and I went up to Edinburgh a couple of times and camped out in the basement, because all the most interesting mammalian science was focused in Edinburgh, actually in Waddington's Institute, at that time. But food was still rationed, petrol was scarce, buses were few, the non-working wives in particular became discontented, there were epic feuds and rows, and by the time I moved to Edinburgh in 1959, Moreton Hall was history. I would have loved to have been part of it."

"You began your career at a time when there were very few women in positions of influence in science – very few role models. Do you think this affected your expectations in your career? Do you think young women have an easier time today?"

"I was lucky; being a woman never seemed to be a disadvantage in my career, if anything it was an advantage, and it certainly never "affected my expectations in my career". When Donald and I were first employed by the Agricultural Research Council (or rather got our first grant), we were puzzled to find that his salary was £850 p.a. and mine only £750 p.a. The explanation was that he was four years older than me and had a bonus for wartime service, which was fair enough. There were quite a few women around, at Oxford, and University College London, and the Institute of Animal Genetics (but not at the Royal Veterinary College of London!!), but I don't think that we thought of ourselves as "women scientists", just scientists. Later women became more self-consciously "women scientists" and started looking for role models (a novel concept for me) and feeling isolated if there weren't other women around—perhaps because there is now more competition. Everyone has a harder time, not an easier time, today, because there are more scientists and relatively less jobs and money."

It was during the Edinburgh period that Anne made her first trip to the US, to an international congress of Zoology in Washington DC. There, she was inspired by a talk by Roy Britten on the use of reannealing of single stranded molecules to study differences in DNA nucleotide sequence. On her return to Edinburgh Anne established a collaboration with Peter Walker to use the hybridization technique with DNA from different inbred strains of mice to study the process of mammalian speciation. However, this molecular approach was really before its time and, undaunted after two years unproductive work, Anne returned to the study of implantation and to the fascinating topic of mouse chimeras.

In 1974, shortly before her election to the Royal Society, Anne was made head of the Medical Research Council (MRC) Unit of Mammalian Development. The MDU (Mammalian Development Unit), as it was fondly known, occupied space formerly presided over by Hans Gruneberg, in a large and unattractive building covered in London grime near Euston Station. The initial impact of this building on an overseas visitor is beautifully described by Peter Koopman in his article "*In situ* hybridization to mRNA: from black art to guiding light" in this volume (pp. 619-622). However, between the years of 1974 and 1992, when the Unit was closed at the time of Anne's statutory retirement, the MDU was a world renowned center of mouse developmental genetics and reproductive biology. All research in the unit was funded by the MRC, and outside funding was disallowed. Anne's leadership, her generous and tolerant mentorship, her enthusiasm for new ideas coupled with her scientific rigor, are all legendary. Many of today's leaders of mammalian developmental genetics either trained there or spent time in the lab, or collaborated with members of the group. Anne was enormously generous in making her expertise available to others. It seemed to me, as a beneficiary of her largess at the time and a complete novice in reproductive techniques, that to Anne the ideas of competitiveness and exclusiveness were complete anathemas.

"In a previous issue of the *International Journal of Developmental Biology* devoted to Developmental Biology in Britain (Volume 44, No. 1 2000) the editor, Jim Smith, made much of the competitive spirit of some prominent British male scientists. Do you feel that you are competitive or as competitive?"

Anne McLaren with John Biggers *(left)* **and Wesley Whitten** *(right)* **in the courtyard of St. John's College, Cambridge.** *The photograph was taken on the occassion of Dr. Whitten receiving the Marshall Medal of The Society for the Study of Fertility. Photo kindly provided by John Biggers.*

"No, I've never felt competitive. I've never knowingly competed with anyone for a job, or a grant, or a scientific goal."

What do you have the least tolerance for in science? If there were three things you could improve about the way science is managed now, what would they be?

"Sloppy thinking, making things more complicated than they need to be, too many abbreviations and initials. As for management, I'm not sure. There's a lot to be said for the old Research Council Unit system. I'd certainly like to see more recognition of, and secure jobs for, research assistants and technicians. People who want to just do science, not necessarily to be group leaders - they need a proper career structure, not short-term contracts. And third? Maybe shorter grant application forms".

Were you ever a member of the Communist party? If so, did this ever make it difficult for you to travel to the USA? I note here that Dorothy Hodgkin, another distinguished British scientist with left-wing political views and later a Nobel prize winner, was for a time denied a visa to the USA [see *Dorothy Hodgkin, A life* by Georgina Ferry, Cold Spring Harbor Laboratory Press].

"Yes. For years, each time I wanted to visit the USA, I had to apply for a visa, get formally refused, then apply for a Waiver for the particular scientific conference or whatever I wanted to attend. Occasionally my hosts got harassed, even though each time I swore that I was not intending to assassinate the President. Eventually (about the time I became Foreign Secretary of the Royal Society) I was granted a multiple-entry visa, and now of course one just fills in a form at the airport."

Anne's research during the MDU years largely evolved from her interest in chimeras generated by aggregating mouse embryos of different genotypes. Although the technique of making chimeras was first developed independently by Krzyztof Tarkowski and Beatrice Mintz, Anne used it very powerfully to address a wide range of important questions in mammalian development. For example, her research into sex determination came directly out of the finding that chimeras are predominantly male, even though, by chance, half of them are made between male and female embryos. Her interest in sex determination also had many fruitful spin-offs. Among these are the debunking of the idea that an H-Y antigen is involved in sex determination, studies on X-inactivation and imprinting, and work on the origin and development of mammalian germ cells and their interactions with the somatic lineages in the developing gonads. Anne has described herself as an "unashamed opportunist" when it comes to choosing problems to work on, but in every case she has catalyzed new ideas and opened up the problem to further enquiry with emerging techniques. I know of one small example from personal experience. Her demonstration, during a Mouse Course at Cold Spring Harbor, of her technique for isolating primordial germ cell from the genital ridge inspired my postdoc, Yasuhisa Matsui, and I to culture germ cells in the presence of multiple growth factors and to derive embryonic germ cell lines from them.

Over the years, Anne has received numerous formal accolades of her work, including a dozen or so Honorary Degrees. In 1985 she received the Marshall Medal of the Society for the Study of Fertility and in 1990 the Royal Society awarded her its Royal Medal, their highest honor in recognition of truly outstanding scientific achievement.

Since her statutory "retirement" from the MRC, Anne has worked at the Wellcome/CRC Laboratory in Cambridge where she continues to be active in research, publishing papers on germ cell development and genomic imprinting, as well as writing lucid commentaries on topics such as cloning and stem cells. Her talks are always models of clarity, as well as diction. Indeed, John Gurdon wryly told me that he was once advised that he really ought to have elocution lessons from Anne McLaren, if he was going to speak English correctly!

What do you see as the most exciting future developments in the field of mammalian genetics?

"How somatic nuclei get reprogrammed by egg cytoplasm."

I have always been in awe of your ability to write and communicate with such clarity and precision, not only to a scientific audience but also to the general public. Did this just come naturally or did you have to work on it? What advice can you give to those less gifted?

"Read a lot when young - not science (but science fiction is OK). Try writing how you talk."

What advice would you give to a young scientist faced with pressures from so many directions (grant writing, competition for jobs, pressure to do "safe" experiments with short term goals rather than to take high risks)?

Note 1: Admin, Administration.

"Mix your bets—do your high risk projects, but make sure you have one or two boring "safe" experiments on the go at the same time. If the pressures are more than you can stand, get out and take an admin job. Admin[1] is easy."

What do you feel about the increasing intercalation of for-profit companies in basic academic science?

"Necessary"

Anne's pioneering demonstration, with John Biggers, that mouse embryos cultured *in vitro* develop normally after transfer to the uterus, was a major step towards the application of assisted reproductive techniques to clinical problems, initially to alleviate infertility. The wider implications of her research did not escape Anne, who has always been acutely aware of the impact of new technologies on society. It was therefore no surprise that between 1982-1984 she was a member of the influential Warnock Committee that drew up the very first guidelines covering the use of *in vitro* fertilized, donated human eggs. She was the only member of the group with relevant scientific experience and, as described in Mary Warnock's article (see. pp. 487-490), her "impeccable clarity" and "genius" in communicating complex scientific ideas to lay people in a patient, non-intimidating way were crucial to the credibility of the Report. The committee recommended the establishment of a Licensing Authority for Human *In vitro* Fertilization and Embryology. At first this functioned as a voluntary group, with Anne as a founding member, but in 1990 the UK Human Fertilization and Embryology Authority was made official, and remains a model to which other countries look for guidance. More recently, Anne has been active in the European Community as a member of various committees, including a Working Group on Human Embryo Research, the Group of Advisors on the Ethics of Biotechnology, and the Group on Ethics in Science and New Technologies. From 1991-1996 she was Foreign Secretary and Vice-President of the Royal Society (the first woman to hold such a position in 332 years). In 1993 Anne was made a Dame, in ceremony at Buckingham Palace which, I believe, she attended without a hat. This honor, which Anne prefers to keep well hidden, is considered the equivalent of a knighthood, which, as John Gurdon so nicely put it to me, is "not available" to women. But most important of all, Anne remains, quite simply, both a superb research scientist, who radically changed the fields in which she works, and one of the leaders of social action in the international scientific community.

Since this interview is for the *International Journal of Developmental Biology* and you have considerable experience in international scientific affairs, I would like to ask about your perceptions about the way that science is done in different countries. Not necessarily in relation to funding and resources, but in the way people think about problems.

"I'm always impressed by the similarities in how people do and think about science in different countries, not the differences."

One of your attributes that I admire very much is your keen sense of social justice, social responsibility and ethical behavior, not only in the area of assisted reproduction and genetics, but in the wider arena of science and society. Where did this sense come from? How can it be encouraged in young scientists today?

"Even as a child I was very aware of social inequalities, and of course in immediately post-war Britain one could hardly help thinking (and talking) about society and the future. For nowadays, maybe discussion of ethical and social issues with students might help - in my experience they're very interested."

Are any of your grandchildren interested in science? What do you think about science education in schools?

"No, not specifically. My 16 year old granddaughter looks likely to end up doing some sort of graphic design job (A levels in photography, mathematics and sociology), the 13 year old has his own punk rock band, and the 11 year old seems set to be an academic historian. The others are too young. Science education in schools? I'm all for it, the earlier the better, provided it's done in such a way as to kindle interest, not extinguish it."

Highlights from Anne McLaren's bibliography

1 MCLAREN, A. AND MICHIE, D. (1958). An effect of the uterine environment upon skeletal morphology in the mouse. *Nature* 181: 1147-1148.
This was the first paper to report a maternal uterine influence on the axial (vertebral) development of the mammalian embryo.

2 MCLAREN, A. AND BIGGERS. J.D. (1958). Successful development and birth of mice cultivated *in vitro* as early embryos. *Nature* 182: 877-878.
This was the first report showing that mouse embryos cultured in vitro develop as normal fertile mice after uterine transfer. This discovery was crucial to the development of technologies for making transgenic and genetically engineered mice.

3 MCLAREN, A. (1969). Stimulus and response during early pregnancy in the mouse. *Nature* 221: 739-741.
This Nature paper was the first to identify explicitly the various interactions between embryo and uterus during implantation. It was quite influential.

4 MCLAREN, A. AND BOWMAN, P. (1969). Mouse chimeras derived from fusion of embryos differing by nine genetic factors. *Nature* 224: 238-240.
This was the first of a whole series of papers in which Anne exploited the power of mouse chimeras to investigate important developmental processes. It also provided the first colored Nature cover!

5 MCLAREN, A. (1972). Numerology of development. *Nature* 239: 274-276.
An analysis of the basis of cell distribution in mammalian development. This paper using mouse chimeras was widely quoted.

6 MCLAREN, A. (1979). The impact of pre-fertilization events on post-fertilization development in mammals. In *Maternal Effects in Development* (eds. D.R. Newth and M. Balls). British Society for Developmental Biology Symposium 4, Cambridge University Press pp. 287-320.
This review pointed the way to what is now known as epigenetics and genomic imprinting.

7 DE FELICI, M. AND MCLAREN, A. (1983). *In vitro* culture of mouse primordial germ cells. *Exp. Cell Res.* 144: 417-427.
The first successful attempt to culture mouse germ cells. This led to a great increase in interest in this topic, and eventually to their immortalization.

8 MCLAREN, A. (1984). Where to draw the line? *Proc. Roy. Inst. of Gt. Brtn.* 56: 101-121.
This semi-popular paper, and the thinking behind it, had a considerable effect on the Warnock Report and the eventual (1990) legislation, with respect to the so-called "14-day rule" that human embryos should not be cultured in vitro beyond the primitive streak stage.

9 MCLAREN, A., SIMPSON, E., TOMONARI, K., CHANDLER, P. AND HOGG, H. (1984). Male sexual differentiation in mice lacking H-Y antigen. *Nature* 312: 552-555.
The Nature paper that debunked the "H-Y hypothesis" of sex determination.

10 MCLAREN, A. (1989). IVF: regulation or prohibition? *Nature* 342: 469-470.
A campaigning paper, appealing to scientists to make their voices heard in the run-up to the 1990 legislation.

11. GINSBURG, M., SNOW, M.H. AND MCLAREN, A. (1990). Primordial germ cells in the mouse embryo during gastrulation. *Development* 110: 521-528.
A descriptive account of the earliest identifiable mouse germ cells.

12. MCLAREN, A. AND SOUTHEE, D. (1997). Entry of mouse germ cells into meiosis. *Dev. Biol.* 187: 107-113.
One of Anne's most recent research paper, on the basis of sex determination in mouse germ cells and the factors influencing the early entry into meiosis that determines oogenesis rather than spermatogenesis.

13. MCLAREN, A. (1999). Too late for the midwife toad. Stress, variability and Hsp90. *Trends Genet.* 15: 169-171.
This brilliant review reminds readers of a shameful episode in the history of genetics in which the Austrian scientist, Paul Kammerer, was persecuted by the scientific establishment for his unorthodox ideas about the influence of environmental changes on inherited characteristics.