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Mammalian development in the UK (1950-1995)

CHRIS GRAHAM*

Zoology Department, Oxford University, Oxford, United Kingdom

This is a brief history of mammalian developmental biology research performed in the UK. It attempts to identify the wishes of British society for developmental biology research, as expressed by politicians and refined by government funded research councils and charitable agencies. The response of the mammalian development community of scientists is analyzed and found to have diverse origins. The major research achievements originated from pure academic curiosity and very defined practical goals, with no obvious rules for making discoveries. During the period of this history, the scientists became more effective at influencing the wishes of British society.

Most British mammalian developmental biologists that have existed are alive, and they will have equally valid views about the sequence of events and seminal influences. From the mid-1960s on, the Society for the Study of Fertility and the British Society of Developmental Biology ensured annual contacts with workers in North America and Europe, and it is impossible to isolate a uniquely British contribution to the field. Instead, geographic location in Britain has set the limits to this economic, political, and scientific history. Achievements in reproductive biology and pure developmental genetics are mentioned when they impacted on developmental biology, but those subjects should write their own histories.

Stimulating funds and origins

Mammalian developmental biology in Britain owes much to nationals of other countries who visited for longer or shorter periods *(hereinafter names in italic)*. This flux of talent could have been promoted by the intellectual distinction of the UK. However, North American scientists attributed at least equal importance to avoiding the Vietnam war and free child birth on the National Health system, Commonwealth citizens felt it a duty to visit relatives in the 'home' country, and it took longer for scientific funding to build up in continental Europe.

The first 20th century pulse is inextricably mixed with the distinct ferments of derivatives from the Marshall school of reproductive physiology in Cambridge and Waddington's Institute of Animal Genetics in Edinburgh. Their programme was to improve farm animal breeds and breeding, and this practical goal generated new or neater techniques of super-ovulation (Edwards), embryo transfer (McLaren), and persistent but failed attempts to produce parthenogenetic mice and rabbits (Austin, Beatty, *Braden, Fischberg*, Edwards, *Pincus*; see Beatty, 1957; Austin, 1961). This dual origin inextricably linked academic mammalian embryology with genetics, physiology and the application of science: a powerful cocktail.

In the 1945-1965 period, the public became acutely aware of the dangers of nuclear weapons and the politicians' sop was heavy funding of mutation research, with the Medical Research Council (MRC) maintaining six centres of radiation biology, of which only MRC Harwell was to survive the cutbacks in the early 1970s. Practical goals, when left to scientists, often lead to fundamental discovery. A measure of the embryology:genetics link was that the Mary Lyon hypothesis of X-chromosome inactivation depended on

Abbreviations used in this paper: ARC, Agriculture Research Council; BBSRC, Biotechnology and Biological Sciences Research Council; CRC, Cancer Research Campaign; EC, embryonal carcinoma; ES, embryonic stem; ICRF, Imperial Cancer Research Fund; MRC, Medical Research Council; NIMR, National Institute of Medical Research; SRY/Sry, Sex-reversed Y.

***Address for reprints:** Zoology Department, Oxford University, South Parks Road, Oxford OX1 3PS, United Kingdom. FAX: 01865 271228. e-mail: chris.graham@zoo.ox.ac.uk

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events in the early embryo, and Bruce Cattanach's observations on paternal and maternal duplications gave the genetic seal to gene imprinting. An equally important consequence of radiation biology was the generation of mouse mutants, with the Medical Research Council (MRC) Harwell and the Jackson Laboratory linking to produce the free Mouse News Letter. The best descriptions of mouse developmental anatomy were in the analyses of mutants by the genetics group of Hans Grüneberg at University College, London, creating a tradition of meticulous anatomical description which achieved monumental proportions (Kaufman, 1992). The rich crop of mutants was decisive in nudging the British community towards adopting mice as the "E. coli" of developmental biology, particularly because British developmental biologists were slow to recognise the awesome power of *Drosophila* genetics.

Worries about radiation overlapped with and were soon supported by fears of over-population: the new imperative was to develop better methods of human birth control and to continue to improve farm stock productivity. For birth control, the scientists were allowed to set the agenda and state that fundamental knowledge was required about the metabolism of the mammalian conceptus. Money began to flow into Britain from the Ford Foundation, World Population Council, and the Lalor Foundation to top up the increased funding from the Agricultural Research Council (ARC, now BBSRC) and the MRC. The National Institutes of Health and the March of Dimes readily provided travelling fellowships for American citizens to postdoc in the UK and directly funded research in the UK. At a guess, North American funds probably doubled the active mammalian development research community in the UK from 1960-1980 and the money mixed up research workers with different national and scientific backgrounds.

The prelude

The prelude to mammalian embryology was played by Anne McLaren, first defining the best conditions for embryo transfer and then linking with Biggers to combine embryo culture with transfer (1958), thus opening up the pre-implantation window of opportunity for embryo manipulation and subsequent development to term. The final bars of the introduction were composed in the USA, where fertilised 1-cell mouse embryos were grown to the blastocyst stage and shown to be viable. The technique was quickly transferred by individual visits to the UK (Biggers, *Brinster, Whitten*; see Biggers, 1981; Hogan *et al.,* 1994). Everything was ready to launch an attack on mouse development.

The increased funding and the atmosphere of the swinging 60's created the freedom to just investigate the mouse embryo. It is odd that these possibilities were not noticed in the well funded centres of learning, and it was an isolated academic environment which started mammalian experimental embryology in the UK, following up Nicholls' brilliant spasm in the States. A visiting postdoc and a PhD student were based in Brambell's department in Bangor on the wind swept coast of Wales: here Tarkowski tore off the zona pellucida, pushed denuded pairs of embryos together, and created the first experimental mouse chimaeras, and Wilson pioneered the use of injected lineage tracers to follow cell fate, together demonstrating that the mouse conceptus was robust and experimentally tractable. Ever sensitive to competition, Cambridge, Edinburgh, and Oxford joined in when they noticed what had happened. The state of play at about this time can be gauged from a Ciba Foundation meeting (Wolstenholme and O'Connor, 1965).

Mouse embryology

Cambridge contributed with the appointment of a self-effacing professor with broad interests to the Darwin chair of Animal Embryology. Bunny Austin fronted for two lecturers, Bob Edwards and Denis New, and sponsored a remarkable aggregation of research students and postdocs, each beginning with a subject apparently unrelated to mammalian development: Richard Gardner on sexing rabbit blastocysts, Martin Johnson on sperm antigens, Dave Whittingham on the metabolism of the preimplantation embryo, and Azim Surani on mouse protein synthesis. Gillian Morriss-Kay in Anatomy carried forward Denis New's work to analyse teratology with cultured post-implantation stages. Each of these scientists was to head distinct mouse developmental biology groups for at least 15 years. What sets these individuals apart from others in the UK is that they were not diverted by talk of other model systems, such as teratocarcinoma: they stuck closely to the embryonic material and could thus analyse what really happened. They also differed from their scientific offspring because they were able to pursue productive careers in the UK.

Three fundamental features of mouse development were exposed by this laboratory's protégés. First in time, was cell fate and cell commitment of the two cell populations of the blastocyst. Second was the detailed investigation of the cell and molecular biology events which preceded the divergence of these two populations: arguably, this is the best study of the origins and consequences of asymmetric cell division in any developing system. Third was the analysis of gene imprinting which has more to do with developmental genetics (later section).

The first study had the greatest impact on both developmental genetics and embryology because the techniques could be used to introduce single cells into the blastocyst for further development, and it thus provided one of the tools for the current gene manipulation techniques which inform about mouse development and much else besides.

Gardner and his colleagues brought their skills to Oxford, but their lineage analysis could not flower until there were good markers. These were provided by somatic cell genetics. Somatic cell genetics required clear electrophoretic differences between the isozymes of mouse and man, and one source of this variation were the inbred strains of mice: isozyme variation between strains was to become the only cell marker for the first ten years of lineage studies. During a one year postdoc in Anne McLaren's laboratory in Edinburgh, *Verne Chapman* from Frank Ruddle's group in the States, visited most mouse development groups in the UK, demonstrated the techniques, and persuaded all to adopt isozyme markers. Combining clever and intricate micro manipulation with isozyme analysis, the time of commitment and colonisation behaviour of the emerging extra-embryonic layers of the conceptus could be defined in detail by Richard Gardner, Janet Rossant, and *Ginny Papaioannou*. An early lineage map of the post-implantation embryo was brought out of the same Oxford school by Rosa Beddington. In Edinburgh, Anne McLaren's group conducted detailed analysis of cell mixing and lineage in aggregation chimeras and *Verne Chapman's* visit defined the role of cell fusion in trophoblast giant cell formation.

At this time, most groups combined embryology with reproductive physiology, and often the same person would be working on embryology and subjects such as the signals which elicited implantation, or the biochemical analysis of uterine secretions, or

the metabolism of the embryo, or gametogenesis. Few group leaders regarded mammalian developmental biology as a mature full time subject and needed a second subject to maintain funds for their laboratory. These mixed aims of the international and UK mammalian development community are reflected in edited texts and proceedings of meetings (Raspé, 1970, 1971; Balls and Wilde, 1975; Elliott and O'Connor, 1976; Rossant and Pedersen, 1986; McLaren and Siracusa, 1987). The first prestige group in the world to concentrate most of its effort on mammalian developmental biology was probably Francois Jacob's at the Pasteur Institute in Paris: it provided an example of the virtues of concentrated effort which influenced future UK scientists (who tend to be individualists).

Farm stock embryology

It is difficult to accept that farm stock embryology was not only keeping up with advances in mouse work but was sometimes doing better. At the Agriculture Research Council's Animal Research Station in Cambridge were the pioneers of the following techniques in domestic species: sperm and egg freezing, *in vitro* fertilisation, embryo transfer, and the maturation *in vitro* of fully grown oocytes for fertilisation. The most exotic product was a sheep-goat chimera. The developmentally important demonstrations were totipotency of single blastomeres from 8-cell stage sheep and triplets from a quartered cow 8-cell stage (Chris Polge, *Steen Willadsen*). The mouse could not match these achievements and there was a clear hint that some things might be better done with big creatures, as was finally proved by successful nuclear transfer and cloning of live sheep using nuclear donors from the 8-cell stage (*Steen Willadsen*; see Papaioannou and Ebert, 1986 for summary). However, mouse embryologists did not follow these leads and put on their gumboots, and the Research Council responded to these successes on the farm by absorbing and then closing down the Animal Research Station.

Developmental genetics: techniques

If the mouse was to be the 'E. coli of developmental biology' then its large genome was a problem. Further, the mutants from radiation studies did not give an immediate guide to a gene or a biochemical property which influenced development. The next phases of developmental genetics now became dependent on advances in molecular and cellular biology.

Somatic cell genetics had provided the technique for mammalian nuclear transplant (cell fusion) and it now contributed methods for selecting mouse genetic mutants in culture. Many became diverted from the true path of mouse developmental biology when somatic cell geneticists also announced that all problems in mammalian development would be solved with mouse embryonal carcinoma (EC) cells and the fusion of various differentiated cell types: cancer growth would now be regarded simply as a failure to differentiate (articles in Sherman and Solter, 1975). The immediate consequence of these dubious insights was that the major cancer charities, Cancer Research Campaign (CRC) and Imperial Cancer Research Fund (ICRF), began to substantially fund mouse development, and John Cairns' ICRF laboratory acquired Brigid Hogan for mammalian studies. Grant applicants pursued the tantalising mirage of cancer cure by differentiation therapy in the period 1970-80. Much information was gathered about vitamin A derivatives, their receptors, and the DNA binding sites of the ligand receptor complexes: all this subsequently contributed to an analysis of vertebrate limb development and of mouse *Hox* gene expression, particularly in the nervous system *(Rob Krumlauf)*.

Despite visits from *Roy Stevens, Barry Pierce*, and *Davor Solter*, UK scientists had failed to notice the potential of embryonal carcinoma cells. In turn, Martin Evans and Martin Hooper visited Boris Ephrussi's laboratory in France and learnt about his laboratory's culture work with mouse teratocarcinomas. Martin Evans and *Gail Martin* established protocols for maintaining the multipotentiality of the EC cells in culture (feeder cells) and then differentiating the cells in mass culture (bacteriological dishes); EC cells were established as good mimics of early development which could be handled for bulk production and differentiation. The system was quickly exploited for the analysis of these cells antigenic, biochemical and genetic differentiation and these markers were mapped into the mouse conceptus (Adamson, Barlow, Chada, *McBurney*, Stern).

Unfortunately, heroic efforts to make embryonal carcinoma cells contribute to the germ line failed (Evans, Gardner, *McBurney*, *Papaioannou*, Stewart). However, the strategy of manipulating cells in culture and then returning them to the blastocyst had been established and it remains the essential technique of mouse developmental genetics.

It was to be another ten years before embryonic stem cells were produced by the original pioneers of cultured EC cells and arenas of biology and biotechnology depend on their start. The first embryonic stem (ES) cells in the UK were a bye-product of Britain's historic interest in parthenogenesis (see above). Matt Kaufman made enlarged haploid parthenogenetic and normal fertilised blastocysts by holding embryos in ovariectomy delay, and Martin Evans suggested their culture: they found that both the normal fertilised and the diploidized parthenogenetic blastocysts grew well on the feeder cell system previously introduced for EC cells and the vehicles for carrying *in vitro* generated mutations back into the germ line had been found.

It was the Martin Hooper and Martin Evans laboratories which were to get the first mutant ES cells, selected in culture, to contribute to the germ-line and produce viable offspring. Liz Robertson, Alan Bradley, and Robin Lovell-Badge began their research careers in Martin Evans laboratory in Genetics, Cambridge and made potent use of this blend of mutation and selection.

The last technique, injection transgenesis was again contributed by Frank Ruddle's laboratory in the States. *Frank Constantini* and *Liz Lacy* heard of Jon Gordon's work on injection transgenesis, quickly junked the programmes of their visiting fellowships at Oxford (nuclear transplant), visited Jon Gordon on their Christmas holidays, and began the work which was to lead to the expression of the first transgene which stably transmitted and expressed under its own promoter.

Developmental genetics of germ cells, X-chromosomes, and gene imprinting

From the mid 1970's, most major molecular biology groups in the UK also worked on mouse development and most recently cloned mammalian genes had their developmental profile analysed in the mouse. The subject became both dispersed and in the main stream of molecular biology. Achievements are now attributed to groups rather than individuals.

McLaren's MRC Mammalian Development Unit (1974-92) became the London hub of efforts to understand sex determination and X-chromosome inactivation. First, somatic gonadal sex was shown to be paramount in determining germ cell sex in bizarre genotype combinations which were made in experimental chimeric mice. Second, the determinant of testis characters was fine mapped on the Y, separating it from the H-Y antigen and picking up a mutation which disrupted its effect (the mutation originated during random viral mutagenesis of ES cells). All this led to the cloning of the human and mouse genes *(SRY/Sry)* which were sufficient as transgenics to convert females to the male gonadal sex (groups of Peter Goodfellow at the London ICRF Laboratories and Robin Lovell-Badge at the MRC National Institute of Medical Research, NIMR).

This London MRC Unit also traced the expression of X-chromosomes during gametogenesis and defined the global changes of methylation which the genome encountered during early development, work which was later to impress on both X-chromosome inactivation and gene imprinting (Marilyn Monk). The final analysis of the X-chromosome inactivating centre depended on the MRC laboratories at the Clinical Research Centre (group of Sohaila Rastan).

Britain's prolonged and frustrated efforts to make parthenogenetic and polyploid mammals were finally terminated by a careful analysis of the demise of tetraploid mice (Snow) and the demonstration that sperm and egg pronuclei could not substitute for each other in maintaining normal mouse development (Surani). Relieved of this burden, the detailed molecular analysis of the mysterious process of gene imprinting prospered, initially at Babraham, Cambridge (groups of Azim Surani and *Wolf Reik*).

Developmental genetics: the comparative approach and the nervous system

Unfortunately, a working knowledge of the lineage, a 1000 or so mutants of the mouse genome, the availability of embryonic stem cell vehicles for carrying selected metabolic mutations into the germ line, and numerous markers shared by embryonal carcinoma and inner cell mass cells did not give instant access to the genetic and cellular control of developmental events. The older group leaders (above) could not immediately sink their pride and borrow and steal from fruit fly development and the emerging molecular embryology of frogs. The next British generation had no such inhibitions, pulled out the mouse homologues, inactivated them by homologous recombination, and monitored the consequences. Lacking adequate funding and with posts blocked by their progenitors, they migrated on mass to North America, consummating abroad the drawn out engagement of mouse genetics and embryology. In short, many UK scientists now had to work in North America, Austria, France, Germany, and Holland to get the opportunity to understand the experimental embryology in molecular terms. A diaspora of UK mammalian developmental biologists tracked funding around the globe, rather as oil workers congregate around newly discovered oil fields.

The following generation in the UK has a different programme. The funding motive is to deal with the next economic pressure: the cost of maintaining mentally disabled children and senile adults on a state funded welfare system (medicine and living expenses). This programme is the complete unravelling of developmentally important events in the mammalian nervous system.

The major centres are currently the MRC NIMR at Mill Hill, MRC Harwell, and Andrew Lumsden's laboratory at Guy's. The Mill Hill groups did not emerge from any old tradition and they brought a fresh molecular biology drive to the mouse. Brigid Hogan and her first associates, *Rob Krumlauf*, Peter Holland, and Andy McMahon were and are committed comparative developmental biologists and there is no longer any sense of a mammalian developmental biology which is distinct from that of other vertebrates. Frequently, a *Drosophila* gene will be found to have a developmental function, and then the most similar gene in mouse, frog, and chick will be isolated: in the mouse, the gene will be knocked out, in the frog it will be over expressed, and in the chick it will be over-expressed in a limited site by grafting. Wonderful debates began about the meaning of homology, recreating the musty atmosphere of late 19th century comparative embryology.

Comparative developmental and cellular biology had become the mode and this fashion required developmental biologists to crowd together. The single university lecturer with two research students had been replaced with institutes, copying the Pasteur's example. NIMR and the CRC/Wellcome Institute continue to flower, while the ICRF Developmental Biology Unit at Oxford had an equally productive but briefer summer, eventually scattering its group leaders to ICRF London, Bath, and Sheffield and its pupils across the world. Not to be out done in the drive for size, MRC announced that all funded 3 year project work should be pursued in crowds of grant holders. The early mammalian developmental biologists who failed to aggregate quickly turned their research to practical clinical projects.

Did the man and woman in the street get their money's worth?

The current view of all political parties in the UK is that current science should be of service to industry and society in a short span of years. Did the scientists provide this service to Britain in the second half of the 20th century?

Probably the greatest service to society is human *in vitro* fertility clinics. Not only was the technique pioneered in the UK but most successful programmes now have a post-doctoral embryologist trained in a mouse laboratory. Further, the techniques of pre-implantation diagnosis by single cell biopsy were developed in regular mouse developmental biology laboratories before translation to the clinic, with the MRC Mammalian Development Unit in London playing a prominent part (Marilyn Monk, Andy McMahon).

The British public did get something less tangible. They obtained greater insight into the origins of their bodies in development: pictures of fertilisation and the first few days of human life, comprehension of the genetic mistakes which cause particular childhood abnormalities, and an extension of their vision of human origins. Mammalian developmental biologists had been forced to become political during the House of Commons debates on *in vitro* fertilisation and on the times when observations could be made on the human conceptus (up to 14 days after *in vitro* fertilisation). They had sat on the Warnock committee which had devised the principles and practices which were the basis of the government's bill, they had lurked in the Commons passing speech notes to sympathetic Members of Parliament (MPs), they had arranged for local MPs to visit each *in vitro* fertilisation clinic, and they had briefed the Prime Minister (Margaret Thatcher). In short, mammalian developmental biologists had learnt to explain themselves.

The country and scientists benefited by a paradoxical combination of tight regulation and hot debate. Animal and human embryo

research is very highly regulated whatever the source of funds, with each procedure requiring a licence and open to inspection (Animals [Scientific Procedures] Act 1986, administered by the Home Office; Human Fertilisation and Embryology Act 1990, administered by the Human Fertilisation and Embryology Authority). With these legal restrictions in place, an informed public and media vigorously debate the ethical issues but no pressure group has yet limited the clinical application of the science or prevented academic progress in animal research: scientists are harassed and threatened but not killed.

Did British industry increase their profits as a consequence of developmental biology discoveries? Probably not yet. This is partly because established British industry has an even shorter term view of research than the political parties and also because a generation of group leaders have left the UK to work abroad. It is also because there is little intellectual exchange between industry and academics. For instance, which company has invested in new methods of teratology testing using either differentiating embryonic stem cell cultures, or post-implantation embryo culture, or culture of individual organs? All these techniques could provide preliminary screens of new compounds.

Did the farmers and horse breeders benefit? The Animal Research Station at Cambridge had given them the techniques for freezing eggs and sperm and it is hard to imagine any current farm stock or horse breeding programme which does not rely on these techniques. Farmers got their money's worth. This research station had also produced the first sheep cloned by nuclear transfer, and this technique holds potential for their prosperity in the future.

Arguably, the most successful transfer to the market has been achieved by the Roslin Institute near Edinburgh where related companies produce transgenic protein products in sheep's milk: venture capital funded and currently eases progress with nuclear transplant at the institute. However, the British disease of being in at the start but failing in the market place is still too evident in developmental biology, as in other branches of science. For instance, the announcement of successful development of a sheep, after the transfer of a nucleus from an adult, coincided with the substantial withdrawal of funds from the Roslin Institute by the Ministry of Agriculture, Food, and Fisheries (MAFF).

Was any mammalian developmental problem solved?

There is a sense in which developmental biologists have danced around the problems of mammalian development but have never kicked answers out of them. For instance, can anybody produce the complete circuit of genetic interactions which lead to the formation of the trophectoderm layer of the placenta? This structure defines placental mammals and is of obvious medical importance.

The prominent block to progress is that a knowledge of the form and function of every mouse homologue of every fruit fly and frog gene is unlikely to inform about the features of mammalian and human development which are peculiar to these species and to the clinical problems of reproduction. Or are we shackled by ancient thoughts about the independent invention of extra-embryonic membranes in different phyla? Will it turn out that the amnio-sclerosa of the fly is a good guide to the development of the mammalian extra-embryonic membranes?

The wisdom of the age is that the Human Genome Project must provide the candidate genes for functional analysis in the mouse. Or will the mouse still drive the field? After all it was a random mutagenesis study which threw up a sex-reversed mice, parent of origin effects on gene expression, and which also contributed to the understanding of sex determination. Scientists use rational arguments to predict future discovery but they rarely do better than those who gaze into crystal balls.

KEY WORDS: *parthenogenesis, nuclear transfer, imprinting, transgenesis, embryonic stem cells*

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References

Working scientists are poor historians and frequently rewrite history. They tend to reveal themselves in rapidly written articles for symposia, which expose the temporary preoccupations of the mammalian development community. The following references provide a guide to moments in the progress of mammalian development, and monitor who was meeting who as the subject started. The list makes it clear that mammalian developmental biology has always been an international subject.

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