Int. J. Dev. Biol. 44: 5-8 (2000)

The recent development of development in Britain

JONATHAN M.W.SLACK*

Developmental Biology Programme, Department of Biology and Biochemistry, University of Bath, Bath, United Kingdom

In recent decades Britain has been an important international centre for developmental biology research. Today there are literally hundreds of principal investigators in the field with significant positions on the world stage. There are thousands of workers altogether if you include all the postdocs, PhD students and research assistants. For this reason alone it is quite impossible to mention everyone who has made a significant contribution to British Developmental Biology. In what follows, I shall just describe things as I saw them myself. My account should not in any way be regarded as an attempt to assign credit or ascribe importance in any sort of objective way. It is simply a biased, individual, personal perception. Further comments on the motivations, aspirations and *modus operandi* of life scientists, particularly developmental biologists, can be found in my book "Egg and Ego" (Slack, 1999).

Britain participated in a small way in the pre-Second World War phase of experimental and biochemical embryology, mainly through the work of Waddington (Cambridge, then Edinburgh), and Needham (Cambridge). But the problems of development became somewhat eclipsed in the 1950s and 60s by the early growth of molecular biology. Somehow, the solution of the problem of inheritance seemed to make the problems of development disappear. One of the few well known British developmental biologists active in the 1960s, John Gurdon (Oxford, then Cambridge), extended the amphibian nuclear transplantation experiments of Briggs and King, and was able to obtain development at least as far as the early tadpole stage from nuclei of fully differentiated cells. This result rapidly became featured in chapter 1 of all developmental biology textbooks, as it confirmed the general belief that all the genes persisted in somatic cells and that development was therefore essentially a matter of differential gene regulation. For this reason, most people interested in development in the 1970s felt that they should study simple examples of gene regulation, such as the expression of globin in red blood cell precursors or of ribosomal RNA from the ribosomal genes. This was the period of my own PhD and although I was supposed to be interested in development, the prevailing climate meant that my work at the time actually consisted of structural studies on ribosomal RNA.

Once molecular cloning was invented in the 1970s, most people interested in development threw themselves with great enthusiasm into the molecular biology boom, during which the techniques were invented that everyone now uses every day. For example, my colleague Jeff Williams (ICRF London) carried out the first differential cDNA screen on a developing system. Although the techniques did later become of enormous importance for solving biological problems, at the time, this style of work led to an obsessive concern with technicalities and so prolonged the period of low profile for developmental biology. Outside the mainstream, there were just a few people on the fringes who were working in developmental genetics or experimental embryology. Their work, along with the

Abbreviations used in this paper: NIMR, National Institute for Medical Research, London; KCL, King's College, London; UCL, University College, London; ICRF, Imperial Cancer Research Fund, London.

***Address for reprints:** Developmental Biology Programme, Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, United Kingdom. FAX: 44 1225 826779. e-mail: j.m.w.slack@bath.ac.uk

0214-6282/2000/$20.00

Printed in Spain
www.ehu.es/ijdb

new molecular technology, helped to lay the basis for the later explosive growth of molecular developmental biology in the 1980s.

One of these was Lewis Wolpert (Middlesex Hospital London, later UCL), in whose lab I was privileged to spend 2 years as a postdoctoral fellow. His enormous enthusiasm and magnetic personality drew our attention toward the old problems of experimental embryology, most of which had lain unsolved for many years, and seemed to me much more interesting than the minutiae of how to make a library or how to get a primer extension reaction to work. Wolpert had spent some time working on the regeneration of *Hydra*, but recently moved to the chick limb, which he considered to manifest all of the problems of development in one readily accessible organ. The great Francis Crick had recently applied a small portion of his intellectual powers to development and published two influential papers on the physics of diffusion gradients. These had a strong effect on the Wolpert lab members, who were trying to update the older and less precisely specified embryological gradient concept. Cheryll Tickle was already in the lab and, while I was there, she carried out the basic embryological experiments on the zone of polarising activity that have set the scene for much of the subsequent work on limb development in the last 20 years. At the time, it was thought that inductive signals travelled through gap junctions and the gap junction patterns of many embryo types were mapped by Anne Warner (UCL).

Another member of the fringe was Peter Lawrence (Cambridge), who also worked on gradients and who helped to popularise and extend the work of the Spanish *Drosophila* group on compartments and selector (=homeotic) genes. Cambridge has long been a centre for *Drosophila* research and in this period much of the technology and intellectual stimulation was due to the activity of Michael Ashburner. Another organism, and one that was entirely domesticated in Cambridge, was *Caenorhabditis elegans*. Sydney Brenner had started work on this small nematode back in the 1960s, initially with the hope of understanding the functioning of an entire animal nervous system using genetics. During the 1970s the small worm group kept going, although at that time most of the seminars seemed to consist of being told for 55 minutes what a wonderful organism *C. elegans* was, followed by 5 minutes of preliminary results. In more recent times, *C. elegans* has, of course, justified the efforts of these early workers and generated many interesting results, particularly on the mechanism of cell death and of unequal cell division.

The 1970s were a most interesting time because, in addition to these various pieces of work that were in progress, there was extensive debate about what sort of explanation was required for developmental phenomena, or more particularly those of regional specification exemplified by "gradient-like" and regulative behaviour. Those who worked on topics such as the regulation of globin expression, felt that gradients were just vitalistic nonsense and that you had to study things that were comprehensible in molecular terms and could be investigated using existing techniques. Others, including myself, who had less understanding of the impending power of molecular biology, felt that an acceptable explanation could be achieved through theoretical models, or through genetics, and that the complexity of development might defeat any attempt at a molecule-by-molecule approach. Although the school I supported turned out to be wrong, we did at least revive experimental embryology and turn some of its problems into a form suitable for molecular analysis. Interestingly, one rather abstract model of those days, formulated by Jonathan Cooke (NIMR), was the "clock and wavefront" model for somitogenesis. Largely forgotten for 20 years, this has recently been revived in a molecular form and seems to be essentially correct.

A typical product of the 1970s was the "polar coordinate" model to explain regional specification during regeneration. This was formulated by Vernon French (NIMR, later Edinburgh) together with Sue and Peter Bryant (UC Irvine). It explained the regeneration of insect and vertebrate appendages and was uncompromisingly non-molecular, being a higher level formalism faintly reminiscent of Ptolemaic astronomy. The model has been in eclipse for many years but may soon be explained in molecular terms now that *Drosophila* imaginal disc development is becoming understood in molecular detail. Another mysterious gradient-like phenomenon was the formation and regeneration of the nerve connections between the eye and brain of lower vertebrates. This was studied by Mike Gaze (NIMR, later Edinburgh). Again, this work was completely non-molecular but it laid the basis for the recent work in which these processes have been explained as interactions of the Eph-ephrin system.

Slightly to one side of the debate about types of explanation lay the important work on mammalian genetics and development. Richard Gardner (Cambridge, later Oxford), in a remarkable PhD of the late 1960s, introduced a method for the injection of cells into the mouse blastocyst. He went on to use this to establish the basic steps in early determination of the mouse embryo, assisted by Janet Rossant, Rosa Beddington and Virginia Papaiannou, all of whom later became important mammalian embryologists in their own right. The microsurgical techniques perfected by Gardner would, later, be essential for the creation of knockouts. Meanwhile, closer to the molecular biology mainstream, the laboratory of Chris Graham (Oxford) was doing some of the first experiments on transgenesis, by injecting DNA directly into mouse eggs.

Britain has a strong tradition of mouse genetics and the essential facts of X inactivation had been deduced in the 1960s by Mary Lyon (Harwell). Also at Harwell, Bruce Cattenach did the complex genetic experiments proving the existence of imprinting, the phenomenon whereby some genes are expressed from only one of the parental chromosomes. Anne McLaren (UCL, later Cambridge) exploited the power of genetic mosaics to analyse various developmental phenomena, such as pigmentation patterns, muscle development and germ cell differentiation. Using more embryological methods Martin Johnson (Cambridge) worked out that the first step of cell commitment in the mouse embryo involved a polarisation of cells. In 1981, ES cells were isolated by Martin Evans and Matt Kaufman (Cambridge, later Cardiff and Edinburgh respectively). They were simultaneously discovered by Gail Martin in the USA, and have of course been essential tools for the knockout technology of recent years. Britain is also the home of human *in vitro* fertilisation, originally put into practice by Patrick Steptoe and Robert Edwards at an ordinary hospital in Oldham, Greater Manchester. Research on the developmental mechanisms of human embryos themselves have not advanced much because of the ethical problems of doing research on human material, and the necessary legal constraints that arise from such concerns. However, the high level of homology of developmental processes that has been discovered in recent years suggests that much of what is learned from mouse, chick, *Xenopus* and zebrafish will also be true for the human embryo.

The early 1980s were the dawn of the molecular era. The real breakthroughs that initiated modern molecular developmental biology came initially from the cloning of developmental genes in *Drosophila*. Most of these had been identified in the mammouth mutagenesis screens of Janni Nüsslein Volhard, and some were already known from Ed Lewis' work on the bithorax complex. Of course, none of this occurred in Britain, it was very much a German and US enterprise. But British scientists became active in this area in the early 1980s. For example, Michael Akam (Cambridge) used the new technique of *in situ* hybridisations for mRNA to show the region of activity of a homeotic gene: *Ultrabithorax* (*Antennapedia* was done simultaneously in Walter Gehring's lab in Basel). In the 1970s, the idea of the "domain of action" of a homeotic gene had been an extremely abstract concept only understood by the most advanced adepts of developmental genetics. Once *in situs* started, you could see domains of gene action down the microscope, and everyone could understand easily what was going on. During the latter half of the 1980s there was a mad rush to clone all the interesting developmental genes from *Drosophila*. Much of this activity was in the USA, but in Britain, *hairy* was cloned by David Ish Horowicz and *hedgehog* by Phil Ingham, both colleagues of mine at the ICRF Developmental Biology Unit in Oxford.

It was also a time when the mysterious "morphogens" started to acquire a chemical reality. The first to hit the headlines was retinoic acid, although its endogenous role is still under debate. Its effects on limb development were initially noticed by Niazi in India, but they were fully investigated by Cheryll Tickle for the chick limb and Malcolm Maden (NIMR, later KCL) for the regenerating amphibian limb. There was also the DIF factor from slime moulds, isolated by my colleague Rob Kay (ICRF London, then Cambridge). I like to feel that the rise to prominence of *Xenopus* in the 1980s was partly because of the work of myself, then at Oxford, and of Jim Smith (NIMR) who identified the first pure inducing factors of animal embryos, respectively FGF and activin. These factors have both turned out to be prototypes for a wide range of inducing factors important in many developmental systems. *Xenopus* research in Britain was also greatly strengthened by the continued activity of John Gurdon, who had also turned his attention to mesoderm induction, and of Chris Wylie and Janet Heasman, (London, then Cambridge, then Minneapolis), who invented the antisense ablation method for maternal mRNA. Meanwhile, Brigid Hogan (NIMR, later Vanderbilt) had been laying much of the basis for the molecular biological study of the mouse embryo, and Claudio Stern (Oxford, later Columbia) subsequently did a similar job for the chick embryo.

The late 1980s produced two other influential results from British developmental biologists. Andrew Lumsden (Guy's, London) revived the rhombomeres from their nineteenth century limbo and showed that they were real units of CNS development in terms of cell lineage and domains of gene activity. Robb Krumlauf (NIMR, London), along with Denis Duboule (EMBL, later Geneva), discovered the celebrated colinearity of *Hox* genes in mice and *Drosophila*, indirectly proving the monophyly of all animals and initiating an international boom in "Evodevo" that is still gathering momentum. An important landmark of evodevo was the analysis of key developmental genes of Amphioxus by Peter Holland (Oxford, then Reading), showing that vertebrate evolution has been accompanied by numerous gene duplications. In the early 1990s, the *SRY* gene was isolated by Peter Goodfellow (Cambridge) and Robin Lovell Badge (NIMR), a decisive step in the understanding of the mechanism of mammalian sex determination. Work on *Drosophila* continued to be filled in, notably an understanding of the anteroposterior pattern from Daniel St Johnston (Cambridge). Although we normally think of "developmental biology" as concerning the development of animals, there has also been activity in plant developmental biology. An important British worker in this area has been Enrico Coen (John Innes Institute) who discovered various genes controlling the basic pattern of flowers.

But as we entered the 1990s, the character of developmental biology was beginning to change. By then the molecular genetic revolution had become well established and many of the main problems of early regional specification had been solved. During the 1990s the subject has become mature, some might even say middle-aged. There is no longer any philosophical debate about the types of explanation required, and the number of workers involved in developmental biology research has increased by a factor of at least 10. Inevitably, the topics under investigation have become more detailed and the chances of making a big breakthrough correspondingly reduced. Some of the institutional developments mirror this change. The most extreme case is the Sanger Centre, set up by the Wellcome Trust as a huge factory for genome sequencing. One of its early successes has been the complete sequencing, under the leadership of John Sulston, of the genome of *C. elegans*, the worm originally domesticated in Cambridge thirty five years earlier. Reorganisations of London Medical Schools have produced large concentrations of workers, notably a centre at the Guy's campus of King's College with 20-30 faculty all working on developmental neurobiology. Large concentrations of developmental biologists, though less focused in research topics, have also been created at Cambridge (Wellcome/CRC institute), Edinburgh (Inst. Cell and Molecular Biology) and Dundee (Wellcome Building). These are all "research hotels", a new organisational species derived from American practice, in which the faculty members have their salaries paid not by the university but from their own research grants.

With the new millennium we are now entering a period in which the complete genome sequences will soon be available for all the standard model organisms, and nucleic acid chip technology will enable a comprehensive catalogue of gene activations and repressions to be documented for any physiological or developmental process. The nature of developmental biology will necessarily change from the opening of black boxes by a few eccentrics to high throughput screening procedures conducted by thousands of workers and costing millions of pounds. Such changes are neither good nor bad, they are inevitable and simply reflect the rapid growth of developmental biology and of related areas in the molecular life sciences.

Ironically, the most famous developmental biology discovery of the 1990s came not from this industrial scale activity, nor even from the mainstream developmental biologists themselves, but from the Roslin Institute, near Edinburgh, where Dolly the sheep was created by Ian Wilmut. This has created a never-ending media furore, with anxious speculation about human cloning or mad scientists creating a master race by genetic engineering. Apart from demonstrating the need to maintain public support for scientific research, this has shown that our politicians, as well as the general public, sorely need some basic biological background, such as understanding the difference between molecular cloning and the cloning of whole animals, or the difference between simple characters amenable to genetic alteration, and complex ones that depend both on numerous genes and on the environment.

It will be clear to readers that a remarkable number of the discoveries mentioned were made at London, Oxford or Cambridge. Indeed these places dominated the membership list of the British Society for Developmental Biology (BSDB) while I was secretary. Oxford regrettably seems to have decided that developmental biology has little future, as most of the former lab heads have now left without replacement, but Cambridge continues to be a leading centre. An important nucleus in Cambridge is the Wellcome/CRC Institute founded by Chris Wylie and John Gurdon. In London, the Department of Anatomy and Developmental Biology at University College has long been an important centre, and was incidentally the original home of the BSDB. King's College London was the location during the 1990s of the Developmental Biology Research Centre, created by Nigel Holder. This laboratory has now been fused with the departments of Guy's Hospital Medical School, and has moved to the Guy's campus. Tragically, Nigel Holder himself died shortly after becoming head of the department at UCL. Also in London are the National Institute for Medical Research, concentrating on basic developmental problems, and the Institute for Child Health, which specialises in problems with clinical applications. Provincial universities with significant developmental biology interests are Warwick, which has maintained a presence in the field for many years; Edinburgh, long an important centre for molecular biology; Dundee, with its shiny new Wellcome Institute; Sheffield, with a large unit recently set up around Phil Ingham; and Bath, home to my own little group. In plant development, the John Innes Institute is associated with the University of East Anglia in Norwich.

Despite the rather depressing challenges of complexity posed by genome maps and chip technology, there are still fundamental developmental problems to be tackled. Among these might be mentioned the control of growth, both absolute size and relative proportions, issues that are still not understood at all, but have been well discussed by Martin Raff (UCL). Then there is the mechanisms of regeneration. The spectacular regeneration of limbs by lower vertebrates is a problem kept alive almost single handed in the 1990s by Jeremy Brockes (UCL). The less dramatic but perhaps ultimately more clinically relevant tissue repair in mammals may eventually pave the way for new therapies for several of the debilitating degenerative diseases. Whether via the high throughput route or the high intellect route, developmental biology will certainly continue to prosper and there is no doubt that the British contribution will continue to be a significant one.

Reference

SLACK, J.M.W. (1999). *Egg and Ego – An almost true story of life in the Biology lab*. Springer Verlag, NY.