

Not a total waste of time

An interview with John Gurdon

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John Gurdon is John Humphrey Plummer Professor of Cell Biology in Cambridge, Chairman of the Wellcome/CRC Institute, Master of Magdalene College, and Governor of the Wellcome Trust. Like the rest of us (many of whom complain about having too much to do), he also runs a research group, writes papers, goes to meetings and does more than his fair share of refereeing. How then, does he find time (as he does) to do experiments as well? This is one of the questions I was keen to ask this remarkable man. I also wanted to know how John Gurdon started in developmental biology, and was amused to find that one of his school teachers actually regarded John Gurdon as the worst biology student he had ever had, and indeed, that his continuing to study biology would be a total waste of time. Hardly!

Since these school days, John has carried out pioneering experiments in developmental biology, some of which we discuss below. All this work is characterised by careful and logical reasoning that is reflected in the clarity of his lectures. John Gurdon was knighted for his services to Developmental Biology in 1995, and this is just one of a list of prizes and awards that occupies many lines of *Who's Who*.

When did you first become interested in biology?

My first interest in life sciences arose from an aunt who used to take me butterfly collecting at the age of about 6, and I then

collected these amazing insects and retained an interest in them from a somewhat amateurish point of view ever since, on and off. Even now I'm fascinated by the problem of how intrinsic colour patterns can be controlled genetically. For example, I took a trip to the Solomon Islands with an entomological expedition last year, partly because I wanted to see what the Solomon Islands and New Guinea are like, but it happened also to coincide with seeing rather spectacular and interesting colour patterns of bird wing-butterflies and some moths.

Did you study science at school and was there a favourite teacher who influenced you?

That's a good question and curiously the answer is partly the converse in the sense that I used to infuriate my House Master at school by growing millions of caterpillars. This was Eton. He could never see the point in this. I started studying biology with some enthusiasm at the age of 15 but by the end of the first term I had the most crippling report from the Biology Master, a copy of which I keep to remind me of the occasion. The sort of thing it says is "Gurdon has been a terrible student, there has even been talk of him continuing to study biology but this would be a total waste of time, both on his part and on those whose job it was to teach him." He then went on further, just to rub it in, to say I was the worst pupil he had ever taught in his whole career. This was when he was in

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his 60's and about to retire. So, naturally enough my House Master said "well, what is absolutely clear is that science is not for you, so we will move you from that". So I then studied Greek, Latin and German for the rest of my time at school. My poor parents were then persuaded that really my interests were in science—biology, and were generous enough to pay for another year of cramming to survive the early years of science exams.

You must have been very keen on science to have persuaded your parents to do that.

Yes, my parents were good enough to see that my real interests lay in science. And in fairness the excellent Greek and Latin Master who taught me ended up saying that it was perfectly clear that my interest was in science and good luck to me if I wished to change back to it.

But you must have been devastated by what the Biology Master was saying.

In retrospect it was probably one of those happy events in your life, in that the Biology Master was notorious for being one of the worst Masters in school and certainly would have discouraged anyone from studying the subject if he continued to teach it. Indeed in my time at Eton I don't think there were any people who went on to study science or medicine, possibly because they were so discouraged by the bad teaching. In a sense, it was a great fortune to be got off the subject early enough not to be discouraged from it for the rest of one's time.

Just in case it's helpful to continue this story, there was then the question of where I should try to go to university. There was then one of those curious things in those days in which my school House Master particularly wanted his son to be accepted to go to an Oxford college where the Head was a friend of my uncle, who was

at another college. A deal was done by which the school Master's son could be accepted into one college if my college then accepted me. So I took the entrance in Greek and Latin and the response was that they would happily find a place for me, on one condition, that I did not propose to study Greek or Latin. My Greek and Latin were below the proper standard, and indeed it was always understood by the school master that I was doing these subjects as a sort of relaxation study, and it wasn't at a level that would allow one to survive at University. So that was another curious back-door step. Indeed they had to allow me a whole extra year beyond the normal three to get to the point of being able to start doing biology at Oxford.

So you arrive at Oxford reading what?

I arrived with a view to reading Zoology and they said "in order to accept you, you must do a first year which would get you up to A-level standard." So you have a year of cramming before you go and then you do a year of this elementary work and then if you survive that, you are allowed to do the full three years in zoology.

You chose zoology because of the interest in butterflies?

I suppose that is probably right –again it happened that my parents were very good friends of the Head of the Zoology Department who was an extremely pleasant and supportive individual, and we thought between us it would be a suitable subject, possibly because I was rather interested in zoology.

That's an extraordinary introduction to your university career. Did you enjoy zoology at Oxford?

Up to a point. In those days the zoology course was roughly 50% animal anatomy and particularly paleontology, so we used to do three days a week learning dinosaur bones, every bone that had ever been dug up as far as I could see, and the name of it and shape of it and only a very small amount of experimental biology came in. So only up to a point did I enjoy that, but the next stage arose because of a very sympathetic man who taught embryology, Michael Fishberg, and he was kind enough to enquire whether I might be interested in doing PhD work.

I should say that this was after my first but unwise inclination had been disposed of, and that was to do a PhD in essentially insect ecology and, happily, I was rejected by the Department of Entomology.

So this was your main inspiration.

Yes, it was really.

And your introduction to *Xenopus* as well.

Yes, Fishberg offered me a number of PhD projects and the one he started me off on was a rather old fashioned one of making what they call andromerogones. This means you fertilise an egg with a sperm of some genetically different kind and remove the egg nucleus or not and you look at the morphology and characters of the resulting embryo and decide whether they came from the incoming genetic material or the maternal one. In this way, you

work towards an understanding of development. Well, that went on for three months but I didn't warm to it a great deal.

Did you publish anything from this work?

No. My very first paper, curiously, touches back on insects in the sense that when the spring came I used to like to go and see what insects were around and I went to the nature reserve in Oxford called Wytham Woods. It was a cold March day and I couldn't find anything that was flying around at all so I caught the first thing which emerged from the trees and it turned out amazingly to be a new species of insect, which was pretty exasperating for the Entomology Department since they had many projects and they'd never found this thing, so that was my first little published paper on a new kind of saw fly.

But that early success wasn't enough to make you want to become an entomologist.

Not really, well only enough to enquire about a PhD, and happily that was rejected. Then I had a much more substantial interest in mechanistic things –how things actually work– and this became possible through Michael Fishberg.

I should have explained, that having got relatively uninterested in the earlier project, Fishberg pointed out that Briggs and King had found a way of transplanting nuclei and it might be interesting, and indeed he was right, to try it on a species like *Xenopus*, which was much more convenient experimentally. Happily that took off, with a number of pieces of luck, but it did take off very quickly and so three months after starting, I switched completely over to that and of course this was a fascinating subject and developed quite well.

And you've never looked back.

Well, I've happily had a career in this field ever since, and that's very fortunate. But very much, I must say, due to the management of my supervisor. I feel increasingly grateful to him; unfortunately, he died some years ago. He really was an outstandingly good supervisor –giving you enormous freedom. If you were interested in something, he'd say "fine give it a try and see what you make of it." And once something worked he was enthusiastic and encouraged you to go on. He was really absolutely crucial in the field in which I have worked ever since.

In parentheses, do you think doing a PhD now is very much different from then? I imagine it is, a lot more pressured.

Yes, I would agree with that. In those days you did what you could and it was sort of assumed that if you did whatever you felt you could do, it would get a PhD. Unless by bad luck you were examined by one of the horrors of the time, as far as PhD examining was concerned, an example of which was known to be Professor Darlington, who had a reputation for failing theses.

I imagine he wasn't called upon to examine many theses. Perhaps it was his way of getting out of it.



Correct, although sometimes you got given him as an examiner like it or not.

I am interested to know, since you have worked on *Xenopus* for so long, whether you've been tempted by other organisms or whether *Xenopus* has met all your experimental and intellectual needs.

Yes, I did have a few forays into other areas and a good example of that is when I finished my PhD with Michael Fishberg. I had been offered post-docs in the main nuclear transplantation labs in America, not too surprisingly, but again he was very wise and said "there is absolutely no point in doing what you've done already; do something entirely different." He had met Beadle from Caltech and persuaded him to offer me a post-doc there. I went over there and was actually intending to work on viruses with Dulbecco. When I got there, they said "if you don't already know how to work with viruses (which I didn't) you would be unwise to try and learn because he is much too busy to show you. Instead you should work with a much younger faculty person called Bob Edgar on bacteriophage." So I took that piece of advice and worked for a year with a quite inordinate lack of success. I couldn't get a tidy mutant to do anything. But I learnt a great deal because I had no remote understanding of anything, even a tiny bit biochemical or molecular, and that was an excellent environment in which to understand a little of how it works. Again, it was extremely good advice from my supervisor and I had a very rewarding year in the sense that I learnt a lot, but never published anything and indeed came to realise that I was so much better suited to embryos than bacteriophage genetics.

Then a few years later, I felt it would be sensible to try doing nuclear transplantation in *Drosophila*, but the reasons probably weren't particularly well thought out, so I tinkered with that a bit and found it troublesome.

Where was this, in Oxford, on your return?

Yes. By fortunate circumstances my boss, Fishberg, while I was away had taken a job as Professor of Zoology in Geneva thereby



vacating his own job, which I was then offered at a lower level than his, of course. But I had that job in the same Zoology Department, like an assistant professor, and started a little group and began to see whether branching out into *Drosophila* was sensible. But I wasn't very successful and perhaps in retrospect it wasn't a particularly important avenue to follow. Then I rather quickly returned to *Xenopus* and have never really considered leaving it since. I thought that you are mostly better at doing those things you can at least to some extent do, then trying to branch out too widely.

In Oxford, then, you are studying the potency of nuclei. Do you see this as different from your current work, which addresses how cells become different from each other? Was there something that pushed you down that latter road?

I would, I think, argue that the earlier nuclear transplantation work that I, and indeed Briggs and King, did was actually directed to what I see as a developmental question, for the following reason. The idea at that time, or the uncertainty at that time, was whether all cells had the same genes or they don't, and if it had turned out that they don't, which was actually the conclusion reached by Briggs and King, then the question would almost certainly arise as to how come the right genes are lost and what is the mechanism, because that would be expected to have something to do with cell differentiation and development. So having persuaded myself, and perhaps eventually others, that any loss of genes or permanent switching off of genes is not a feature of development, you then reach the next question of how are genes differentially expressed. I would argue that as the nuclear transplantation work finished up, and it took some years to keep tidying up little bits of it, that is really what I have moved to – mainly in more recent times with an interest in signalling, which I see as very close to the problem of development as you know yourself.

Developmental biologists can be passionate about their subject. Do you have a passionate desire to solve development?

I think I do; and from the earliest stages of nuclear transplantation I have been aware of what I would like to know. In other words, if you suddenly said to me "reveal one key scientific fact without me having to do any experiments", I would like to know how an egg turns into a variety of differentiated cells. I don't terribly mind once you go beyond the larval stage – it seems to me that the principles have been established by then. So I do see that as a single major question, starting with "are the genes the same" and then going on to 'how you get differential transcription.' I tend to think this has a lot to do with signalling between cells and hence, I would ask what is the mechanism by which cells send signals and turn the signals into differential gene expression.

You lead me to ask two almost philosophical questions. The first is that, when I hear you speak, your lectures are a model of clarity and logic and are therefore very easy to follow. I wonder whether this reflects in any way the way you think about development. The second question is, what you would regard as an answer to development: what is the level of understanding you strive towards?

Well, I'm sure you are being unreasonably generous to suggest my lectures are clear, but insofar as they might be, then I think a good deal of tidying up is done between doing the experiments and trying to put them together in some coherent whole. This is almost imposed upon me because I can never understand anything at all that's complicated, so I simplify it to a level where I can understand it. So, I think I always feel that I operate a bit opportunistically, in the sense that if you see an experiment that you really think could be done very nicely and give an answer, even though it wasn't exactly the next answer that I wanted, I would do it and try to tidy it all up later into some reasonable logical sequence.

Then the second question was what level answer is one looking for? I think that I see the end point of my own interest being a complete understanding in molecular terms but not atomic terms of how differentiated cells appear, whether it be a muscle cell or a nerve cell. If you could explain how you go from an egg to the appearance of a muscle cell, for example, that would be what I view as an end point to the level of my enquiry. So, it's more a level of an interest in cell differentiation than in pattern formation. You could say, why muscle cells are arranged in a particular order or relationship to each other, well that may have something to do with why they become a muscle cell at all but I would be rather less interested in, shall we say, why a muscle is a particular shape, it's still a muscle. To me, the fundamental question, my interest, is how you go from the egg or embryonic cell to this highly specialised cell.

Again, I think my own interest would be in understanding that in terms of populations of molecules; so I think eventually we will have to know pretty much the molecular content of cells as they go from egg or an embryo cell into a mature cell. We need to know more or less the numbers of the different molecules, where they are and how long they spend interacting with each other. Solving all of that will last beyond my time, I have no doubt. But it does seem to me that unless we know that we are probably not going to really understand the process.

I suppose I could add one other point to that and say that my own feeling is that when we really think we understand development we should actually be able to take it backwards from the end right to the beginning and then send it out on a different route. I was asked recently: imagine yourself many decades hence when your subject might be well understood, what use would that be to people? And my own answer to that would be that I would think that we should be able to contribute to human welfare, particularly through the route of cell correction or even replacement. So, when we suffer from some defect –some organ or tissue has not gone right– we should be able to correct the cells that have gone wrong or even replace them with ones that we have grown in culture, perhaps from embryonic cells or even from adult fibroblasts. We should be able to send them back down development to some kind of embryonic stage and then by use of factors and so on send them off in the direction we want.

So, if you know the road that the cell took to get from egg to muscle you could return back along that same road and if it had made a mistake on the way you could stop and say you went right here, you should have gone left.

Yes, that's right.

That's a good way of thinking.

I'd like to think of it that way and of course, thinking of the usefulness to humans, one could say, "well when a baby is born why don't you just take a few cells out of it and put them in the fridge?" You could do that and actually if you did it for 50 million people it would take a liquid nitrogen container about the size of a swimming pool –it wouldn't be particularly large– but it could be more practical actually to wait till someone needs extra cells and then grow fibroblasts out and rejuvenate them and, as you say, you can send them along a different road.

Thinking about the roads one might send a cell down, don't you worry that they are going to be enormously complicated? We all work on particular genes, and we all draw little diagrams in which our particular molecule interacts with a number of other molecules, and our own molecule is always at the middle of the diagram with lots of arrows radiating from it. But if you try to put everybody's diagrams of that sort together you will end up, as I said to Lewis Wolpert, with one of those charts of the metabolic pathways that used to adorn every lab. But charts of that sort which attempt to explain development would be much more complicated because they would be in three or four dimensions.

I think those metabolic charts lack some quite important things, however complicated they indeed are, but at the moment I feel particularly sensitive to the point that the concentration of molecules is very critical. So, we draw a diagram from A to B to C but that may only be true under conditions where you have that pathway being pre-eminent. Maybe there are several hundred thousand pathways but I would guess that most of them are not actually relevant to the way a cell works. So, what we really want to know is which are the ones that really matter, and I guess those would be a lot simpler than the three dimensional metabolic chart. I think, to be honest, our field

at the moment is rather insensitive to this; we tend to take a gene, over-express it and it turns on gene B, but we might be over-expressing it by a hundred fold, and it may turn out to be completely irrelevant –what we want to know is which are the routes that really matter. I am always impressed that such small changes in concentration can make an enormous difference. I think the problem may be less severe once we limit everything to relevant concentrations.

Another thing I am interested in, is the fact that you still do experiments with your own hands, despite your college commitments, the Wellcome Trust, the demands of the Wellcome/CRC Institute and so on. How do you do that? What's the secret? Many people would like to know!

Well, thank you for pointing out the thing I much enjoy being able to do. I think I am probably a bad supervisor –what I do not do at all is go round the lab every day and say "how did your experiment work yesterday" or even last week –because often as not I may have forgotten what experiment they are doing. But I like to think that my contribution is likely to be greater, certainly to myself and possibly even to colleagues, if I do the things that interest me, and then when, as sometimes happens, they work well, that provides interesting avenues for other people to work on. So, I spend very little time surveying the effects of others, though I greatly appreciate having a group who are doing things and we sort of talk in a very informal way, usually at coffee or tea, or in the passage or on the way to a lecture and that does leave one quite a lot of time for my own experiments.

So I have a certain routine, which is that, unless it's absolutely crucial, every Tuesday of each week is kept totally clear of every commitment, and usually the next morning as well. That is then my actual experimental day and sometimes night and sometimes next morning. Of course, I should say that I do not do my own *in situ* hybridisations, I don't grow my own clones and so, I really only do work of an embryological kind, work that I am to some extent suited for. But I feel strongly that it keeps me in touch with what can be done, and I'd like to think that there have been a number of cases where I followed a line that I happened to find interesting and it's turned out to be interesting not only to me, but really quite useful to a number of my colleagues. So, I'm a strong believer in however elderly you might be, in being able to arrange one's life such that one does still do the things that have worked well for one.

You raise, quite rightly, these other things that one takes on in life. Just to mention these briefly, the College commitment came about by invitation, as it does, and I said I would be happy to have my name considered with all the others as long as it wouldn't significantly take me out of the lab. And so, they had to decide whether that was acceptable or not, and in the event they decided it was, and indeed they get a very small amount of time. Usually only an hour or two from 6.30 in the evening.

Then the Wellcome Trust does take significant time. On the other hand, one learns quite a lot and, I almost always decline anything to do that involves a Tuesday.

The Wellcome/CRC Institute here is absolutely a marvellous place to work and the reason that my Chairmanship doesn't take much time is two-fold. The main one is that we have chosen to work as a democracy, so all the group leaders, of whom there are now 17, take all major decisions and I am absolutely not a director, I just chair a committee. Of course, the happy thing is it works in my view

extremely well because all group leaders feel they are part of the process by which the Institute runs and they are extremely cooperative. So, really nasty things like worrying about computers, animal inspectors and nightmares like that, are shared out amongst these people. I should also emphasise that I have an extremely efficient administrator or secretary who basically tells me what I have to do and when. So it's a matter of shelving a lot of things onto other people who are good enough to take them on. I really am personally very dedicated to doing one's own experimental work, even though I clearly do not spend 7 days a week on experiments, but I get enough done to be worthwhile.

The other thing I am afraid I do rather ruthlessly is to have a start time and an end time. If someone says 'will you go to a committee' I usually ask 'when does it start' and 'when does it end'. I'm afraid I keep to that—if it isn't finished, one stops!

Would you define yourself as ambitious? I asked Lewis Wolpert the same question, and I'll tell you why. The three of us were at a meeting in a castle in Germany and we were playing "round the table table-tennis." The last players left in were you and Lewis, and you were both playing with great determination and occasionally guile. Does this desire to succeed cross over into your scientific life?

I remember the meeting, well at least I think I do, but I can't recall the rest. I think I would probably say from my school days I was rather competitive at sports, so my ambition at that time was to be Captain of the school's squash club. I did work extremely hard and got there. Then another one of my ambitions was to get a gold medal for skiing, again I had to work very hard, and happily I got there. So I do have a sort of inclination to achieve at least at the appropriate athletic level. Whether that extends to being competitive in science...

...maybe ambitious is a better word...

I think one has ambition in the sense I would like to think that I wish to be able to feel I am making a worthwhile contribution to the field I'm in and that constitutes, I suppose, an ambition. One has to set oneself realistic ambitions and always adjust upwards and downwards, but at least they are subject to adjustment. So one should have ambitions, hopefully, not at other people's expense!

Let me ask you a question Lewis was hoping I would ask him when I spoke to him: if you were starting out to do a PhD now, what would be the subject, and who might be the supervisor?

Well, as it happens I haven't devoted much thought to it, and one would never reach a decision on the spur of the moment.

Well, I won't press you to give me a supervisor! That would be unfair.

Well I suppose it varies from time to time but the area that does undoubtedly intrigue me a great deal at the moment is essentially that of trying to make development go backwards and thereby redirect the fate of cells. It's not too far from what I've been trying to do for a while, but I think if I were starting again I would probably want to do a post-doc or PhD in an area I don't know much about,

namely cell culture. In this way, I would want to try to find out what changing conditions really can do to determine the fate of a cell. This would be on the grounds that we know quite a lot now and about changing the genetic constitution and expression of genes in a cell, which is of course crucial, but it is also clear that how you grow cells can make an enormous difference.

The sort of thing one would like to know more about is "can you take a cell at some stage in its development" —say it has reached a state from going to C to D in its pathway. Now you say "can I amplify C exhaustively so I have millions of cells of C and then can I turn them on to D, and then to E, and then amplify E, and can I then switch it on to another route?." Then the area that I think is important is to understand, not just how that's done at the genetic level but also at the environmental level. So I would be quite likely to think of taking training in that area—using cell culture to ask what contribution a cell's environment can make on its fate.

But what you could do is tell me how you would answer that question.

Well, I really do want to understand morphogenesis —what makes a cell change its shape and move in a particular direction. I think this is a field that is really poorly understood. You can imagine mechanisms that turn a gene on in an embryo, and although this is a very dangerous statement to make, I don't believe there are going to be any major surprises in this area. But when it comes to asking how does a cell change its shape and know it should move in that direction or that direction, there I think we know much less and there are surprises in store, perhaps even new principles, so I would like to do something along those lines.

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Nuclear transplantation

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Mesoderm and muscle embryology

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