© 2018. Published by The Company of Biologists Ltd | Development (2018) 145, dev167858. doi:10.1242/dev.167858

SPOTLIGHT

An interview with Richard Gardner

Aidan Maartens*,‡

Richard Gardner began his career as a PhD student with Bob Edwards and ran his own lab, focusing on patterning of the early mammalian embryo, at the University of Oxford from 1973 until his retirement in 2008. A Fellow of the Royal Society since 1979, he was knighted for services to Biological Sciences in 2005 and received an Honorary Doctorate from Cambridge University in 2012. This year he was awarded the British Society of Developmental Biology (BSDB) Waddington Medal for major contributions to developmental biology in the UK. We caught up with him at the society's Spring Meeting in Warwick and discussed how a book of birds set him on a path to science, how his research was complemented by decades of advising government on scientific policy and why picking the right mentor in research is so important.

You're here in Warwick to receive the BSDB's Waddington Medal – what does the award mean to you?

It means a very great deal to me – it was extremely gratifying, and even more so because I used to run the ICRF Developmental Biology Unit (DBU) in Oxford, and all these other characters who headed laboratories there, namely Jonathan Slack, Julian Lewis, David Ish-Horowicz and Phil Ingham, have also received the medal. If one adds Rosa Beddington, who started in my laboratory (and also designed the medal), then approaching a third of recipients of this very prestigious award were members of the DBU!

Going right back to the beginning, what first got you interested in science?

It really began when I was about ten or so – I was ill in bed for some time and had been given the Observer's Book of Birds for an earlier birthday. Out of boredom, sitting there in bed, I started to look through it. I'd never really thought of it before, but seeing, for instance, the brilliant colours of the goldfinch, I suddenly realised that these amazing animals were all around me. It began as a casual interest and then got a bit more serious – I did nesting surveys, a very detailed study of the roosting habits of over-wintering thrushes and some bird ringing, which allowed me to confirm some of David Lack's observations on bird territories. It amounted to rather dull piles of information when I look back at it, but it was exciting at the time. No longer enamoured of going in the direction of modern languages, useful as they were, ornithology made the scientific route seem more appealing. But the biology staff at my school were completely unhelpful – they were not interested in people who change direction at that late stage. So I went to what is now called the North East Surrey College of Technology near Epsom, where the A-level biology teacher was a wonderful man called George Fluck. In contrast to the head of biology at my previous school, who had so honed his set of notes over 30 years he could almost teach it in his sleep, George would introduce contemporary information, things he'd read in Nature the week before. It was a very good transition from school to university, because they were very good teachers but it was entirely up to you – you weren't sat over.

My primary choice of subject when I went up to Cambridge was zoology, and alongside that I initially did physiology and biochemistry. But for some reason my supervisor felt it would be good for my soul to do organic chemistry, which I have to say I hated. I didn't know what I was doing in practicals, and in almost every one there seemed to be a minor conflagration. My main contribution to the new labs in Lensfield Road came during an organic preparation that involved sodium: I got the sodium out from under oil and thought that the water condenser wasn't operating fast enough, so turned up the tap, sprayed the sodium and it just disappeared earthwards through the bench. I hated the subject so much that the textbook we had – Peter Sykes' Reaction Mechanisms in Organic Chemistry – is the only book I've ever ceremoniously burned.

And how did you come to do a PhD with Bob Edwards?

By the time I entered my final year it was clear that I wanted to do research. Bob Edwards had a course quite late in that year that seduced both Martin Johnson and I to his work – we were actually given views of one of Bob's very early human oocytes, for instance. Luckily for us, since he hadn't had research students before, he was able to take us both on together. It wouldn't have suited everyone, but as a supervisor he was perfect for me: he basically told me to go away for three months and read in conjunction with learning basic techniques, because if what you are doing comes from your own head you'll be much more prepared to survive the difficult times when

*Online Editor, Development

‡Author for correspondence (aidan.maartens@biologists.com)

A.M., 0000-0001-7112-819X

Development (2018) 145, dev167858. doi:10.1242/dev.167858

things aren't working out than if a topic is simply imposed on you. And my project was then very much prejudiced by contact with Peter Lawrence, who was also at St Catharine's but a few years ahead of me. Through him I learned about cell-lineage tracing through somatic recombination in *Drosophila*, and so the idea of clonal analysis in the mammalian embryo came to mind quite early. And the blastocyst stage – because it was the last stage before implantation and the first stage of unquestionable cellular diversification – seemed the obvious place to start.

I was surprised to find your first two papers, published in Nature in 1967 and 1968, were on rabbits, not mice – how did this come about?

Between 1966 and 1968, Bob Edwards' progress with *in vitro* fertilisation (IVF) came to a complete halt until he made contact with Steptoe and could recover human oocytes by laparoscopy from the ovary. Bob was always active and ahead of his time, and started thinking of preimplantation diagnosis for people who were at risk of passing on genetic diseases but against the idea of abortion. In fact, from his time in Edinburgh and thereafter, his prime interest was the possibility that chromosomal abnormalities in the oocyte were responsible for a lot of malformations; that was really his top priority in looking at IVF. Later, when he teamed up with Steptoe, who through years of experience as an obstetrician understood the devastating effect that infertility caused, Bob changed his order of priorities. He didn't lose interest in chromosomal disorders but the treatment of infertility came to the top of the list.

But back then, in the mid 1960s, long before recombinant DNA, we fixed on the rabbit, which seemed perfect for the problem: the embryo grows to more than 5 mm before it implants, and there was very clear evidence that sex chromatin was present in trophectoderm cells of female blastocysts before implantation, which might enable us to sex them. But when we started doing microsurgery, it turned out to be an absolute pain – the sexed blastocysts tended to collapse and be expelled through the vagina when transferred to the uterus. So in doing the biopsies I had to make a tiny slit in the zona, well away from the inner cell mass, suck out a little column of trophoblast, and snip it off with Iris scissors before we did the genotyping; only in this way could contraction of the blastocyst and its expulsion from the uterus be prevented. I handed Bob the first six blastocysts for which the operation had gone perfectly for him to transfer to the uterus. He turned around with a sickly grin on his face with six pearls shining on the lapel of his lab coat! Martin said I just stormed out of the lab without saying a word – but we managed matters well in the end, and were able to show in these papers that the sexing was correct in all the blastocysts that developed to term. It was 22 years later that Handyside and Winston started to do preimplantation genetic diagnosis in humans.

There was scope for taking the mouse blastocyst apart – people simply knew nothing about it

When did your own trajectory diverge from Edwards'?

I realised from my experience using rabbits that the mouse was the species to work on, which in addition had a quicker life cycle and more genetic information available. And back at the beginning of my PhD, when I came back after my 3 months reading, I had suggested to Bob that there was scope for taking the mouse blastocyst apart – people simply knew nothing about it. They had guessed that the trophectoderm would only form placental structures, but they didn't know the fate of the two types of cells in the inner cell mass. My aim was then to develop techniques to separate the two tissues to see how they behave on their own and after recombining one with the other. I have to say the journey was a long struggle for 2 years, trying to develop techniques such as cutting away the trophectoderm. I used old brittle steel razor blades, hitting them with a chisel to fashion little scalpels, and also made various types of glass micro-instruments; most parts of my body were penetrated by odd bits of glass from trying to make needles and pipettes of different shapes and sizes. I was lucky that after spending so long developing the techniques that my MRC studentship was about to expire, Bob Edwards was able to get me a postdoctoral fellowship to continue the work, even though I was still pre-doctoral.

Since talking to Peter Lawrence, I'd also always had in the back of my mind that clonal analysis would be the most incisive approach to lineage, but I had no idea how successful my experiments in making chimeras would be. When I'd got to the point where I could actually make chimeras from single cells, it immediately struck me that, if there were suitable markers, might this approach be used to see when X inactivation happens? I therefore contacted Mary Lyon at MRC Harwell to find out whether coat colour markers existed that would enable activity of the two X chromosomes in females to be distinguished. She told me about a translocation in which the wild-type gene for tyrosinase was inserted into the X chromosome, and came to Cambridge with the relevant strains of mice for a sabbatical year with me in 1970. I relinquished the desk in my tiny lab-cum-office for this very distinguished geneticist who was an inveterate eater of chocolates: the top drawer of the desk ended up full of Mars Bars and Smarties, and the like! After my retirement, whenever I came back down to Oxford I'd try to make time to buy chocolates to take to Mary at her home in Dry Drayton, where she was under full-time care for Parkinson's but mentally completely alert. You could ask her what the latest was on whatever gene you were interested in, and always get a precise answer; it was absolutely remarkable. If one sits back and looks at what she achieved during her career, it is quite extraordinary. She was certainly the most remarkable person I ever worked with, and I still fail to understand why, when they gave the Nobel Prize in 1983 to Barbara McClintock on transposable elements in maize, they didn't use the opportunity to honour her as well.

Why did you then move from Cambridge to Oxford?

John Gurdon had relinquished his lectureship in zoology in 1972 to go to Cambridge, and I was sent the advert for it by a former colleague who said it was tailor made for me. I was very unconvinced; by then I'd had 7 years of freedom, essentially doing full-time research, and as Bob Edwards' work was funded by the Ford Foundation of America I didn't have to apply for grants. So when I went for the interview – which in fact was the only one I've ever been to – I was so equivocal about whether I wanted the job that I had a wonderful time, feeling totally relaxed. When I was offered the post I finally decided it was probably time that I developed a little responsibility. But moving was a baptism of fire: suddenly, having never had to worry about consumables or anything relating to running a lab, I had to apply for a MRC grant, and then discover the horrendous cost of the materials I'd been using in such a profligate manner! And there was also teaching for the college and the university.

Initially, it was just me and my first research student, Janet Rossant, and though I gradually recruited people I was finding life difficult as the microsurgery took up so much time. I had a moan to Henry Harris (who had chaired the committee that hired me), telling him I was considering leaving and going to a research institute

Development (2018) 145, dev167858. doi:10.1242/dev.167858

because my work was being adversely affected. He later called me over to his office and told me that Sir James Gowans was standing down as a Royal Society Research Professor: did I have any objections to having my name put forward to take his place? I thought it was ridiculous because all such professors had been Fellows for years, and had knighthoods or similar badges of distinction, but the Society was worried about the brain drain and ended up appointing a couple of us in our 30s. I started in 1978 and occupied that post through to retirement in 2008 – I was perhaps the longest serving Royal Society Research Professor. Regulation number one of the professorship was that I wasn't allowed to do anything, paid or otherwise, than my research without permission of the President and Council of the Royal Society. While this didn't get me out of domestic duties at home, it enabled me to avoid all sorts of other distractions. I was thus very privileged.

And the professorship also led to your engagement with policy work?

This began in the early 1980s when Andrew Huxley was President of the Royal Society, and the Warnock Inquiry into human embryo research was coming up. He wanted me to chair an ad hoc committee to submit evidence to Warnock, and then when the Warnock Report was produced, we were asked to produce a document on how the whole system of human embryo research should be policed, and it went on from there. At the time, we really just wanted to convey an accurate picture of what the status of the embryo was at that stage, what type of research might be warranted and what the benefits of the research might be. But it got to the point where we were producing all these papers for the Department of Health with no evidence they weren't just being filed away somewhere gathering dust. I raised this with the then President, George Porter, and he obviously took it on board because within 3 weeks he'd arranged for myself, Anne McLaren and Chris Graham to meet the Prime Minister, who at that time was Margaret Thatcher. She gave us a quarter of an hour each without interruption to explain all the issues. She was very bright – she picked up everything straight away, though I have to say that her two scientific advisors sitting nearby were much less impressive!

After Warnock, matters rumbled on. There was the build up to the 1990 Human Fertilisation and Embryology Act when we had to brief both Houses of Parliament about the case for human embryo research. After the Act was passed, we were confronted with the issue of ovarian donation, followed by cloning (prompted by Dolly), then the use of foetal material in research and treatment, and then mitochondrial disease. It was pretty much non-stop from 1982 until the 2000s.

The experience was valuable in several respects. It brought home to me just how low the level of scientific literacy was in the House of Commons compared with the House of Lords. It also made me very aware of the duty of scientists to inform the public of what they were doing in areas with possible practical implications for society. In addition, it brought home to me just how poorly scientific issues are often dealt with by the media. I've found that talking to sixth formers seems to be the most effective way of presenting scientific matters in a dispassionate way, providing unnecessary jargon was avoided, and it offered the bonus that those present may then enlighten friends and relatives.

From the start, your lab was always kept fairly small – was this a conscious choice on your part?

I have to say I was very selfish – I was determined above all else that I should have all the time I needed to develop and exploit micro-surgical techniques. I'm an experimental embryologist, and had round me a small number of people who could easily be trained up to help in that, or who were working largely independently. I don't think my group ever exceeded five or six people at any one time. Nowadays, procedures like blastocyst injections of embryonic stem cells can be done by commercial organisations, but it's different if you're trying to do things that haven't been done before and would never really be done on a large scale. My work with Azim Surani is a good case in point. It had been claimed that parthenogenetic embryos developed the foetus well, but not the extra-embryonic structures, and Anne McLaren among various people said that if you were to actually wrap a parthenogenetic diploid epiblast in extra-embryonic tissue that was derived from a normal fertilisation, it should work. I wasn't entirely convinced, but with Azim decided to test whether this was indeed the case. Azim sent the parthenogenetic diploid embryos to Oxford from Cambridge, and I had to do what amounted to a triple tissue blastocyst reconstitution – I had to put parthenogenetic epiblast cells from one set of blastocysts, plus fertilisation-derived endoderm from a second set, into trophectoderm vesicles minus the inner cell mass from a third set! The result was that we got more advanced parthenogenetic embryo development than anyone else had seen, but it was nevertheless not normal. The point here is that to get to that answer required a lot of technical innovation that would never be adopted routinely, but was developed to address a particular question.

In your Waddington Medal lecture you discussed whether the early mouse embryo was prepatterned – how did you get interested in this question?

When people started to manipulate the mammalian embryo, Tarkowski and others were interpreting early mammalian development on the basis of what was known in frogs – the assumption was that there was a prepattern there and that everything was really rather fixed. Then, when people developed technique for embryo culture and basic manipulation, that notion was completely rejected: the new view was that the mouse zygote was a blank canvas, and all the cells up to the eight- or sixteen-cell stage were totipotent and equivalent. Inside-outside signalling then operated to precipitate divergence of the inner cell mass from the trophectoderm. And I accepted that as everyone else did. But then I had to account for papers from Jean Smith (1980, 1985), purely descriptive studies with quite careful reconstruction of specimens fixed and sectioned *in utero* which showed quite convincingly that by the time it was implanting, the mouse blastocyst was asymmetrical. The inner cell mass was tilted, and this tilting, according to Smith, defined the anterior-posterior axis, and was conserved through to postimplantation stages. But she herself accepted that there couldn't possibly be any form of prepatterning, and therefore had to argue that these asymmetries were imposed by the uterus surrounding the embryo, which I found rather improbable.

These findings kept exercising me until I thought the obvious thing is to ask if there are departures from symmetry in blastocysts recovered from the uterus or which had developed purely *in vitro*. I found that they were oval, and also that two-thirds of early blastocysts had an intact second polar body that more or less stayed at the site of the first cleavage plane. This body was set at one end of the greater diameter at the equator of the oval blastocyst. Further experiments marking the zona with mineral oil backed this up, and I just thought, how do you explain this? When I did the statistics, the probability of those results being merely due to chance came to millions to one against. Everything seemed to point towards the idea that the embryonic-abembryonic axis is set roughly orthogonal to the plane of first cleavage. We carried this work much further to

Development (2018) 145, dev167858. doi:10.1242/dev.167858

show that the late zygote in the majority of cases is already bilateral – it elongates to become oval, and the first cleavage plane is very accurately orthogonal to its greater diameter at that stage. It has been accepted right back to the Hertwig's that cells divide perpendicular to their longer axis, so of course it fits with this.

Is this all trivial and meaningless? I don't know. But the slightly disappointing thing is that rather than others going in and doing exciting experiments to prove me wrong, they have largely ignored the issue – it doesn't fit their paradigm, so they don't feel they need to do anything about it. Colleagues are seduced by the idea that if something is highly regulative, it can't have prepatterning, but the sea urchin is highly regulative and there are indices of prepatterning there – the two are not mutually exclusive. You could imagine evolutionarily conserved cues that establish basic aspects of patterning in normal development, but that the embryo can recover even if those cues are perturbed. Janet Rossant and others are doing fantastic work on cell type specification up to the blastocyst stage, but nothing serious has ever been done to discover what determines the orientation of the embryonic-abembryonic axis – we have absolutely no clue about that, even though we know so much about other aspects of patterning. I'd encourage anyone interested in this question to read my papers (Gardner, 1997, 2001; Gardner and Davies, 2006), and would be delighted to offer advice for anyone with an inclination to take this further.

If you have serious intention of becoming an independent scientist, choose a supervisor who will give you great freedom

Is there any advice you would give to someone considering a career in research?

I would say that if you have serious intention of becoming an independent scientist, choose a supervisor who will give you great freedom – within limits – of choosing your own topic. Always in research you have periodic depressive lows, and I think you're more likely to survive those if, as much as possible, what you're doing is a product of your own interests and inclinations. This doesn't suit everybody, but I do think people who are too dependent on supervisors are going to have a difficult time post-doctorally. The really good ones often come along with a clear idea of what they want to do – which is what I experienced with Janet Rossant, Rosa Beddington and Paul Tesar, for example.

Another piece of advice, following Medawar, is that it is worth being informed about the literature but not too well informed. With the internet and instant access to information, a collective wisdom builds up, and people have real difficulty in being free to think outside that. Much scientific advance comes from outside conventional lines, from people who are thinking their own thoughts and going their own way, and young researchers should also keep that in mind. Choosing an enlightened supervisor will certainly help young researchers with that.

Finally, is there anything Development readers might be surprised to find out about you?

Well I'm a keen painter. About 30 years ago I found out I was finding it harder and harder to disengage from science, and I thought about watercolour painting because unlike oils (which I had been keen on as a teenager), you have to plan in advance – the scope for first aid, once you've painted something too dark for instance, is very limited indeed. I talked to this old artist who gave me four pieces of advice: firstly, don't be seduced by these great paint boxes with about 30 different colours, just stick with a basic set of 6 or so and thoroughly learn how to mix them; secondly, don't worry about fancy brushes at great expense; thirdly, at the risk of people leaning over your shoulder and being critical, go out and paint from nature as much as possible – it forces you to abstract, whereas if you do it indoors you can become overwhelmed by detail; and finally, when you think you're near the end of a painting, leave it overnight – if you keep on adding detail, you'll often get to the point where you wish you'd stopped half an hour ago. I followed these pieces of advice and have enjoyed watercolours ever since. Otherwise, I also enjoy reading, including books about the history of science – the early correspondence of Darwin I've found particularly fascinating.

References

Gardner, R. L. (1997). The early blastocyst is bilaterally symmetrical and its axis of symmetry is aligned with the animal-vegetal axis of the zygote in the mouse. *Development* **124**, 289-301.

Gardner, R. L. (2001). Specification of embryonic axes begins before cleavage in normal mouse development. *Development* **128**, 839-847.

Gardner, R. L. and Davies, T. J. (2006). An investigation of the origin and significance of bilateral symmetry of the pronuclear zygote in the mouse. *Hum. Reprod.* **21**, 492-502.

Smith, L. J. (1980). Embryonic axis orientation in the mouse and its correlation with blastocyst relationships to the uterus. Part I. Relationships between 82 hours and 41/4 days. *J. Embryol. Exp. Morphol.* **55**, 257-277.

Smith, L. J. (1985). Embryonic axis orientation in the mouse and its correlation with blastocyst relationships to the uterus. Part II. Relationships from 41/4 to 91/2 days. *J. Embryol. Exp. Morphol.* **89**, 15-35.