

From engineering to positional information to public understanding

An interview with Lewis Wolpert

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Lewis Wolpert is one of the most influential developmental biologists in Britain and the world. His concept of positional information, developed 30 years ago, changed the way we think about pattern formation in the embryo and allowed new generations of molecular developmental biologists to frame their questions in a way that would give sensible answers. One measure of the success of the concept, as we discuss briefly below, is that the original paper, published in 1969, is now hardly ever cited. Its influence, however, clearly pervades current attempts to understand the generation of spatial pattern in systems as diverse as insect imaginal disks, amphibian gastrulae and vertebrate limbs.

Positional information as an idea would have succeeded on its own, but its acceptance by the community of developmental biologists (after a brief hiccup—see below!) has been accelerated by Wolpert's clear writing and brilliant lectures: he is a charismatic speaker and performer. These qualities have resulted in invitations to give lectures, to present television and radio programmes and to give the Royal Institution Christmas Lectures. His interviews with scientists have been published in two volumes, and he has also written books on developmental biology (one textbook and one popular account), on *The Unnatural Nature of Science*

and, most recently, on depression (*Malignant Sadness*). He is one of the few Fellows of the Royal Society who is also a Fellow of the Royal Society of Literature, and in addition he has been awarded the CBE¹.

As is well known, Wolpert began his career as an engineer. I was interested to know what got him interested in biology, where the idea of positional information came from, and what he thinks about the Public Understanding of Science.

Part of I want to do today is take you through your life to discover how you became a developmental biologist and what influenced your ideas.

I've always wanted to interview myself!

You came here from South Africa where you were a civil engineer who specialised in soil mechanics. What got you into engineering? You don't fit the usual stereotype of the engineer!

I was good at maths at school and I was good at science; those were my best subjects. I wasn't bad at the others but maths and science were easy and I liked them. I made model aeroplanes, I

¹CBE, Comander of the British Empire

had a chemistry set and an electric train, I made radios that didn't work... I remember I was very jealous of my cousin, who although a year younger, understood electricity before me (I think he was about 9). When I had to decide what to do at University I didn't want to go into medicine, and in those days if you were from a bourgeois Jewish culture you didn't go and do science –in fact, I never met anyone who did science. I chose engineering, but civil engineering because it seemed less greasy than mechanical.

From the moment I got there I regretted it! My friends were doing arts, the girls were very pretty and it seemed so much more fun than what I was doing. At one stage I thought of becoming a mathematician, but I wasn't really good enough. When I finally finished engineering, I didn't know quite what to do, but I got an offer to be the assistant to the Director of the National Building Research Institute in Pretoria. He was interested in soil mechanics and that is how I got interested in it. I was in Pretoria for two years –this was 1951/1952– and had a wonderful time.

So at that time you were never interested in biology?

I had lots of friends in medicine and I used to go to seminars on genetics and the philosophy of science, but I knew nothing about biology whatsoever. But you know, by the time I was in Pretoria I was already thinking of how to get out of engineering –I really didn't want to spend my time as an engineer. So I thought of going to Israel, which to my family was much more acceptable than what I wanted to do, which was to go to England. I also thought that maybe I could do something useful with my engineering –but I was already thinking “how can I get out of it?”

Why England?

I had been on a student tour of Europe in 1950, which was wild and magical and I wanted to come back to London –I thought it was terrific, even in the winter. I also wanted to get away from the politics. I was quite involved in politics in South Africa –I knew Mandela, I was involved in the left– but I didn't like politics, I wasn't good at it, I didn't like selling left-wing newspapers. What I wanted to do was come to Europe and get away from my family. In Johannesburg my family lived in a sort of bourgeois environment and it was difficult for me to go anywhere –let me put it this way: I couldn't have taken a flat in Johannesburg because my family would say, why aren't you living at home?

So you went to Israel as an engineer, but in the back of your mind, you're going to London.

Oh yes, oh yes, oh yes. Israel was the only place I experienced anti-Semitism. In Pretoria I worked for a government organisation where I was the only Jew –absolutely no problems. In Israel I worked in an organisation run by Bulgarian Jews and they persecuted me. I was very angry with them –I left after a year, I didn't stay long. What happened was that I got a bursary to do a diploma at Imperial College in Soil Mechanics. The Director of Building Research had given me a very strong recommendation.

Coming to London in 1954 was like heaven. I was totally anonymous, there were beautiful girls, I went to drinking clubs in Soho ... I can't say it was a happy time, but it was a very wild time! In my first year I was doing a diploma in soil mechanics, absolutely desperate to get out of engineering. I became interested in the life

sciences for some reason and I thought I would do medicine, but my family said they wouldn't give me any money.

What was that reason?

It's very hard to describe. It's a terrible thing to say but I didn't want to spend the rest of my life with engineers. Also, although the problems were interesting technical ones I didn't really care about the answers. So I first came to see the Professor of Physiology here at University College. He was very encouraging and I was terribly excited –I came off the streets and the Professor of Physiology, here at University College, spent half an hour with me, even though he had no idea who I was. To see the professor in South Africa you'd have to get an appointment six months in advance! But then the real crucial thing is that my friend Wilfred Stein was getting married. He was a very close friend, and a chemist in those days, and he was coming to London to do a PhD with Danielli. Wilfred came from Durban but was getting married in Cape Town, and they said: "get out of the house we have a few things to do". So he went to the Cape Town public library and was glancing through journals and came across an article by Swann and Mitchison where they were looking at the mechanical properties of the cell membrane. He immediately wrote a letter to me saying, "Lewis '(he knew that I wanted to get out of engineering),' I've found what you should do: mechanical properties of the cell membrane. Why don't you go and speak to Danielli at King's?"

I went to Danielli, who was very excited and said “we would be delighted to have you”. The Nuffield Foundation in those days was offering people the chance to change from the physical to the biological sciences, whether you were in mathematics, chemistry or physics. I remember when I went to Danielli the first time he said: “maybe you should meet Bernal”. J.D. Bernal, the great physicist who was interested in clays and the origin of life, spent a whole morning with me, I did not understand one single word, but Danielli said that he would take me, and Nuffield gave me a scholarship. Life changed, but I went on drinking in Soho!

Now you were at King's doing a PhD on the mechanics of cell division...

It took me quite a long time, because I had to do my undergraduate work –I don't think I got my PhD until 1960, '61. You know, quite a long time.

Did you publish much?

No, the first paper I published was wrong. I said that ATP blocked cell cleavage, but it was an artefact, because I hadn't corrected the pH. I just didn't know, I'd used pH paper to correct the pH and with seawater it doesn't work –you have to use a pH meter.

After my PhD I got a lectureship almost at once, Assistant Lectureship.

By this time you're thinking about sea urchins, is that right?

Not really. For my PhD I started with amoebae. There were a lot of amoebae about. But then Danielli introduced me to sea urchins, which you could only work with in the summer. For the first summer I went to Millport in Scotland, and I thought, “I can't spend another summer here, I'll die”, although the sea urchins were good. So I looked where other people went and they seemed to go to Sweden.

I got a grant from the Browne Fund at the Royal Society, who gave money for people to go to marine stations, and I went to Sweden to work on sea urchins where I met Gustafson. And that's how I got involved in sea urchin development.

So sea urchins were initially a source of interesting cells rather than an interesting embryo.

Cleavage, purely cleavage. I did some very nice experiments with them showing cortical contraction. We were the first people to identify a structure in the cleavage furrow. At the same time Danielli was very keen on amoebae, so I was doing two things really. We were the very first people to isolate motile cytoplasm. Tom Pollard made great progress with our technique. He acknowledged it recently in *Current Biology*. And we were amongst the first to purify cell membranes from amoebae, we made an antibody against the membranes, put fluorescein onto the antibody, labelled living cells and showed that the membrane was fluid. (Wolpert and O'Neill, 1962). Probably one of the best papers I ever wrote and totally and utterly neglected.

So we made two major technical advances, but while I was working in Sweden, I met Gustafson who was filming sea urchins and we became very friendly and that's how we started. That was my first introduction to embryos. I knew nothing about embryos whatsoever before that.

Most people, when you talk to them about development, say how much they want to understand how a single cell, the fertilised egg, becomes an embryo and so on. But I don't get the impression that this was one of your abiding concerns.

Not originally, but I became fascinated by morphogenesis when I looked at his wonderful films, and then I became interested in how the embryo developed, sure. We showed that one could account for sea urchin morphogenesis in terms of just a few cellular activities.

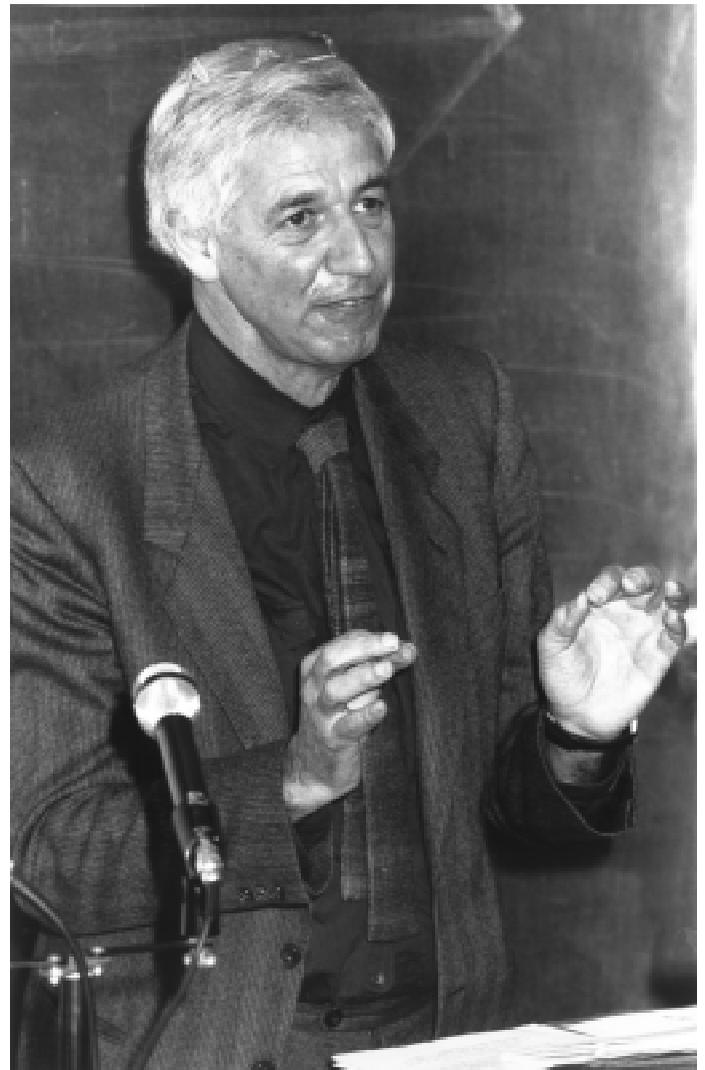
In those days there was the Swedish school of gradients and things like that and I felt a little uncomfortable and wasn't persuaded that they got it right. That is how I started to think about embryos –and then I needed a winter animal that I could work on in London and I chose hydra.

What did you do with hydra? Was it this work which led to the French flag model?

I was trying to understand regeneration, but I think I had invented the French flag problem already, because I knew about sea urchins and hydra seemed rather like sea urchins. I even had a theoretician, Michael Apter, working with me to think of what sort of models would work.

You say you had invented the French flag problem, but where did it come from?

I can tell you exactly where it came from. What I knew from sea urchins was that irrespective of how big the embryo, the proportions were right. You know, if you had a quarter embryo, the proportions were right, and if you had a double size one, eight times bigger, the endoderm:mesoderm:ectoderm ratios were the same. And with hydra, whether you had a big hydra, or a small hydra, the



proportions were more or less the same. So, how does one think about that, and I just thought to simplify, it...

So the problem really did come before the solution –it wasn't that you had this neat idea and then thought of a problem to fit it!

Absolutely not! The solution took a long time to come. We had lots of theoretical discussion and there were all sorts of people in the lab thinking about it. As well as Michael Apter there was a PhD student, Gerry Webster, for example. One day, and I can't even remember when it was, the answer suddenly struck me, and it seemed to solve everything I was thinking about.

And there was another driving thought, which was important. I was unhappy with developmental biology in the sense that I couldn't stand my envy of the molecular biologists having general principles. I decided that if evolution had taken the trouble to have general principles for the genetic code there was absolutely going to be general principles for development. So I wasn't looking for specific solutions, I was quite convinced that there was going to be some general answer.

Positional information had a mixed reception, I believe.



I invented the term 'pattern formation' through this work, although it was sort of in the Waddington tradition. Wadd was supportive, although he didn't like positional information, he hated it, but at least he took it seriously!

For me, coming into the field in 1976, positional information was a distinct way of thinking that really helped one explain and think about experiments.

Yes, in the *Journal of Theoretical Biology* paper I could take all the relevant literature and explain much of it; and it all suddenly became clear. So it was a widely exciting time, very, very exciting, it really was. You were there, it was fun.

To return briefly to your career, to put this into context –during this period you became Head of the Department of Biology as Applied to Medicine at the Middlesex Hospital Medical School. You were working on Hydra, but you weren't doing experiments yourself...

Good God no! Amata [Hornbruch] was there, Stuart Clarkson, Judy Hicklin...

Why didn't you do experiments?

I'm bad at it. I isolated membranes for my PhD, but I'm not good at it and I don't like it and I get anxious. It's not my skill. I'm the one that says I don't know why anyone cooks if they live near Marks and Spencer's! Do you understand?

I think my wife and I might subscribe to that view...but this means you depend on your colleagues a great deal.

Absolutely, Amata was my hands for many years. My skill is to persuade other people to do experiments.

You were saying that the years after positional information were fun. I think part of it was that there was never really any 'right' or 'wrong' answer –you could interpret experiments any way you liked and design more experiments to test your model. Somehow this simultaneously made things more fun and less pressured. There was none of this business of racing to clone something...

Well you know what Peter Lawrence writes about –it was a very different world. It was easier to get money, more relaxed, just very different.

It's been 30 years since the *Journal of Theoretical Biology* paper –would you say the idea is correct?

I still think it's a very interesting idea. I think its doing pretty well, frankly, I think the interesting thing at the moment is how you set up and interpret gradients. This is a really open and exciting question.

It was more complicated than that. I first gave it at one of Waddington's meetings on theoretical biology at the Villa Serbelloni on the shores of Lake Como. I told Brian Goodwin about it in the taxi from the airport and he was wildly excited about it, and that is where his phase shift model came from. People at the meeting were interested and that was the first time I published it.

But then I went in 1968 to Wood's Hole, where I was invited because of my morphogenesis stuff. I gave this grand Friday night lecture on positional information and patterning, and that was met with hostility. They wouldn't speak to me. I swear to you that when I went to the reception afterwards no one spoke to me and when someone introduced me to Ed Zwillig, he turned his back on me. I got very depressed. The next morning I asked a mate of mine what was going on, he said "Lewis they're all saying –who the bloody hell does he think he is?"

But it was Sydney Brenner who saved me. Sydney said 'pay no attention, I think what you're doing is really interesting. Francis Crick and I have been thinking a little bit about it, it's really exciting, write it up and pay no attention.'

Sydney's influence there was absolutely crucial and I wrote it up for *The Journal of Theoretical Biology*. That had a fabulous response and then what really made me respectable is that Francis quoted it in *Nature*. But Peter Lawrence was of course already thinking along similar lines. I think Francis's involvement gave it respectability, but the Americans –it's taken, I would say, 20 years for them!

What was it that they didn't like?

In part they thought it was just another gradient model, but the real problem was that they couldn't bear that I told them they totally had missed the point, that they had been thinking about development of pattern in the wrong way; knowing about epithelial-mesenchymal interactions in the limb didn't tell you anything about the limb patterning whatsoever! The Americans just weren't interested in pattern formation –the fashion was to just go and look what molecules are made and where they are made and don't worry about general principles.

What are the results that have given you the most pleasure with respect to positional information? How about Nüsslein-Volhard and Driever's work on Hunchback and Bicoid?

That was wonderful of course, but it wasn't in a multi-cellular system. I like some of the other insect work too, like dpp gradients, and I think the discovery of *sonic hedgehog* was so exciting! But we still don't understand—that's one of the curious things, after all that effort it's still not clear how sonic specifies position in the limb.

What do mean we don't understand—what do you regard as a solution to development?

I think that is a very difficult question. In fact, I said it to Jani [Nüsslein-Volhard]—how much do you really want to know? I suppose my criterion would be, can you make a good simulation, a real model, with reasonable numbers that fit the experiments—you don't want all the binding constants...

...some people might. I might.

I personally wouldn't, but I would like a plausible model where if you put in reasonable numbers, you would see that in principle the thing would work and there are no real holes in it. That would be a solution. But I suppose on the whole, if it looks like the model really works then I would lose interest—I'm not interested in detail, I must confess.

It does worry me that the answer is going to be immensely complicated—how can it not be. Do you remember those charts of biochemical pathways that used to be stuck up on every lab wall? It'll be like that, only a million times worse.

Well, that's the trouble. I'm still recovering from the trauma of Tony Hunter, who said in a lecture that 4% or 10% of the genome encodes kinase receptors. I don't know—as a developmental biologist I can't get involved in all that detail!

What has had an enormous influence on my thinking recently is a young man I met at a meeting in Lausanne organised by a group of people who use my book *The Triumph of the Embryo* to design computer programs. The meeting was hysterical—I didn't understand a single word—but I did meet an electronic engineer called from Sussex, Adrian Thompson.

Let me tell you what Thompson does. He wants to design an electronic circuit so that if you go 'whoof' a light goes on. He puts the components together in a computer programme—links them all up all pretty randomly—and then imposes a selection procedure as to which of the multiple circuits he generates does approximately what he wants, and he then mutates the whole thing again and eventually ends up with something that works. The surprise is, he has no idea *how* it works, so he then spends the next month trying to find out how it does it, and he finds he has invented a clock. There are all sorts of things that no electronic engineer in a million years would have put into the design, but the selection procedure does it. If you want to make a system which is temperature insensitive, this is the way to do it! For me it's the most important idea I have heard this decade. That random change and selection give you solutions which you would never think of. So all these crazy things that we see and don't make any sense—no they don't make sense, but they work!

Isn't this Dawkins's *Blind Watchmaker*?

Yes, but Richard has never done specifics—that's the surprising thing about Thompson's work.

We had better leave the positional information paper and move on to more recent work. Since then, for example, you discovered the effects of retinoic acid on limb development.

Well, we were lucky and a little brave to discover that. No, I think the most important thing I have done recently was the F molecule and handedness paper with Nigel Brown. I think it's a really nice piece of work. It came about because *Development* asked me to write a review. I had already become interested in left-right asymmetry with Nigel Brown so we wrote the review but then they said why should we publish a review on something that no one is interested in? Peculiar! I then took it away and I discussed it with Peter Lawrence and Peter said: "look it's no good you doing this unless you have a model". So we came up with a model, and people have been very generous—it's one of my most quoted papers actually.

Like the positional information paper, it's been pretty influential. I assume this gives you pleasure.

I'm delighted that people use positional information as a terminology, that pleases me.

And the major accolade of course is that nobody cites the original paper

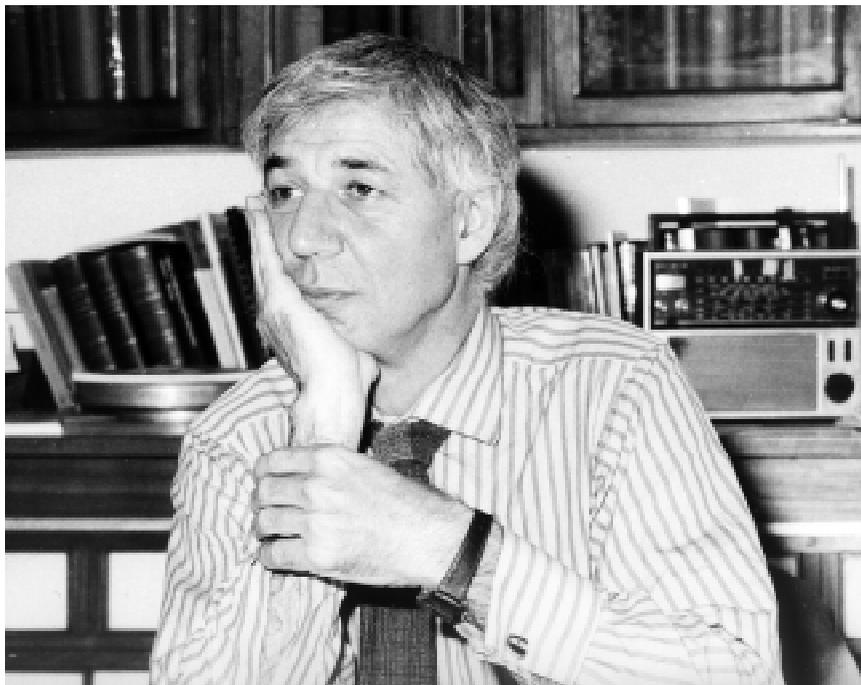
That's a point, that pleases me. Let me put it this way: even if positional information is wrong, at least it's interesting and it inspired some experiments. I suppose I do live my life in terms of ideas—they are what I care about.

Would you describe yourself as ambitious? I ask because I am going to speak to another British developmental biologist—John Gurdon. Many people would regard the two of you as being different in many respects, but I remember watching the two of you play table tennis with each other in a castle in Germany. I was astounded at how competitive you both were!

In ball games.

Not in life?

You must understand that I'm a tennis player. Somebody once said "what do you really want" and I said want a better backhand. I grew up in a competitive sporting environment! And I am competitive about my ideas—that's not about being ambitious, that's something quite different; competitive is not being ambitious. Anyway, ambitious for what? What do I want? I think once one is in the Royal Society, that's a very big thing, you know. Being in doesn't matter but being out is intolerable. I like my books to sell and I'd like my work to be recognised. I admit I can be quite confrontational—I have been called the Lord High contradicter—particularly when it's sociologists of science and that sort of thing.



This brings us on to Public Understanding of Science, where until recently you were Chairman of COPUS [Committee on the Public Understanding of Science]. Do you have a driving desire to educate?

No, absolutely not. I do care about science.

Then why do you do it?

I'm a performer, a natural performer—it comes easily to me. I know what I can do at my age. I've got a good backhand at tennis, I'm a good chairman and I can perform. I've always performed—I won a debating medal at school.

I think I was quite interested in the nature of science and that led to all those radio interviews with Alison [Richards]—I had an idea they would be interesting. On the whole, I think I was irritated by the way science was presented, but I don't have a driving ambition to educate. But I do want the public to have an appreciation of science and its beauty.

My line on public understanding of science is absolutely clear—access. What I'm concerned with is that those interested in science should have access to it easily, and that has always been my function. I'm not interested in public relations, I'm not interested in persuading—I'm happy to do so, but my main aim is that everyone should have access, that those people who want it should find it easy.

Too much in public understanding in science is like going to the dentist really. The only way you can make people understand science is by making it fun, or why else would they want to do it?

I'm against fun in science to be absolutely honest. It trivialises it.

But you do have to make it enjoyable, otherwise why would anyone want to carry on doing it!

Because it's interesting and important.

Well, interesting is fun. You get them in with the enjoyment and catch them on the interest.

Well, I simply don't know. I find teaching very difficult; I have no idea how to teach. The public understanding stuff I just do because it's my job—it's one of the things I do and it just goes on. People say "will you be chairman of this or will you do that or will you give the Christmas lectures." I don't know how I came to give the Christmas lectures. Once you get into this then you get known and then people ask you more and more and more.

I discovered writing really quite late in life. For some bizarre reason, I don't know why, I was asked to give the Radcliffe lectures in Warwick in 1990 and that was the origin of *The Unnatural Nature of Science*. I don't know how that came about unless it was because the Royal College of Physicians had previously asked me to give some lecture and I was irritated at the time by the anti-science lobby and so I began to think about it.

You make highly efficient use of everything you do! You said that your lectures in Warwick turned into *The Unnatural Nature of Science*, and more recently your depression turned into an interview in *The Guardian* and another book—*Malignant Sadness*.

People ask me why did I write the book? Writing books is what I do, that's one of the things I do. I don't know why *The Guardian* asked me to write an article about my depression, I don't know how they knew about it or where it came from, but they did. I wrote it—I thought the article was rather good and the response to it was astonishing—and then I became interested in the topic.

I can understand becoming interested. But you almost sound fatalistic, as if it was inevitable that you should write the book.

Not entirely fatalistic—it's what I do, I do it quite well, and once you get a reputation for doing something of a particular kind then you begin to mix with those people and new opportunities arise. Again, it's fun and you get lots of good friends in all sorts of strange jobs.

You keep saying that writing books, performing, is what you do. It's as if you have a job and that job is being Lewis Wolpert.

Yes, there is a sense of that, Jim. I think it's terribly important to understand where one's skills are and to recognise them. One of the things I do is write books, and I do quite like writing books! My skills are not in doing experiments and I'm not a very good theoretician. My skill is to define the problem sufficiently well that my friend Michel [Kerszberg] will solve it. But he can't do it without me, and he knows that. And I can be critical, so I can give him the feedback. Michel would never, ever, have got involved in our long-range signalling model if I hadn't said to him 'come on Michel, we've got to think about this'. And how did Michel and I get together? Because he wrote an article with Changeux about interpreting positional information I wrote to him, and you know, one collaborates.

Can we discuss depression, which isn't developmental biology but it's a great part of what you are doing at the moment. I don't want to talk about the episode itself because that's in your book, but did you find it easy to 'come out' about it?

I had no difficulty whatsoever. Absolutely not. Although it's interesting, Denis Duboule pointed out something very funny – Denis said: "why do you keep saying there is no stigma to depression yet insist that yours is biological and not psychological?" – and I do say that in the book. But I find no difficulty whatsoever in talking about it.

This is another aspect of your desire to perform!

I think I'm moderately self-confident. First of all in my position and at my age it's neither here nor there what other people think of me. I really don't care. If my friends didn't like it I wouldn't like that, but I mean, people keep saying how brave I am, it's absolute nonsense! It is a very common illness of which one should not be ashamed.

In 'coming out' and writing the book, is it your aim to understand the problem or is it primarily to help other sufferers?

It's a mixture. I wanted to write the book because I wanted to understand more about depression. I also thought it could help depressives because I had such a positive response to *The Guardian* article. They [depressives] are a very neglected group and if this book could help them and their careers understand what depression is about, then I would be pleased. So, I'm very pleased when Martin Blanchard, one of my psychiatrists, says, as he did a few days ago, that he is going to recommend the book to students, because that means it really will be helpful to doctors in understanding their depressed patients. So that pleases me, but it isn't why I wrote the book.

Is there any experience you have had that you wouldn't write about?

Certainly.

Good!

Well I'm not sure. It's an interesting question. As I get older I recognise some quirky psychological things that I have and it would be interesting to spend some time thinking about them – but whether I really want to put them in the public domain is another question.

Finally, the lazy man's question, but one which might be forgiven since I am interviewing the interviewer... what would you ask yourself if, as we discussed at the beginning, you were interviewing yourself?

I would ask what would I work on if I were doing a PhD now?

Well, what would you work on if you were doing a PhD now?

I think I would go to Jeremy Brockes and I would want to work on the nature of positional information in limb regeneration. That's an

interesting and important problem... how are the positional values encoded?

Acknowledgement

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