Q & A

Michael Ashburner

Michael Ashburner was born in Brighton, on the south coast of England and spent the first 10 years of his life living high on the South Downs. He then was moved to the Home Counties, and went to high school in High Wycombe. He was an undergraduate in Cambridge and has never really left, doing his PhD in the Department of Genetics (1968) and then rising through the ranks of the faculty until, in 1991, he was appointed Professor of Biology. His life has not been as parochial as that may sound, since he was a postdoc with Herschel Mitchell in Caltech and has spent sabbaticals in both UCSF and in Berkeley. He was elected a Member of the Academia Europaea in 1989, a Fellow of the Royal Society of London in 1990, and a Foreign Honorary Member of the American Academy of Arts and Sciences in 1993. He served as President of the UK Genetics Society from 1997–2000. For six years (1994–2001) he worked at the European Bioinformatics Institute, first as Research Programme Coordinator and then as Joint-Head with Graham Cameron. By trade he is a Drosophila *geneticist and now works in two fields: genome evolution in* Drosophila *and the provision of infrastructure for the computational analyses of biological data.*

How did you become interested in biology? We lived in the country in a curious settlement called Peacehaven on the South Downs in Sussex, next to a farm and open downland. An interest in natural history was encouraged by my father, who would give me a penny for every different species of wild flower that I could identify. I collected flowers, butterflies, beetles, fossils, birds eggs, hedgehogs… you name it. But this interest lapsed in my early teens, which were dominated by competitive dinghy sailing. However, I was extraordinarily lucky to have a brilliant and inspiring teacher in my last years at school in High Wycombe. He was Simon Lambert who came to the school from the London Zoo. He had a habit of turning up on a Monday morning with animals that had died in the Zoo over the weekend and saying "here, dissect this crocodile and see what you can find". He encouraged me, and his other students, including Ron Laskey and Richard Shelton, to think for ourselves and to read *Nature* every week. He also encouraged me to apply to Cambridge where I had determined to be a zoologist. However, the Department of Zoology refused me for Part 2 and, by default, I ended up in the then very small Department of Genetics.

If you knew what you know now earlier on, would you have followed the same career? Yes, in broad outline I think. There are things that I would have done differently — for example, I would have made much greater efforts than I did to become more numerate. As a young scientist I spent a lot of time on fruitless experiments, but I do not think that was a mistake as even a failed experiment can teach you a lot. Despite working most of my life with *Drosophila* I have moved fields quite a lot — I think that is a good thing, though there have been times when I thought I should have been more focused on a 'big' question. I was very lucky in my early career. In 1967 I published my first serious paper on puffing in the polytene chromosomes of *Drosophila*. It was not really original — it built on work done by Hans-Joachim Becker — but it was read by Herschel Mitchell at Caltech. He invited me to his lab. I first said no: go from Cambridge to an Institute of Technology? I had also just got my first job, as Assistant in Research in Cambridge (a post previously held by Luca Cavalli-Sforza) and purchased my first house. Luckily, Mitch persisted and I flew to LA the day Robert Kennedy was assassinated in June 1968. I was so ignorant that I had not realized that Caltech was the home of fly research! There I met and had daily contact with Alfred Sturtevant, Ed Lewis, Seymour Benzer, Max Delbruck, Albert Tyler and Ray Owen, and had John Merriam and Antonio Garcia-Bellido as postdoc colleagues. It was an amazing experience.

Do you have a favorite paper? Oh, several! I simply love the classical papers of *Drosophila* genetics, almost any paper of Alfred Sturtevant's, who is my intellectual hero. In the same spirit, the triplet code paper of 1961 was a great influence, partly for personal reasons — I picked T4 plaques for Sydney Brenner as an undergraduate (I had hoped that he would take me as a PhD student, but he declined the honor to both me and to Brigid Hogan).

What scientists have had the greatest affect on your research directions? I must name three. The first is David Hogness who I met first at Caltech in 1968 — he was on sabbatical with Ed Lewis and beginning to learn *Drosophila*. He gave me enormous encouragement — getting me an invitation to the 1970 Cold Spring Harbor Symposium and to the Nucleic Acids Gordon Conference, and attempting to hire me at Stanford in late 1969. The others are Francis Crick and Sydney Brenner, who convinced me in the mid-1970s to attempt to tackle fundamental genetic problems by the analysis of the *Adh* gene of *Drosophila*. I was also lucky that Peter Lawrence joined my Department as a Fellow in, I think, 1970: we learned a lot together. I also had a negative influence: in 1965 I spent a summer in Europe working in the lab of a scientist who had an idea how hormones might control gene activity. It was wrong, but he was emotionally committed to this idea, body and soul. That taught me never to become emotionally involved with my ideas: most ideas are wrong and you must be able to abandon these like dirty socks. The trick, of course, is knowing when the time has come to change one's socks! I know that it is not fashionable but success in science — unless one is truly outstanding — is

enormously helped by knowing the leaders of your field. My advice to any young scientist is to choose your mentors with care! Not that I did — I just was lucky to be in the right places at the right time.

What has been your biggest mistake in research? In the early 1970s, together with my research assistant Mike Lewis, I was attempting to discover whether or not the polytene chromosome puffs that are induced in *Drosophila* larvae encode proteins. I made two mistakes. The first was technical: we were doing this by running double-labelling experiments — making a tritium-labelled control and a carbon-14-labelled treated sample and separating the proteins on SDS in tube gels. These gels were then sliced into 1 mm slices, each of which was counted in two channels in a scintillation counter. Until Jim Ostell gave me a Fortan IV program to compute the cross-over between the channels, each gel took about a week to analyse using an electromechanical calculator (albeit one that had been used by R.A. Fisher). Had I but known Bill Studier — just up the road at the LMB — had developed a far superior system, running S35-methionine-labelled samples on slab gels and detecting proteins by autoradiography. That was just silly — I should have talked to people! The other mistake was personal. I told a visitor about our preliminary results — for we had indeed discovered heat shock proteins — and he then went away, used Bill Studier's system and beat me to publication. We were left with the second paper on heat shock proteins!

You have had conventional success in science, to what do you attribute this? I was very lucky early in my career that I worked on a system which was of great interest — the hormonal control of gene activity during development — but which was very hard technically: it required detailed analysis of the puffs of polytene chromosomes and few were prepared to do this. So I had had almost no rivals. Also, building on the earlier work of Hans-Joachim Becker and Ulrich Clever in Germany, we were able to build a model for the temporal control of gene activity which excited considerable interest. When I began more formal genetic work, I was frustrated by the absence of didactic material in the field. For this reason I suggested to Mel Green, a grand old man of the field, that we co-edit a text on *Drosophila* genetics. He said no, but suggested that Ed Novitski might collaborate with me. Ed — he died last month — was a brilliant fly geneticist and he agreed to help. This led, with Ed and three other great co-editors, Ted Wright, Jim Thompson and the late Hamp Carson, to a 12 volume series on the *Genetics and Biology of Drosophila*.

What do you think about the electronic revolution and Open Access in publishing? That is two questions! I actually have slightly mixed feelings about the former: I have had many instances of flicking through a journal in the library searching for 'a' and finding 'z' by chance… I miss that. For some reason electronic browsing is less subject to chance. But having electronic access to papers is really fantastic… when you can get access! The University of Cambridge has — at enormous cost — provided us with access to most electronic journals, but even then I frequently come across a paper to which my access is blocked. I hate that, and unless I am really intrigued by the paper's title I will probably not read it. Scientists should realize that if they submit to journals — like those published by Elsevier, Springer, Kluwer, Wiley and the like — then their work will be less accessible and not as widely read as it would be if it was published in an Open Access journal. I signed the original Varmus–Brown letter to Science that lead to the founding of the PLoS journals, and now I simply will not publish a research paper in any journal that is not Open Access. Access by readers is just one side of the coin: in my new career in informatics I have seen the power of computational analysis of full text — MedLine abstracts are great but they are a poor second best. If the entire scientific corpus was electronically available as Open Access text then the benefits to the community would be enormous. It will come!

How did you move from fly genetics to bioinformatics? In about 1980 Mark Bodmer started DNA sequencing in my lab — he was taught by Bart Barrell, Fred Sanger's assistant — and we were totally frustrated by the lack of computational tools for sequence analysis. Luckily, Mark only sequenced 4 kilobases in about three years, so we could do a lot by hand. Neverthless, there had to be a simpler way and I started to work remotely on the Molgen project at Stanford, using an acoustic coupler down a 120-byte phone line — painful. In 1982, when the first EMBL Data Library was released, Martin Bishop and I made this available on the IBM3080 mainframe in Cambridge, using software written by Martin and Charlie Hodgman. This became a *de facto* national sequence analysis service for the UK, though we could never get it funded (it was eventually funded as Seqnet but went to Daresbury, not Cambridge). The early Data Library was full of errors and I complained to Gregg Hamm and then Graham Cameron in Heidelberg. They adopted President Johnson's principle that it was better to have me inside the tent pissing out, than outside pissing in, and put me on their advisory board. I was, therefore, very informed of the planning of what became the EBI. The intention was for the EBI to be in Heidelberg, next to the EMBL Headquarters. Returning from a meeting in Heidelberg in 1992 I had the idea that it would make a lot of sense to put the EBI next to the Sanger Centre (as then was) and suggested as such to John Sulston. John had a similar idea earlier that summer, but had not pursued it. I talked to Philipson, the then head of EMBL, who encouraged us to mount a UK bid. John and I wrote a one-page letter to the MRC

and Wellcome Trust and said we wanted, I think it was £13 million, for this. Within two weeks we had the money and spent the next few months preparing a formal bid to the EMBL Council. I had never planned to become involved to any greater extent. But Fotis Kafatos, who was on sabbatical with me in Cambridge at the time, was coincidentally appointed Philipson's successor as Director-General of the EMBL and he conspired with Charlie Cantor and Marvin Edelman to pressure me into joining the EBI as half-time Research Programme Coordinator.

That was one route. The other was through FlyBase. Fly geneticists had relied for many years on occasionally published catalogs of mutations. In about 1989, when Dan Lindsley and Georgianna Zim were preparing the last of these — the famous Red Book — I suggested to Dan that this be succeeded by an electronic database. Following meetings with both the NSF and NIH this lead to FlyBase being funded in 1992. It was working with FlyBase that I saw the need for structured controlled vocabularies — we now call them ontologies — to be able to rigorously describe attributes of, for example, gene products. That led, in 1998, to Suzi Lewis, Judy Blake, David Botstein, Mike Cherry and I to start the Gene Ontology project.

What next? Who knows? Apart from my work with the Gene Ontology, FlyBase and associated informatics infrastructure projects, my main interest is now trying to understand how chromosomes evolve. We are very lucky in that we have now the 'complete' genome sequences of twelve species of *Drosophila*, so understanding the molecular evolution of chromosomes is now feasible. I am probably too long in the tooth to start something quite new, but I must admit were I to have the chance, then an understanding of the form and function of the fly brain is a big problem!

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Palace flags up science

The home of Britain's monarch, Buckingham Palace in London, is not known for its links with science, but late last month it hosted a day of interactive exhibits visited by more than 800 school science students. On the same day the Queen opened a new centre at the Science Museum and hosted an evening reception for 500 members of the country's scientific community.

The displays for the students highlighted advances in medicine, engineering and space exploration. Amid the chandeliers in the grand ballroom, a replica of a pterosaur was suspended from the ceiling and there was also a giant mosquito on display.

Colin Pillinger, who headed the team that developed the *Beagle* Mars probe, said the event was spectacular. "It looks like the place was made for an exhibition like this," he said.

One student, Aravebthy Nanthanan said: "I didn't think everything would be so interactive. There's a lot more technology. It's strange to see it all at Buckingham Palace."

The new Smith Centre at the Science Museum aims to bring together key figures in science, culture, academia and business to encourage greater philanthropic support for science.

Glittering: The grand ballroom at Buckingham Palace hosted a major science exhibition for students last month, and the Queen also hosted a reception for leading scientists. (Photograph © Buckingham Palace Press Office.)