

Anne McLaren - a tribute from her research students

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Anne McLaren is an exceptional scientist. Her research students have benefited greatly from her professional example and her very special personal qualities. In Edinburgh during the 1960's and 70's, Anne supervised nine graduate students. We wish to add our tribute. She was liked and admired by all of us and we think ourselves very lucky to have been her students. Her particular blend of encouragement, criticism and help has guided us ever since we entered her orbit.

We were in many ways a motley bunch, coming by diverse and unconventional routes to Edinburgh, but we were all united by working on mice. The first to arrive was Eric Bell, who came from America in 1965 with an Arts degree from Oberlin and a Veterinary degree from Pennsylvania. Involved with a summer research project, he read one of Anne's papers and decided he wanted to do a PhD with her. He obtained a National Institute of Health grant and Anne took him on. Initially his project, which had started in the States, was to determine whether the reproductive tract could synthesise antibody to sperm and other antigens. He found infertility occurred in females after immunising them to whole and individual antigens and that the antibodies produced prevented sperm from fertilizing ova in the fallopian tube - an observation that Anne had made earlier.

Eric Bell was introduced to 'The Ford Hut' where most of us were housed. He remembers this prefabricated structure. "It was constructed with funds from the Ford Foundation and was intended for temporary accommodation for a couple of years. It was con-

structed literally over a weekend. It's wooden floors and walls, exposed wall sockets and electric fires would nowadays send the Health and Safety people berserk." The hut was partitioned into small individual spaces with a communal area at the end, containing jointly used scientific equipment.

Here we lived and worked, did our experiments, wrote our theses, had coffee and tea together, entertained visitors and socialised. Anne provided for us a wonderful place to work giving us the rare combination of privacy and easy access to colleagues. She extended this admirable mixture into all her relationships with us. As Terri Hargraves puts it "she set us limits and clear boundaries, a sense of closeness without invasion of privacy."

The next four students came, approximately at the same time in the sixties. The first was Colin Hetherington who arrived with a degree in Agricultural Science from Nottingham and a diploma in Animal Genetics from Edinburgh. He walked into Anne's room one day and asked "What's on offer?" The next three years were spent studying the formation of deciduomata and placentation.

Next was Peter Grant, who came with degrees in Veterinary Sciences from Queensland and Massey. During a research project on the hormonal control of implantation he corresponded with Anne. He already had an offer of a place to do a PhD but, as he recalls, "Anne's clear, friendly and well-written letters prompted me

Abbreviations used in this paper: B.Sc., Bachelor of Science; Ph.D. Doctor of Philosophy.

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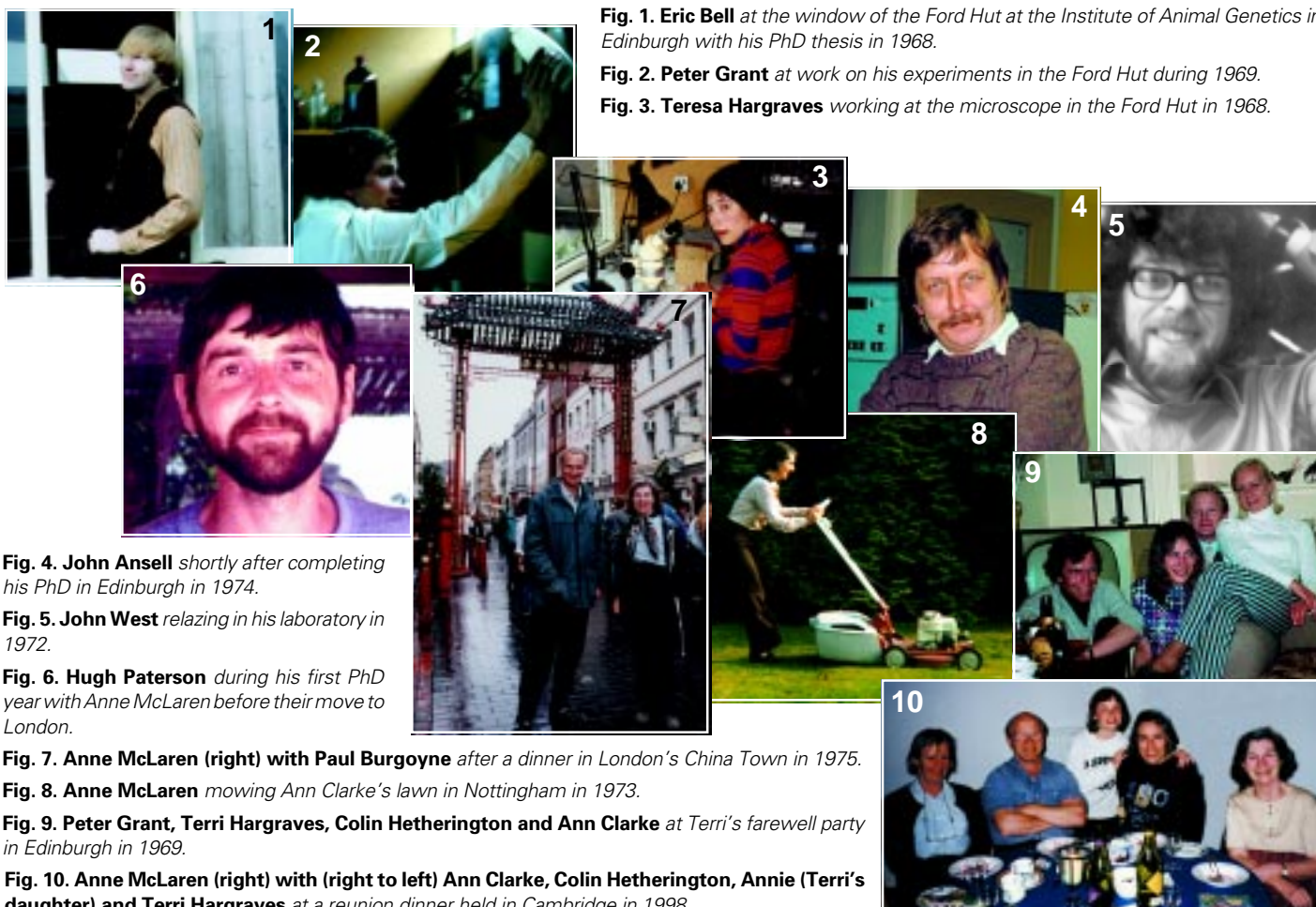


Fig. 1. Eric Bell at the window of the Ford Hut at the Institute of Animal Genetics in Edinburgh with his PhD thesis in 1968.

Fig. 2. Peter Grant at work on his experiments in the Ford Hut during 1969.

Fig. 3. Teresa Hargraves working at the microscope in the Ford Hut in 1968.

Fig. 4. John Ansell shortly after completing his PhD in Edinburgh in 1974.

Fig. 5. John West relaxing in his laboratory in 1972.

Fig. 6. Hugh Paterson during his first PhD year with Anne McLaren before their move to London.

Fig. 7. Anne McLaren (right) with Paul Burgoyne after a dinner in London's China Town in 1975.

Fig. 8. Anne McLaren moving Ann Clarke's lawn in Nottingham in 1973.

Fig. 9. Peter Grant, Terri Hargraves, Colin Hetherington and Ann Clarke at Terri's farewell party in Edinburgh in 1969.

Fig. 10. Anne McLaren (right) with (right to left) Ann Clarke, Colin Hetherington, Annie (Terri's daughter) and Terri Hargraves at a reunion dinner held in Cambridge in 1998.

to ask if I could come to Edinburgh." Supported by her Ford Foundation Grant he studied the hormonal control of egg implantation which involved devising a system in which blastocysts invaded immature uteri in organ culture. He also looked at abnormalities in the offspring of mice treated with synthetic progestins.

Teresa Hargraves (nee Menke), known to all as Terri, was next. She came in 1968 as a Fulbright Scholar with a degree in Biology from Notre Dame in Indiana. One of her teachers had met Anne at a conference and recommended that Terri write to her. Terri recalls her first meeting with Anne "on my first night in Edinburgh she came to find me in a "bed and breakfast" where I was wondering nervously what tomorrow would bring. Through the door walked a very blue-eyed attractive woman in a red mackintosh. She came to welcome me into her life forever." Terri wrote home to her family about her research project "Dr McLaren has a hunch that carbon dioxide produced by the blastocyst lets the uterus know it is there. Then the walls of the uterus change so the trophoblast cells can invade, implant and form an embryo." For the next two years Terri studied carbon dioxide production by preimplantation embryos.

The last of the '1960's four', I, Ann Clarke (nee Jewkes) emerged locally from the Zoology Department in Edinburgh where I did a BSc degree. I was what today would be described as a 'mature student', a rare phenomenon in those days. This did not deter Anne. She came to a talk that I gave on my undergraduate project. She introduced herself and asked me if I would like to do

a PhD with her. Until then, I had no plans to do any such thing but I said "yes". Three months later a letter arrived from the Medical Research Council offering me a Research Studentship. My subject was the immunological interactions between mother and embryo. I studied the effects of maternal antibody against paternal antigens on embryonic and placental development. The ease with which I acquired this funding is an example of Anne's skills in organising things. Peter Grant recalls a similar experience. "I was on a grant that she had organised and it ran like clockwork. We were supported to go to scientific conferences, do extra courses, without any question. The administrative aspects of this part of my life went very smoothly, without my noticing them. It certainly has not happened since."

John Ansell arrived in Edinburgh in the early 1970's with, as he puts it "a not very good upper second class degree in Agricultural Sciences from Nottingham." The project Anne suggested for him was to study the early development of mouse trophoblast and its role in the immunology of pregnancy. He studied primary trophoblast development using the then newly developed iso-enzyme markers of cell lineage. He analysed the trophoblast endometrial interface, looking for cell-fusion between trophoblast and host in chimeras. He also studied immune responses to trophoblast antigens.

The next student, Paul Burgoyne, came from Portsmouth Polytechnic with an external BSc degree in Zoology from the University

of London. Although he was officially one of Dr Alan Beatty's PhD students, studying the inheritance of sperm dimensions, he also worked with Anne on her mouse chimeras. Anne taught him how to make these mice and he used her C3H - B6 mice to show that differences in the shapes of sperm were determined in the germ line.

John West arrived next, in 1970, after graduating from East Anglia in Biological Sciences. He had started a PhD at the Institute of Virology in Glasgow but was unhappy with the project. While there he went to a seminar given by Anne on her work with mouse chimeras and decided that this was what he wanted to do. He initially came to the Institute of Animal Genetics in Edinburgh as a research assistant to Professor Geoffrey Beale, later joining Anne to do a PhD. His project was to study the distribution of the two cell populations in mouse chimeras. There were no transgenic markers at this time so the distribution of cells could only be determined in a limited range of tissues. Study of biochemical variants allowed semi-quantitative analysis of other tissues.

Having completed a BSc in Genetics in Edinburgh, Hugh Paterson became Anne's last PhD student in Scotland. His project was to study the cause of death in embryos homozygous for the *lethal yellow* allele at the *agouti* locus. This later included two other recessive embryonic lethals, *oligosyndactylism* and *tail-short*. As he puts it "After a year in the notorious Ford Hut I migrated with Anne to University College in London for four more happy and enlightening years."

Anne was a model supervisor. We greatly appreciated her particular combination of ready help, an ever open door, and a knack of leaving us alone without interference. Eric Bell sums it up. "There is no doubt Anne was terrific. She taught by example. She was absolutely clear in her thinking and precise in conversation. She could see the larger picture and helped me to pull many diverse experimental strands into a unified project." In John Ansell's words "I couldn't think of a better beginning to an academic career". Peter Grant recalls how "she had a sharp, clear mind and normally only a small part of it was needed to keep me occupied. I would go to her room to talk about work, while she continued to look down a microscope, culture eggs, and transfer blastocytes. My news had to be extra good (or really bad) to stop her in her tracks." Terri Hargraves describes how efficient she was with her time "work sessions with Anne took about fifteen minutes. With terse surgical precision she cut through unnecessary detail, pruned away shabby thinking, exposed the crux of the matter and left one poised to ask the next question. She never wasted my time nor gave me the impression that I wasted hers."

Anne's particular brand of kindness and encouragement came, however, mixed with a tough streak. This aspect of our training is well expressed by Peter Grant "morning tea with Anne in the Ford Hut was enjoyable but also slightly intimidating. I remember her as a reserved yet approachable person who generally responded to conversations rather than initiating them. I was always aware of the given opportunity to make a fool of myself, as she had both a broad and a sharp mind and commented accordingly." Hugh Paterson recalls life in Anne's laboratory "even the most junior members of Anne's group were equipped with the latest top-of-the-line zoom dissecting microscopes for embryonic manipulation. On one occasion I had a chance to look down Anne's own elderly microscope that she used for her pioneering work on chimaeras. It was like peering through a diffraction grating, with the outlines of the

embryo only just discernible." Certainly the other equipment she used for the complicated and intricate manipulation of embryos always struck me as amazingly simple for the task - a pair of forceps, a pair of scissors and a pipette was all that seemed to be needed.

Probably our most rigorous training occurred during coffee after lunch, when informal chat would range over many topics including those of science. The utterance of a vague or incorrect statement was met by an immediate correction from Anne. It trained us to think before we spoke. It was invaluable. Terri recalls "there were limits and boundaries clearly communicated without words, and invitations clearly communicated with them."

Anne had a lasting effect on our scientific development. As John Ansell recalls "the influence of Anne on my ability to think about developmental biology and on how to 'do science' has been profound. She taught us not to be shy about serendipitous experiments, but at the same time to be rigorous in our experimental design and in the clarity of our thinking. She had, and still has, the most acutely developed and sensitive set of 'bullshit' detectors of anybody I have known. This meant that in her company as a PhD student and still now, sloppy thinking was something we were not allowed to do, and publishing weak or incomplete data didn't happen." John West remembers how "Anne used to encourage her students to try what we called her 'gosh experiments', experiments that were unorthodox or unlikely to work, but that would be extremely interesting if they did." I remember her wise advice when I was faced with the task of writing my thesis "only think about and write the next paragraph and forget the rest. If you think about the whole thing you will give up and go the pictures." I also recall a valuable piece of advice she gave me on how to allocate time when doing a piece of research "one third to do the experiments, one third for the analysis and the last third to write the paper." This has proved invariably true.

Our rigorous training, however, had some downsides. For example, a fear of publishing a paper before being absolutely sure of the data led to a tardiness in reporting our results. In my own case it has certainly led to fewer publications than average. There was always another experiment, to make certain of the data. I was surprised in later life to discover that this rigour was not universal in the scientific community. We had a training that the majority of today's PhD students do not enjoy. Anne's discipline combined with our freedom to follow where the science led us meant that we sank or swam on our own merits. Surely, this is the ideal way to prepare an individual for scientific independence.

Anne was a member of that honourable and rare breed of supervisors who did not routinely put their names on their research students' papers. She was occasionally persuaded to add her name but mostly did not. In one of my experiments Anne spent much time splenectomising mice for me but she declined to be an author of the paper. This generosity was deeply appreciated. The 29 papers that resulted from the work of her research students are recorded here. They also belong to Anne, and by rights should be included among her publications.

We worked hard but also had a lot of fun, much of it generated by Anne. As John West recalls "the whole lab met over coffee after lunch and chatted about life, the universe and everything - including work-related matters." This was an excellent way of keeping in touch. It was also as Terri Hargraves points out "a daily check that might have little to do with our science but more to do with the wider

or narrower world in which we lived." Eric Bell puts this well "although Anne was very efficient with her time she was always happy to see you, always encouraging, lively, warm with a good sense of humour and a mischievous laugh." John Ansell recalls an occasion typical of many. "Above all, time spent in Anne's orbit was fun, with legendary lunch times and an enormous array of visitors. One Polish visitor brought some excellent sliwowitz that had to be consumed over lunch, with an added experiment into the effect of such spirit on a Venus Fly-trap plant. It certainly triggered the trap." Peter Grant remembers our get-togethers in the Ford Hut; "She often had a twinkle in her eye, and I remember her amusement at some outrageous snippet one or another of us had produced". She acted "*in loco parentis*" for Terri Hargraves on her birthday, procuring an outlandishly spectacular birthday cake. It was brought by Anne triumphantly to the Ford Hut, unwrapped and duly consumed.

In Anne's sphere, research was not a 'nine to five' occupation. Eric Bell remembers weekends. "Saturday mornings were amusing, Anne would have her two daughters in the lab with her. As she concentrated on the microscope or on writing, the girls would entertain themselves in a competition. They would set a complicated sum and see who could get the answer first. The elder would work it out in her head while the younger would use an ancient mechanical calculating machine."

Anne didn't just look after our scientific development, she saw to our well-being elsewhere. In Terri Hargraves words "science was the matrix which brought us to Anne and the end product which we showed to the professional world. What really happened was so much more." Anne did things for us that did not need to be done. She watched over us. Peter Grant remembers how generous she was with her social support with "frequent parties at Anne's house". She organised these parties with ease. I remember once when the preparations started from scratch two hours before about 40 people were due to arrive. Her daughter came into the kitchen to ask a question about one of Shakespeare's plays. Anne dropped everything and gave her undivided attention for twenty minutes or so until the problem was solved. It was a lesson on the priorities of life. We were ready for the party on time. Anne launched Terri's musical career in Edinburgh (she is a superb singer and guitarist) "Anne advertised that I, among others, was entertaining with my guitar at her birthday party." From that moment her musical career took off. As John West writes "I was so impressed that Anne could find time to work at the bench, attend numerous meetings and spend time with her family, that I decided that there must be three of her." She expected us to do the same. Paul Burgoyne recalls "when later I was with Anne at the Medical Development Unit in London, and had by this time acquired three children, she would tell me off if I worked late into the evening and say I should be at home with my family."

Anne's influence on our lives was not just restricted to our years in Edinburgh. She has, of course, supplied us with the endless references for jobs, research grant and travel funds that are the unenviable tasks of supervisors. All such requests have been met swiftly, with great efficiency, and often in the face of unreasonably short notice. There has, however, been much more. We have variously been given things that have helped our progress; notifications of suitable jobs, ideas for relevant experiments, news of important findings. I have found that most of the successes of my scientific career have had, often unknown at the time, imputes from Anne. Her continuing support has extended beyond our scientific

prosperity. There have been long stays in her houses in Edinburgh, London and Cambridge. She has invited us to interesting functions in her colleges and elsewhere. She has mowed our lawns because they needed it, looked after our children for the same reason and been involved with us in innumerable other ways. When we have written to her with our various problems she has always written back with suggestions of another way out of our particular dilemma of the moment, with generous offers of practical help to overcome a current predicament, with a bolster to our confidence when we have doubted our worth.

As a direct result of the fascination engendered during our time with Anne, most of us have remained in the field of research, many in the areas of reproductive and developmental biology. Those who have not stayed primarily in research have either retained their links to it or have returned to it over the years.

Eric Bell has followed a career in mainline cellular immunology, first at the Wellcome Research Laboratories and then in Edinburgh as a Lecturer. He then moved as a Reader to Manchester University where he currently concentrates on understanding the cellular basis for immunological memory.

Colin Hetherington has continued to study the immunological aspects of pregnancy, amongst other projects. He is currently Scientific Manager of the Biomedical Services in the University of Oxford.

Peter Grant continued research into egg implantation at the University of Uppsala before returning to New Zealand. Since 1991 he has worked as a veterinarian in the Ministry of Agriculture with research interests in environmental and conservation issues.

I have followed a career in research and have continued to work on immunological aspects of pregnancy. My time has been divided between Nottingham University and The Babraham Institute in Cambridge where I am currently studying the role of the thymus in maternal tolerance to embryonic antigens.

Teresa Hargraves left to study medicine at John Hopkins with many returns to Edinburgh to continue her research with Anne on blastocyst metabolism. After many years practising as a paediatrician in the United States she has recently returned to research in clinical medicine.

After a postdoctoral post studying the immunology of pregnancy in horse and donkey hybrids, John Ansell returned to Edinburgh where his research interests lie in the biology of haematopoietic stem cells. Of his current position as Professor and Head of the Department of Oncology in the Medical School he says "Anne must bear a considerable part of the responsibility for this journey."

Paul Burgoyne continued to work on development using mouse chimeras, first in Harvard and Edinburgh before he rejoined Anne for the next thirteen years in the Mammalian Developmental Unit at University College. He is currently at the National Institute for Medical Research in London where he heads a laboratory working on Y chromosome functions in spermatogenesis.

John West first went to the States to work on mouse X-chromosome inactivation before returning to Oxford where he continued his research into development. He then also backtracked to Edinburgh where he is now a Senior Lecturer in the Department of Biomedical Sciences, working again on mouse chimeras as he did during his time with Anne.

Hugh Paterson went to the Imperial Cancer Research Laboratories in London to study the biochemistry of the embryonic

defects he had worked on during his PhD. He then moved to the field of signal transduction, eventually coming to the Institute of Cancer Research where, as he puts it, "he indulges his fascination for microscopy and micromanipulation first developed with Anne."

The quality of Anne as a scientist and as a person is reflected in her role as a supervisor of research students. This story of what she did, and still does for them is a measure of her many talents. In Terri Hargrave's words "she was our role model: scientist, mentor, friend, mother, and now grandmother!" Her students from the Edinburgh days, wish to record our very warm affection and heartfelt thanks.

KEY WORDS: *Anne McLaren, tribute, graduate, students.*

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