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Worm tales

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1969 was a landmark year. But for me it was not Neil Armstrong's giant leap or Woodstock heralding the beginning of the end of the sixties that sticks in my mind. It was a visit I made to Cambridge to meet a "bloke who is starting a new project to study some sort of worm", as my head of department at the Medical Research Council's National Institute of Medical Research informed me. I was on the point of accepting a job offer in industry, but thought that I owed it to the MRC to check out this possibility, particularly as they had funded my undergraduate studies. I arrived in Cambridge wearing my smart new interview suit and was confronted by a strange-looking, chain-smoking individual wearing jeans and a striped tee-shirt. Sydney Brenner talked non-stop about his vision for solving the major problems of developmental and neurobiology using a new model organism, *Caenorhabditis elegans*. I can't remember saying anything at all at this interview, and drove back to London with my head reeling. However, as I drove, I played back poorly recollected fragments of Sydney's stream of consciousness in my mind, and a simple logic emerged that appealed to me: study the nervous system in an small animal with a few hundred nerve cells so the whole neural circuitry could be defined from reconstructions of electron micrographs, deduce the cell lineage of the whole animal by following the development of live embryos using a newly-developed optical sectioning technique, use genetics to reveal biochemical pathways. It all made sense somehow. By the time I arrived home, I had come to the conclusion that Sydney Brenner was a little mad, but that working in his lab could be fun. However, I can't remember actually deciding to come to Cambridge. Matters were decided for me when Sydney called me a few days later. Again, I did not manage to get a word in edgewise. "It will be a simple transfer as you are already employed by the MRC; you might as well start in a couple of weeks." I did.

The Laboratory of Molecular Biology was very different from anything that I had experienced. There was atmosphere of industry and excitement; people seemed to work around the clock. At that time the LMB had few graduate students, but there was a large population of American postdocs. These Jim Watson wannabes were the engines that powered the lab. They were highly selected: as the MRC generally did not fund postdoctoral fellows, they could therefore only come after obtaining their own support. Foreign travel was not nearly as accessible thirty years ago as it is now, so the cultural differences between the American postdocs and the endogenous Brits seemed quite marked. The Americans were the consummate professionals: hardworking, ambitious, hungry yet not too sure how to get to the Garden of Eden. We English, by contrast, thought that we lived in the Garden of Eden. We prided ourselves on being gifted amateurs, more keen on trying to solve problems by discussions over a cup of tea than slogging it out on the bench. The cultural combination proved remarkably successful. The Americans came to enjoy the coffee/lunch/tea breaks, and the LBM canteen was the hothouse where many ideas germinated. However, some deferences were made to American tastes: much to my regret, the kidney had to be omitted from Joy's delicious steak

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Fig. 1. Eileen Southgate worked for many years reconstructing the nervous system of *C. elegans* from serial sections of electron micrographs.

and kidney pies. While few Americans would admit to liking stodgy English food, they eventual got used to it and introduced us to some of their own culinary delicacies. I remember my first introduction to brownies. They were delicious, if a little gritty. I kept on asking for more until I felt inhibited by the raised eyebrows of my host. Riding home on my bicycle that evening was an unforgettable experience.

Max Perutz, who was Chairman of the Board of Governors, headed the LMB at that time. This excellent administrative structure unfortunately did not survive Max's eventual retirement from the post. Sydney Brenner and Francis Crick were co-directors of the Cell Biology division. They shared a rather modest office and seemed quite happy with this arrangement. Their two personalities complemented each other perfectly. Sydney had a phenomenally retentive memory and immersed himself in the minutiae of any subject that interested him, yet perhaps was sometimes too distracted by this minutiae. Francis, on the other hand, was the epitome of the gifted amateur. He had an incredible ability to sift through all the data on any subject and eliminate the dross, yet to synthesise the essential conclusions. He used to amuse us by seemingly sleeping through lectures yet coming up with a question at the end, which cut through, to the heart of the subject matter.

The lab itself was unimpressive and overcrowded. Postdocs only had a four-foot bench and no desk. The corridors were packed with centrifuges and incubators. The only place to write was the library, and even there you had to pack up your papers when you left. The overcrowding was in part deliberate. Sydney and Francis believed that a tightly packed lab encouraged interactions and that desks encouraged time-wasting activities. However, we had a little coffee room. This room survived several attempts to convert it into a lab until it was realised that it was sacrosanct. The coffee room was the focus of the worm group. Every morning around ten, we trickled in to hear Sydney's daily monologue. At their best, these were wonderful witty, entertaining and informative discourses. They rarely covered what Sydney was currently working on or even his former work on lambda genetics. Rather, they were on his current passions that could range from speculations about how neural connectivity is encoded in the genome to Russian films. Many of us learned a lot from these sessions. When I encounter micromanaged American labs, I realise how different it was then and how fortunate we were in Cambridge at that time. Sydney rarely talked to anyone about the details of their project. He let us get on with it. We were like a bunch of kids that were let loose in adventure playground. We didn't know what we were doing, but we tried everything and anything. Nothing much was known about *C. elegans*; it was easy to make some new observation. We had the courage of innocence.

For the first few years, Sydney worked up the genetics of *C. elegans*. He isolated many morphological and behavioural mutants and mapped them. He also reconstructed selected regions of the nervous system of selected behavioural mutants from electron micrographs of serial sections and found differences of connectivity. For example, he correctly characterised the circumferential neural guidance defect of a mutant that was later shown to be a netrin receptor gene. This original mutant screen, perhaps more than anything else, launched *C. elegans* into its distinguished career as a model system. However, this intense period of activity was not enough to entertain Sydney's restless mind. He had long nurtured an interest in computers and algorithms and planned to use computers to reconstruct and archive the neural connectivity of *C. elegans*. We bought a fairly fancy computer for the time, but it had minimal software support. Sydney taught himself to program in assembly language and implemented TRAC, an early string processing language. He was interested in the possibilities of string-processing languages for genome sequence analysis, although at the time there were not too many sequences around to analyse. Sydney

Fig. 2. Sydney Brenner founded the *C. elegans* project in Cambridge in the mid '60s.

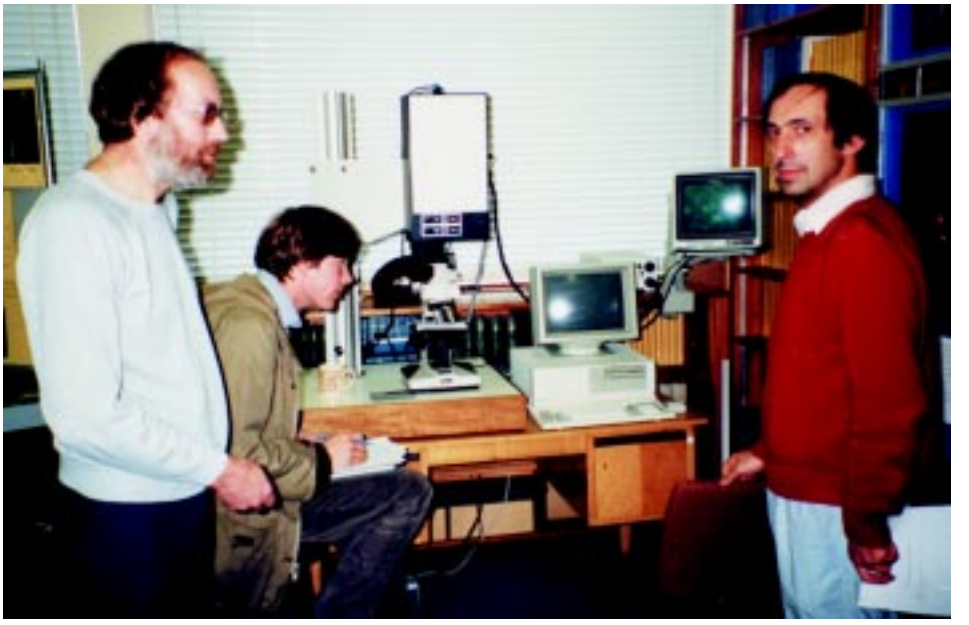

Fig. 3. The *C. elegans* project spawned several technical developments such as a confocal microscope, which was developed to study the cytoarchitecture of the developing *C. elegans* embryo. *This is the commercial prototype a few hours after it was first made to work after an all night effort. John White (right), Richard Durbin (centre) and Mick Fordham (left).*

loved programming. He would delight in showing anyone who would listen his latest recursive algorithm for parsing strings.

The *C. elegans* group in Cambridge was fortunate to have the services of a group of talented and dedicated support staff. These were people that would normally have gone to university, but left school in the austere post-war era and went straight to work. They had a completely different work ethic to the scientists. They liked to keep regular hours, liked to have well-defined tasks and left their work at the lab when they went home. However, they had wonderful skills and were methodical and meticulous. But most importantly of all, they stuck to the job in hand rather than working in bursts of frenetic energy that eventually fizzled out. The reconstruction of the *C. elegans* nervous system was primarily undertaken by the technical staff, and they also played key support roles in genetics and cytology. In addition to the technical staff that worked in the labs, the LMB had excellent mechanical and electronic workshops. These were used to develop a laser ablation system for performing laser microsurgery on *C. elegans* and several prototype confocal microscopes. Unfortunately, when under economic pressure, labs often choose to cut technical support staff. I think that this is usually not a wise decision. Technical staff are usually more productive at routine tasks than research scientists and furthermore, will free up a scientist's time for more strategic tasks. The availability of good workshops facilitates the development of innovative instrumentation to solve problems that arise in the course of research on fundamental problems. In real life, you can't get very far with string and sealing wax.

Sydney originally persuaded the MRC to support the *C. elegans* project by dint of much chatting up and a single page formal application, a far cry from the voluminous, turgid grant applications of today. The first significant paper to come out of the *C. elegans* project, Sydney's paper in *Genetics*, did not come out until 1974. The lineage and anatomy studies came out around a decade later. We were lucky that we were not under pressure to publish every year in order to survive. However, the down side of this freedom was that there were several significant studies done at the MBL that were never published and were only disseminated on the grapevine. Nevertheless, those first years of grace were essential to establish the body of background genetic, developmental and anatomical data that makes *C. elegans* such an attractive model system.

By the end of the '70s, Sydney's interests had ranged beyond *C. elegans*, and it was left to the three Johns (Hodgkin, Sulston and White) to carry the torch. By that time, the first postdocs were finding that they could get jobs studying *C. elegans* back in the U.S. and this in turn encouraged a steady stream of first-class, new postdocs to come to the lab. I was struck by the variety of their personalities. Some were overtly (although rarely obnoxiously) ambitious, constantly striving towards setting up their own research groups. These individuals collected every crumb of information they could get their hands on, usually recorded in minute script in notebooks that they always carried. These crumbs were often much later deployed to good effect: I have several times been reminded, to my amusement, of some odd observation made at that time when it became transformed into a PhD project years later. Other postdocs became totally immersed and enthralled by their studies. These individuals had to be prodded and cajoled to package themselves for the job market. The postdoc community was very close-knit and lively: they worked and played hard. A visit to the lab at midnight would find many people still working there. However, someone might be practising singing in the stair well (apparently it had good acoustics) while another might be having a haircut in the coffee room.

One thing that came out of those early years that still endures is a sense of community among *C. elegans* workers. People were very free to offer their help to others and there was little of the dog-in-the-manger attitude that can so often blight a research field. The establishment of the genome-mapping project, which evolved into the genome-sequencing project, epitomised this spirit of community support. People were encouraged to contribute to and use data from the growing database, but it was established from the outset that these data were always to be in the public domain. The *Worm Breeder's Gazette* was established as a forum to communicate

preliminary information and newly developed techniques. When it was founded, it was decided that nothing in the Gazette was to be cited in a formal publication. The Gazette has proved to be a very effective in keeping the *C. elegans* community together as a cohesive unit. The biannual symposium is another treasured *C. elegans* institution. Remarkably, nearly everyone that works on the organism comes to these meetings; the last had around 1,300 attendees. In spite of this size, the meetings have not succumbed to the bogey of parallel sessions. This allows everyone the opportunity of catching up with all aspects of *C. elegans* research.

The explosive developments of molecular genetics in the 80's had a dramatic impact on *C. elegans* research. However, I remember the beginning of this period as being somewhat arid. Whereas, prior to this time, research projects had involved direct observation of, and experimentation on, the worm, people were now devoting all their efforts into cloning a gene of interest. Initially, this was a major technical challenge that became all consuming, so much so that the reason why a particular gene might be of interest was often given scant attention. I remember many mind-numbing group meetings from this period describing incremental (or non-existent) progress in cloning the next gene. However, technical developments and the Worm Genome Project brought on radical improvements. Soon we had transformation rescue as a definitive way of identifying a cloned gene. More recently, the technique of RNAi has enabled the loss-of-function phenotypes of any of the 19,000 or so identified *C. elegans* genes to be determined with a few days effort. Furthermore, domains of gene activity can now be visualised using GFP reporters. These technical developments have attracted people from other fields to our worm. Genes that have been associated with a human disease, but with little else known about them, can often be identified in the *C. elegans* database. The cell-type expression pattern and the loss-of-function phenotype can then be ascertained in *C. elegans,* thereby providing some clues as to the function of these genes in humans.

As the postdocs moved on from the lab and scientifically colonised the rest of the world, it was inevitable that the LMB at Cambridge should lose its place as the centre of the *C. elegans* universe. However, this is probably an indication of the health of the field. Much of the foundation work such as the establishment of the genetic map, the sequencing of the genome, the determination of the cell lineage and the mapping out of the nervous system, has now been essentially completed. Perhaps, we are therefore now at the stage where the American scientific method, with its vast supply of funds and people applied to projects selected to yield rapid results, is the most effective way of pursuing *C. elegans* research. Nevertheless, I consider myself fortunate to have been part of the early phase of this extraordinary enterprise, when we were given the space and the time to start to get to know this beautiful organism.