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A brief history of Developmental Biology at the National Institute for Medical Research

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The National Institute for Medical Research in London (commonly known as NIMR, or simply Mill Hill, where it is located) is today firmly on the world map of Developmental Biology. This is clearly evident from the programmes of recent international meetings –particularly where early embryogenesis is a major theme. When, how and why has this reputation been acquired? Is it the result of some master plan established by a wise and farsighted governing body? Or on the contrary, has it originated from allowing a free hand to a few opportunistic individuals? In this review, I shall briefly trace the beginning of systematic studies of developmental biology at NIMR that show that these started in a small way without any firm directives from higher authorities and demonstrate how good, free curiosity-driven research at the bench attracts imaginative and talented scientists, in turn responsible for achieving a rapid growth of any new venture.

Late start

Although the NIMR was established in 1913, it moved to its present site in Mill Hill as a fully functional unit of its parent organisation, Medical Research Council (MRC), only in 1950. The Institute was then largely made up of discipline-based divisions such as chemistry, biochemistry, microbiology, parasitology, virology, etc. Its major emphasis was disease-oriented 'useful' research such as chemotherapy, antibiotic action and pharmacology. What could be called developmental biology was covered in a subliminal fashion by the Division of Experimental Biology. Indeed, there is virtually no mention of developmental topics in the annual reports of MRC until the mid-1960s. Yet Britain was for long recognised as a leader in research on animal and plant development, often undertaken within university departments known as embryology, chemical embryology and developmental physiology. Indeed, it is only in the MRC's Annual Report of 1966/67 that there is a brief reference to developmental biological research.

The above report refers very briefly to the work of Conrad H. Waddington's group in Edinburgh and a little less briefly to the pioneering work of John Gurdon (then in Oxford), both receiving support from the MRC. It recognised particularly the importance of Gurdon's work on raising *Xenopus* tadpoles from enucleated unfertilised eggs injected with nuclei from adult differentiated intestinal cells. In the same report, a relatively detailed account was also rather flatteringly given of the work initiated by my small group within the Biochemistry Division of NIMR on amphibian metamorphosis. It was argued that this postembryonic developmental system, which was tightly regulated by hormones, would lend itself better to analysing the regulation of specific gene expression by endocrine signals than in mammals. These studies had to be carried out under rather primitive conditions without facilities for breeding amphibia or raising tadpoles, such that *Xenopus* and bullfrog *(Rana catesbeiana)* tadpoles had to be regularly flown over from South Africa or the United States. Nevertheless, the first results of these investigations of mid-1960s rapidly yielded two

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Sir Peter Medawar, who as Director of NIMR greatly encouraged the growth of research in developmental biology in the 1960s.

very promising results: a) that competence to respond to developmental signals is established very early in embryogenesis, and b) that cell death underlying the resorption of tadpole tail, regulated by thyroid hormone, requires new protein synthesis. Some years later, with the discovery of nuclear and cell membrane receptors and the development of methodology for identifying gene transcripts and their products, these findings led to some important generalisations. At this time, the encouragement from Peter Medawar, who was director of NIMR in the 1960s, proved crucial in the first steps towards initiating and expanding the study of developmental biology at the Institute.

First steps

In 1969-70 the MRC announced the setting up of two new divisions at NIMR, those of Developmental Biology and Genetics with Mike Gaze and Robin Holliday as the respective heads. The main interest of Genetics Division concerned the genetic and biochemical mechanisms of ageing of human cells in culture, translational errors in protein synthesis and DNA replication, recombination and repair in the mold *Ustilago*. That of Developmental Biology Division was the mode of formation and maintenance of nerve connections in developing *Xenopus* embryos and tadpoles. Their studies concerned mainly the developmental topology of the visual system in amphibians, particularly the development of retinotectal and isolateral visual projections in amphibians, the rapid polarisation of the eye and tectum, synaptogenesis in the developing visual system and the genesis of the binocular visual projection. Although this work was of the highest calibre, it was overshadowed by the studies of Sperry at Caltech on the developing visual system. A spin-off of practical value was that for the first time NIMR had reasonable facilities for breeding *Xenopus*, growing embryos and maintaining amphibian tadpoles. The MRC's belated recognition of the importance of developmental biology in biomedical research was certainly responsible for the hiving off of my group from the Division of Biochemistry to the formation of the new Laboratory of Developmental Biochemistry (DBM) in 1973, whose main programme comprised the hormonal regulation of genes involved in amphibian egg development and metamorphosis. The availability of facilities for rearing *Xenopus* and other amphibia thus proved to be very timely for the newly formed laboratory. This, combined with the establishment a few years earlier of an excellent mouse-breeding unit by Medawar and N.A. Mitchison, meant that embryogenesis in two vertebrate species favoured by developmental biologists could be studied at NIMR.

The work of the Developmental Biology Division on the precise neuroanatomical mapping of the developing visual system of *Xenopus* continued along more or less the same lines until the early 1980s. When Arnold Burgen had succeeded Medawar as director of NIMR, a new Laboratory of Neurobiology, with Geoffrey Raisman as its head, was started in 1973, whose special interests involved reinnervation in the central and peripheral nervous system and sex-hormone-determined dimorphism. However, their interests did not include developmental neurobiology as such –an area of research for which NIMR was to receive substantial recognition a few years later. In the early 1970s Jonathan Cooke joined the Developmental Biology Division. With his interests in spatial organisation in early development and autonomy of gastrulation movements in amphibian embryos, the Institute began the first studies on patterning of tissues during early embryogenesis. Later, with Malcolm Maden and Dennis Summerbell, his group extended their work to limb development and regeneration in the axolotl. Cooke also introduced to NIMR an appreciation of the wider issues of developmental biology, such as evolutionary conservation, cell movements and organogenesis. By now it was clear that the MRC had recognised the importance of greater investment in research into developmental biology, best illustrated by the setting up in 1974 of the MRC Mammalian Development Unit in London, directed by Anne McLaren, with the principal goal of studying early mouse embryogenesis.

In the seventies, developmental biologists had begun to realise the extraordinary potential of combining genetics and molecular biology and several groups in the US and Europe had actively started to exploit the rapidly emerging technologies of gene cloning, DNA sequencing and transgenesis. To cite just a few examples, work from the groups of Gehring, Nüsslein-Volhard, Rubin and Spradling working with *Drosophila*, Grüss, Chambon and Leder with mice and Brenner with *Caenorhabditis elegans* promised greater successes to come with their work in identifying developmentally important regulatory genes and creating transgenic animals. Some of us at NIMR realised the urgency of establishing these technologies at Mill Hill, and it was essential to attract a group with the necessary expertise and achievements. Most fortunately for the Institute, Richard A. Flavell and Frank Grosveld in Amsterdam (who had earlier earned considerable praise for their demonstration, with Alec Jeffries, of split genes in eukaryotes) were seeking to move from The Netherlands because of interference there from politicians and other anti-genetic manipulation activists. After much foot-dragging and unnecessary time-wasting negotiations, a new Laboratory of Gene Struc-

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ture and Expression (GSE) was at last established in August 1979 with Flavell as its head. Not only did GSE get moving quickly but, perhaps more importantly, it made available to many of us the techniques and facilities which were lacking then at NIMR to exploit gene technology.

Initially, GSE extended its investigations undertaken in Amsterdam on the structure of the human β-globulin gene and its developmental regulation. The latter project largely concerned gene switching during embryonic and foetal development in normal and pathological situations, as in β°- and β^{+}-thalassaemia. At the molecular level it involved a detailed dissection of the large β-globin gene locus, as determined by nuclease hypersensitivity and DNA methylation. They also initiated a study of the organisation and expression of the genes encoding the major murine histocompatibility H-2 genes, thanks to Dimitris Kioussis (from Philadelphia) joining the laboratory. GSE's rapidly growing reputation attracted an increasing number of excellent visiting workers from the UK and overseas, which continued right into the nineties and led to many fruitful collaborations with groups within and outside NIMR.

The early 1980s witnessed some major changes in the organisation of the Mill Hill Institute accompanying the growing movement towards developmental biology, which were soon to prove highly beneficial to its worldwide reputation in this field. Mike Gaze's departure in 1982 and the subsequent disbandment of Developmental Biology Division was to be followed later by the setting up of the Laboratory of Embryogenesis under Jonathan Cooke. Following Alan Smith's move to the United States and the consequent winding up of the Biochemistry Division, a new Laboratory of Molecular Embryology was established under Brigid Hogan in 1984. Around the same time, Richard Flavell resigned as head of GSE but its continuity was maintained most vigorously under Frank Grosveld's headship. As these changes were gathering pace (now under the directorship of Dai Rees), it was decided to move NIMR to a new institute structure thought to meet better the needs of the rapidly unfolding mechanisms of cellular, molecular and structural biology and related emerging technologies. The new structure meant combining all the existing and future divisions and laboratories into three groups, one of which, Genes and Cellular Controls (GCC), incorporated all the laboratories with a major interest in developmental biology. Peter Rigby was brought in to head GCC with the formation of a new Laboratory of Eukaryotic Molecular Genetics to be directed by him.

The golden period

It is true to say that the mid-1980s saw the blossoming of what could be called the golden era of developmental biology at the NIMR and whose momentum continued to grow over the next decade. Further, new laboratories were set up and novel projects began to sprout as new staff, visiting workers and graduate students were attracted to them. Meanwhile, GSE's own reputation continued to grow and the laboratory's interests widened as, for example, the study of T cell surface protein genes. Robb Krumlauf's arrival from Philadelphia to join the Laboratory of Molecular Embryology greatly helped extend its interests in mammalian embryogenesis to investigating more specifically the structure, expression and function of murine homeobox genes. At around the same time, Andy McMahon and Dave Wilkinson were recruited in the US to join DBM (which until then had almost exclusively concentrated on amphibian postembryonic development) to initiate studies on the developmental role of genes involved in signalling mechanisms during early mouse embryo-

genesis. Thus, it is clear that during the second half of the 1980s, NIMR rapidly built up around some excellent investigators a strong base for attacking from different directions several important problems of mouse embryogenesis. The Institute's work on amphibian development also received a major boost during this period with Jim Smith and Tim Mohun joining the Laboratories of Embryogenesis and Developmental Biochemistry, respectively.

A most important contribution from NIMR during the late 80s and early 90s is surely the work of Jim Smith on mesoderm formation in early *Xenopus* embryogenesis. Devising a sensitive bioassay for mesoderm induction *in vitro* allowed him and his co-workers to purify a mesoderm-inducing factor (MIF) from *Xenopus* XTC-2 cells. In a seminal paper published in *Nature* in 1990 this group identified MIF as the hormone activin. This finding had two important implications: a) that a hormone known to regulate mammalian reproduction (ovarian function in adults) was also an important signalling molecule for early amphibian embryogenesis; b) that early development was controlled by specific signals which are highly conserved through evolution. Smith and Jeremy Green later demonstrated that the morphogenetic responses to activin and other signals were subject to spatial and temporal restrictions during embryogenesis. The principle of signals and their receptors as regulators of morphogenesis is now a major tenet of developmental biology.

It is worth mentioning a few other highlights of work from NIMR and the organisational changes taking place under John Skehel's directorship at about the same time. McMahon and Wilkinson, studying the expression of proto-oncogene *int*-2 during gastrulation and neurulation in mouse, were able to demonstrate the important signalling role of the protein during embryogenesis and were among the early investigators establishing functions of the *wnt* family of genes. Robb Krumlauf and Brigid Hogan characterised the homeobox genes of the *Hox* family in mouse and then established that the spatial and temporal patterns of their expression are crucial to morphogenesis, especially neurogenesis. Krumlauf's contributions in particular (along with those of McGinnis in the US) have laid the foundations of our present-day knowledge of the role of homeobox genes. When Robin Lovell-Badge joined NIMR in 1988, his group began their pioneering studies on the molecular and genetic basis of mammalian sex determination. They first demonstrated, in collaboration with Peter Goodfellow's laboratory, that the *Zfy* gene, then thought to be implicated in the process, was not involved in sex determination but that SRY and its related genes were the key players in male mammalian gonad determination. The departure of Brigid Hogan to the United States combined with the rapidly growing interest in neurogenesis and sex determination necessitated the discontinuation of the Laboratory of Molecular Embryogenesis and the setting up of two new laboratories, those of Developmental Neurobiology and Developmental Genetics, headed by Krumlauf and Lovell-Badge, respectively. At around the same time, the Laboratory of Embryogenesis was also disbanded, with Cooke's group being integrated into Developmental Neurobiology, while Jim Smith headed a new Division of Developmental Biology (DB).

As the roles of individual signalling molecules in early embryogenesis were being elucidated, it became increasingly clear that morphogenesis was the outcome of an intricate interplay between multiple signals operating through their receptors. To cite a few examples, Smith's group turned their attention in the early 1990's to determining the role at first of the *Xenopus* homologue of mouse *Brachyury* gene, and then to *noggin* and *wnt*-8, in mesoderm induction. Later, they extended these studies to the intervention of extracellular matrix (ECM) constituents, such as integrins and fibronectins, in gastrulation and mesodermal determination. At the same time, Mohun's group were also busy identifying newer signalling pathways and regulatory targets underlying myogenesis and cardiogenesis in early amphibian embryos. As regards the mouse groups at NIMR, Krumlauf's laboratory extended their dissection of the spatial and temporal expression of the individual members of the *Hox* family to hindbrain segmentation and rhombomere transposition. In collaboration with P. Charnay's laboratory in Paris, Wilkinson's group were studying in depth the spatially restricted expression and function of *Krox*-20 in hindbrain development, which later led them to demonstrate the importance of tyrosine kinase receptor as one of the key targets. At the same time, Lovell-Badge and his colleagues were extending their work on *SRY* to SOX genes, whose products are now known to regulate morphogenetic functions other than sex determination. In the Division of Developmental Biology, Mike Sargent's group cloned *Slug*, a zinc finger gene and, with Wilkinson, Cooke and Angela Nieto (from Spain), initiated investigations on control of cell behaviour during vertebrate development. Well before the recognition of the importance of signalling mechanisms during early embryogenesis, that of hormones and other morphogens in organogenesis and functional differentiation in postembryonic development had been firmly established. Nowhere is this more dramatically illustrated than in the hormonal control of insect and amphibian metamorphosis (although not as dramatic as amphibian and insect metamorphosis, there are many parallels with hormonally regulated postembryonic development in all vertebrates). In the early 90s, following their observation of the phenomenon of autoinduction of thyroid hormone receptors at the onset of both organogenesis (e.g. limb bud development) and programmed cell death (loss of tail, gills), my group in DBM had suggested that achieving correct receptor thresholds is a pre-requisite for development to proceed. The same phenomenon of a given ligand upregulating its own receptor gene (e.g. retinoid and steroid receptors) has now been observed in other postembryonic (and early embryogenetic) developmental systems.

In 1993-94, the NIMR received a further boost to its developmental biology effort when Rosa Beddington arrived at the Institute to form a new Laboratory of Mammalian Development, at about the same time as Paul Burgoyne's group was added to Developmental Genetics. The latter group's activities concern the molecular and genetic basis of mouse Y chromosome structure and spermiogenesis while the Beddington group has rapidly extended its work on early studies of postimplantation of mouse embryo. These new changes coincided roughly with Frank Grosveld's move to Amsterdam and closure of Gene Structure and Expression. Although GSE's major effort was not directed towards developmental biology, its expertise in gene technology was important for the more biologically orientated groups, which was particularly crucial during the 80s in rapidly exploiting the technology for analysing developmental problems. Later, with the closure of DBM, Tim Mohun's group was incorporated into the Division of Developmental Biology. It has long been recognised that the study of a single organism is unlikely to elucidate all the major problems of biology, and so it is essential to select the organism best suited to answer a given question. Until quite

recently, the NIMR had relied heavily only on the mouse and frog as model organisms. It is therefore most appropriate that, thanks to the arrival of Jean-Paul Vincent and Derek Stempl and their groups at NIMR, work is now proceeding on two organisms which lend themselves admirably to genetics combined with molecular biology, namely *Drosophila* and zebrafish.

Conclusions

It is clear from the above historical survey that the NIMR by the mid-1990s had come to occupy a prominent position as a leading establishment for research in developmental biology. What are the factors that have contributed to NIMR so successfully acquiring this position in a relatively short period of time?

One of the major advantages of working at this institute are the cross-disciplinary and interdivisional collaborations, which have been encouraged by all the directors, past and present. The absence of making frequent applications for research grants, and then trying to justify them, has made it easier for the younger members of the staff to undertake opportunistic research without too many directives from above (although all are subjected to regular reviews). Although the premature departures of senior and middle-order scientists can be disruptive, the fact that many of them have received prestigious positions elsewhere indicates the reputation of developmental biological research at NIMR. On the other hand, a turnover of staff offers opportunities to bring in new blood and adds to the flexibility of reorganising groups as newer concepts and technologies appear on the scene. There is no doubt that if the Institute is to retain its position in this field, it will have to exploit the newly emerging technologies and concepts of structural and cell biology, just as it has so successfully applied genetics and molecular biology to solving developmental problems. Finally, and most importantly, a small core of good science practised by a few can be highly autocatalytic in attracting more good science and excellent scientists. This has been certainly true for developmental biology at the National Institute for Medical Research.

Further information

For more detailed accounts of what has been written above the reader should consult the Annual Reports and lists of publications of MRC and NIMR.

Apologies

I tender my apologies to numerous members (of the NIMR), past and present, who have also made contributions to the study of developmental biology at NIMR but whose work I have not cited in this brief account.

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