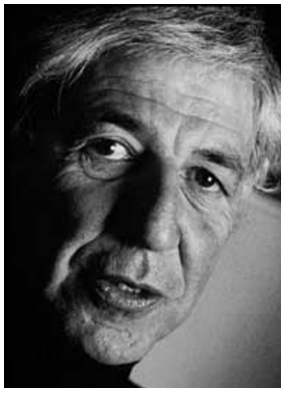

Lewis Wolpert discusses development and depression

Interview by Joanne Clough

Lewis Wolpert, Professor of Biology as Applied to Medicine, Department of Anatomy and Developmental Biology, University College London

Lewis Wolpert is Professor of Biology as Applied to Medicine in the Department of Anatomy and Developmental Biology at University College, London, UK. His research interests focus on the mechanisms that are involved in embryonic development. Lewis originally trained as a civil engineer in South Africa but in 1955 made the move to research in cellular biology at King's College, London. He was made a Fellow of the Royal Society in 1980 and awarded the CBE in 1990. Lewis was also made a Fellow of the Royal Society of Literature in 1999 and has presented science on both radio and TV for several years. He was awarded The Royal Society Michael Faraday Prize in 2000 for his contribution to the public understanding of science, most notably through his Chairmanship of the Committee for the Public Understanding of Science (COPUS; 1993–1998). He is the author of numerous books, including *Malignant Sadness: The Anatomy of Depression, Principles of Development, The Unnatural Nature of Science* and *The Triumph of the Embryo*. He also writes a regular column for *The Independent*.

Can you tell me a bit about yourself and your career so far?
I studied Civil Engineering in South Africa, and then worked with the Buildings Research Institute in Pretoria for a couple of years. I then worked as an engineer in Israel for a year, before I came to London to do a further degree in soil mechanics at Imperial College. I wasn't terribly happy doing engineering and I wanted to change. A friend of mine read an article where people were looking at the mechanics of cell membranes and he said 'Lewis you should change to this' and that's what I did. I went to King's College [London] and I did a PhD on the mechanics of cell membranes. And then I got involved in developmental biology – it was a wonderful move.

What does your day-to-day work involve?
I don't have a laboratory or students anymore but I do collaborate with various people in Hungary and France, and we do theoretical work. There are quite a few things on the go at the moment – I am quite involved with the evolution of the embryo and we have recently written several papers about the origin of the embryo – how single cells became multicellular [1]. I am very involved with – but we haven't yet made much progress – how cells set up gradients, which are very important in developmental biology. I am also very interested in the mechanics of gastrulation in the chick embryo. So there's quite a lot going on. And I have just written a book on the biology of belief, which I think is quite interesting.

'At school, students are not taught any developmental biology and that is monstrous.'

You say you are disappointed that so little is taught about embryonic development to students today. Why do you think this is, considering the media coverage of topics such as cloning and stem cells?
At A' level, not at university, but at school students are not taught any developmental biology and that is monstrous. They are supposed to discuss the ethics of cloning and stem cells and yet they don't learn anything about development.

You said you would offer a bottle of champagne to anyone who could tell you a new ethical reason for opposing human reproductive cloning other than safety. Has anyone received that bottle of champagne yet?
No one has yet received this but there is a catch – if I show you that it isn't [a new reason] you have got to give me two bottles! And no one has yet attempted to win the bottle.

'How ever clever you think cells are, they're cleverer'

What do you think the field of developmental biology has contributed to medical research and development?
We have made very good progress in understanding how genes and proteins control development but there is still an enormous amount of detail missing. My line is always, 'however clever you think cells are, they're cleverer!' Its a very complex situation; if you take cancer for example, look at how much work has gone into cancer [research] and look at how little success there has been in designing drugs – of course there are some exceptions [in cancer drug development] but in most cases, where there is not a single gene defect, it is very difficult to do something about it. As far as applications are concerned, developmental biology has helped with prenatal diagnosis but in terms of curing people of anything I cannot think of a single example. Understanding what has gone wrong in development and the general principles – yes, developmental biology has contributed a lot, but most abnormalities are multi- or polygenic and to identify the genes of polygenic illnesses is very difficult.

What do you think is the public perception of the pharmaceutical industry and the promise of personalized medicine in light of the contradictory media surrounding the ever-increasing time to develop new drugs?
What we have got to remember is that it is very complicated – the principles aren't that bad but the details are terrifying. If we take, for example, the promise of gene therapy, [because of various complications] this just hasn't happened. It is not as though the approach isn't good but it is very complicated and one has to be very patient. There are of course lots of

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successful drugs; for example, one of the most successful drugs is lithium, which came from that amazing Australian who was just looking at the urine of manic depressives [psychiatrist John Cade who, in 1949, published the first paper on the use of lithium in the treatment of acute mania]. In terms of development, in very few cases do we know the full detail about how a gene leads to abnormalities. We do know the principles; we know that there are certain *hox* genes – homeobox containing genes – which, if mutated result in deformations in fingers and toes, but the details from that gene and what its targets are, are still not known.

'It is not the number of genes but the control regions that matter – there are only 26 letters in the alphabet but there's an awful lot of words!'

Since the publication of the Human Genome, how do you feel about the low number of human genes compared with, for example, the nematode, from the point of developmental research.
Its not the number of genes but the control regions that matter – there are only 26 letters in the alphabet but there's an awful lot of words! And its the same thing – its the control regions, its where and when the genes are turned on that matter, not the genes themselves. Many genes, for example the pair rule genes in the fruit fly, there are seven stripes each with a different control region. So it is not the number of genes that matter but where and when they are made.

'If Prozac grew on trees, people would be happier with it.'

You have written a lot on the subject of depression; what are your views on the current pharmacotherapies for depression?
I take my anti-depressant every morning and I think it's a lifesaver. All the hostility and media about the dangers of anti-depressants totally misses the positive effect. My joke is that if Prozac grew on trees people would be much happier with it – but it is very serious when the media tries to frighten people about anti-depressants. Many more people would commit suicide if there weren't anti-depressants.

In your opinion, who is doing really exciting, innovative research at present?
There are all sorts of different levels where people are doing all sorts of exciting things and the level of detail is becoming quite spooky. I'm revising my textbook at the moment and its quite difficult – there are lots of people doing quite excellent research. The zebrafish work is zooming along; drosophila is still very important, there is lots of work on chicks and mice. In terms of gene networks, Eric Davidson on the sea urchin is doing amazing stuff, working out the connections between gene regulatory networks and control regions, which is very complex. In terms of technologies, imaging studies – although not that new – [are interesting]. Being able to visualize a lot of what is going on with microscopic techniques and labelling proteins with GFP has enabled people to follow the movement of molecules during development. And there is also, of course, the process of RNA interference, which has opened up a whole new world.

What do you envisage as being the next big 'breakthrough' or what would you like to be the next milestone in scientific research?
I think there are quite a lot of people working on systems, who are trying to simulate cell behaviour in terms of all the interactions between proteins and genes and I think if this could be done in a reliable way this would be very helpful [for medical research]. But for the many specific problems, for example the problem that I'm involved in, the question is trying to understand how cells acquire a unique identity and we just don't know the answer.

Who or what have been the greatest influences in your careers?
There have been many people, including those that I've collaborated with – I got involved in sea urchin work and that had an enormous influence on me when I went to work in Sweden. I was actually working on the mechanics of the cell membrane but I was working on sea urchin eggs and I got involved with Trygve Gustafson – we worked on morphogenesis in the sea urchin and that was an enormously important influence. All sorts of people have influenced me; Sydney Brenner has been very supportive on various occasions but I cannot really single one person out.

What do you think is your greatest professional achievement to date?
The idea of positional information, that is my main contribution but as for my others, I'm not sure other people see them in quite the same light!

I believe your first presentation on positional information and pattern formation [2] was not well received by many at the time.
Yes, people hated it! In those days gradients had a very bad name but its changed now and its perfectly fashionable but of course this took 20 years. Sydney Brenner and Francis Crick were very supportive and that was important.

'The idea of positional information, that is my main contribution but as for my others, I'm not sure other people see them in quite the same light!'

What would you like to have accomplished at the end of your career?
To try and get this book [on belief] published – I have got a publisher but am waiting for people's comments to revise it. I would really like to solve the problem of gradients and I would also like to solve the problem of gastrulation in chicks. And I'd also like to understand depression.

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