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OBITUARY

Lewis Wolpert (1929-2021)

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Lewis Wolpert, who died on 28 January 2021, was an inspirational figure to generations of developmental biologists, and a man whose influence extended far beyond his subject. By seeing significance in the commonplace, and by identifying and re-framing research questions, he inspired new ways of thinking about embryonic development. As a teacher and as a lecturer he was nonpareil, and his ideas were brilliantly distilled in his textbook *Principles of Development*, which will continue to imbue students with his clarity of thought. In writing about his depression, Wolpert reduced the stigma associated with the disease and provided scientific understanding, solace and hope. An open, kind and generous man, he went out of his way to support young scientists.

Lewis Wolpert with his long-time colleague Amata Hornbruch. Photograph by the author.

Early days

Lewis Wolpert was born in Johannesburg in 1929. His mother, Sarah Suzman, was one of eight children in a family of Lithuanian Orthodox Jews. One of her brothers, Moses, married Helen Gavronsky, who as Helen Suzman became a prominent South African anti-apartheid activist and politician; another brother, Saul, was the father of actor Janet Suzman. Lewis's father, William, was born in Belfast, but moved to Johannesburg when young, eventually to become a general manager at the Central News Agency.

As a child, Wolpert enjoyed science: he was good at maths, he liked electric trains and he made model aeroplanes and radios (Wolpert, 2000). But he explained that people from a background like his didn't do science at university, so when he went to the University of Witwatersrand, he studied civil engineering instead – less greasy, apparently, than mechanical engineering. That engineering background may well have influenced Wolpert's thinking as a biologist, but it wasn't long before he wanted out – engineering wasn't enough fun, and there weren't enough girls. So, after a further 2 years in Pretoria as a soil mechanic, he hitch-hiked up Africa to Israel – to escape his parents, to escape apartheid (he disliked the way his parents treated their black servants and by this time had met Nelson Mandela), and to gain a springboard for his ultimate destination of London (where he had been on a student trip 4 years previously).

Wolpert arrived in London in 1954 and loved it, especially the drinking clubs of Soho. In a final nod to his background in engineering he was doing a diploma in Soil Mechanics at Imperial College, but there then came one of those Damascene moments when, on the advice of his friend Wilf Stein, he read a paper by Mitchison and Swann on the mechanical properties of cell membranes (Mitchison and Swann, 1954). The idea that physical approaches might be applied to biology inspired Wolpert to speak to Jim Danielli at King's College London, with whom, in 1961, he eventually got his PhD on the analysis of cleavage, first in amoebae and then, crucially, in sea urchin embryos.

The first stirrings of developmental biology

Wolpert's first forays into the mechanisms of sea urchin cleavage took place at the Millport Marine Station in Scotland, but he soon found the Kristineberg Marine Research Station in Sweden to be a more congenial location, and one with the additional benefit that Tryggve Gustafson worked there. Gustafson was making films of early sea urchin development, and – like anyone who watches embryos develop – Wolpert was fascinated. He and Gustafson analysed the films carefully and, by applying Wolpert's engineering skills, showed that one could account for sea urchin morphogenesis in terms of just a few distinct cellular activities. The two worked rapidly and published five papers in 1961 (Gustafson and Wolpert, 1961a,b,c; Wolpert and Gustafson, 1961a,b), one in 1962 (Gustafson and Wolpert, 1962) and a magisterial review in 1963 (Gustafson and Wolpert, 1963).

But Wolpert's interest in sea urchins went beyond morphogenesis, and he was especially interested in the work of Hans Driesch, who had shown, in 1892, that half- or quarter-sized sea urchin embryos would develop into small embryos that were nevertheless perfectly proportioned. The mechanism by which this happened intrigued Wolpert. By now an Assistant Lecturer at King's College, he quickly recognised that the problem applied to many other developmental systems, including the regeneration of vertebrate limbs and of hydroids and planaria. So, as children came along (he had married Elizabeth Brownstein in 1961), and summer trips to Sweden became more difficult, he decided to adopt hydra as his experimental organism.

Positional information and the French flag

Wolpert's initial work on hydra, with PhD student Gerald Webster, was carried out at King's, but in 1966 he moved to the Middlesex

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Hospital Medical School as Professor of Biology as Applied to Medicine. He continued to work on hydra for a few years, but in a slightly uncharacteristic capitulation, he took the name of his department to heart, and shifted his work to the more medical question of chick limb development. This was to serve him well.

The move to the Middlesex, or perhaps the adoption of a new model system, gave him the answer to the problem of pattern regulation. Wolpert didn't remember where he got the idea from, but he drew the powerful analogy between embryos and flags, noting that both have the same proportionate patterns irrespective of their sizes. In both cases, he argued, if position within the system were specified in a polarised coordinate system relative to its boundaries, and if position defined cell type or colour, the problem is solved. He was at pains, in his first papers, to emphasise that although this positional information could be specified by the graded distribution of a substance, this was not the only mechanism, and he made specific reference to the phase-shift model of Goodwin and Cohen (Goodwin and Cohen, 1969) and referred to Peter Lawrence's work on polarity in the abdominal segments of the milkweed bug *Oncopeltus fasciatus* (Lawrence, 1966).

Wolpert first presented his ideas at a meeting organised by C. H. Waddington at the Villa Serbelloni by Lake Como in Italy. The essay written after the symposium (Wolpert, 1968) makes the now-familiar cases for a polarised system and for the ability of cells to switch from one state to another at critical threshold values. It also emphasises the importance of a spontaneous self-limiting reaction – a property Wolpert found harder to define, but which ensures that positional information is established and maintained at the correct levels.

The Villa Serbelloni meeting was a triumph, but a 1968 lecture at the Woods Hole Marine Biological Laboratory was a disaster. Wolpert tells the story that he was invited to present his ideas at a Friday evening discourse, but that his presentation was poorly received. His audience didn't like to be told (no doubt, in no uncertain terms) that they had missed the point – who, they asked, does he think he is? At the reception afterwards, no one would speak to him, and a prominent limb developmental biologist went so far as to turn his back on him. Even at the age of 38, Wolpert was devastated. But Sydney Brenner, whom he met on the beach the following morning, rescued him, saying that he and Francis Crick liked Wolpert's ideas and had been thinking along similar lines themselves. He advised Wolpert to publish his ideas immediately, which he did in 1969 in the *Journal of Theoretical Biology* (Wolpert, 1969), and in 1971 in *Current Topics in Developmental Biology* (Wolpert, 1971). Sandwiched between these papers was a piece by Crick entitled *Diffusion in Embryogenesis* (Crick, 1970), which provided a fillip both for Wolpert himself and for positional information as an idea. Beginning with a quote from Wolpert's 1969 paper about the sizes of embryonic fields, Crick went on to suggest that diffusion may underlie the establishment of morphogenetic gradients, a suggestion that Wolpert himself adopted for a while but was later to doubt.

Chick limb development

Wolpert was already thinking about the development of the chick limb in his paper of 1969, and his application of positional information to limb development was powerful and compelling. The engineer in him first began to ask questions about precision. Most people regard it as obvious that one's arms are the same length as each other, but to Wolpert this was a way of analysing the precision of development, and by comparing the lengths of left and right wings at 9-11 days of incubation, he and his PhD student Dennis Summerbell concluded that the initial specification of the length of elements, such as humerus, ulna and digit III, was accurate to within one cell in 20 – an important observation in thinking about how specification might occur (Summerbell and Wolpert, 1973). (The paper was sent to *Nature* on 17 April 1973 and was in print on 27 July. Those were the days.)

Wolpert assembled a powerful group around him during the 1970s, and together they made outstanding progress. Amata Hornbruch acted as Wolpert's experimental hands for a quarter of a century. Summerbell (who went on to marry Amata) had joined as a PhD student; Jonathan Slack came to study limb regeneration; and Cheryll Tickle worked both on invasiveness and on the zone of polarising activity (ZPA). Julian Lewis, originally a physicist, came from Russia and brought with him an analytical approach to development, and Larry Honig joined from the University of California, Berkeley, to introduce biochemistry. Later PhD students during the 1970s included Geoff Shellswell, John McLachlan, Nigel Holder and me.

In all the time I knew him, Wolpert never carried out a single experiment, but his great ability was to design experiments and get others to do them for him. Most significantly, with Summerbell and Lewis he defined the 'Progress Zone' model for the specification of positional information along the proximo-distal axis of the limb, a model which suggested that mesodermal cells acquire positional information according to how long they remain at the tip of the limb beneath the apical ectodermal ridge (AER) (Summerbell et al., 1973). This model later received support from experiments in which limb buds were irradiated; as cells divided to repopulate the developing limb they remained longer in the vicinity of the AER, and became more distal (Wolpert et al., 1979). With Tickle and Summerbell, Wolpert then built on the work of Saunders and colleagues (Saunders and Gasseling, 1968) to describe a gradient model for the specification of digits along the antero-posterior axis of the limb, proposing that a diffusible signal produced by the ZPA specified digit type according to its concentration (Tickle et al., 1975). Experiments in which the signal from the grafted ZPA was attenuated, either by γ-radiation (Smith et al., 1978) or by implanting smaller numbers of cells (Tickle, 1981) supported this idea.

As a principal investigator, Wolpert always gave credit and was generous with authorship. My first-ever paper was co-authored with Tickle and Wolpert, but thereafter he said that I should include him as an author only if I thought he had made a contribution – having published one paper with him, he said, people would know where I came from. Accordingly (I can hardly believe I had the nerve to do this), my second and third papers were single-author jobs, but I included him on the fourth and he and I were co-authors on the fifth, led by Larry Honig. (It was much easier to publish papers in the 1970s.)

To Wolpert, the model was the thing; as the situation became more detailed he tended to lose interest, and I remember him saying to me: 'Jim, if I gave you a tube of the ZPA morphogen, what would you do with it?' It was ironic, then, that in 1982, and with Tickle, Bruce Alberts and Juliet Lee (Tickle et al., 1982), he found that retinoic acid could mimic the concentration-dependent effects of the ZPA. It seemed indeed as if one could get plenty of tubes of the ZPA morphogen, and retinoic acid's candidacy as the elusive molecule was strengthened in 1987 by Thaller and Eichele's observation (Thaller and Eichele, 1987) that its concentration is higher in posterior regions of the limb bud than anterior. After much excitement about retinoic acid, a stronger candidate for the endogenous signal later emerged in sonic hedgehog (Riddle et al., 1993), although even this may specify digit type indirectly (McQueen and Towers, 2020). There are still plenty of details to sort out for those who like sorting out details.

Wolpert the public intellectual

As Wolpert's science progressed, so too did his public profile. He was a charismatic and witty performer, who, as an interviewer, had the knack of asking just the right questions. His radio programmes included *A Passion for Science* and *The Dark Lady of DNA* (about Rosalind Franklin), and on television he presented *Antenna* and in 1986 gave the Royal Institution Christmas Lectures on *Frankenstein's Quest*, in which he described embryonic development. For five years he was chair of the Committee on Understanding of Science, and he was also a writer. His book *The Unnatural Nature of Science* (Wolpert, 1993) made clear his view not only that science is the best way to understand the world, but also that scientific ideas are frequently counter-intuitive, and that the application of common sense to science just doesn't work. There were few topics on which Wolpert didn't hold a firmly held opinion – religion, ethics and philosophy were all grist to his mill – and he was frequently the contrarian, unafraid of making his position completely clear. Thus, as well as writing a popular guide to developmental biology called *The Triumph of the Embryo* (Wolpert, 1991), he wrote about belief (Wolpert, 2006), cells (Wolpert, 2009), ageing (Wolpert, 2011) and the evolution of sex and gender (Wolpert, 2014). For developmental biologists, it was exciting to see one of our number so visible and so in support of science. And his wonderful textbook *Principles of Development* (Wolpert, 1998), now in its sixth edition and in the safe hands of Cheryll Tickle and Alfonso Martinez Arias, entertains, informs and encapsulates Wolpert's way of thinking. It is an indispensable aid to anyone teaching the subject.

Depression

In the mid-90s, at the age of 65, Wolpert suffered a period of depression. There was no reason, he said, that he should have done so. He was healthy, happily married (now to Jill Neville), and a professor at University College London. But he went through a period that he described as the worst of his life – worse, he said, than later watching Jill die of cancer. He could not think properly, or work, he couldn't sleep, and he became suicidal. He only refrained from suicide because his wife told him what an intolerable effect suicide would have on her and on his children, and because she said she would help him in a year's time if his condition didn't improve.

His condition did improve, after three weeks in hospital and with the help of antidepressants and cognitive behavioural therapy. And his recovery was accompanied by a keen interest to understand his illness and a strong desire to help fellow sufferers. He first wrote an article in *The Guardian*, which was widely praised for its candour and its courage. This was followed by a book, *Malignant Sadness* (whose very title illustrates his ability to grasp a concept and make it understandable to others) (Wolpert, 1999), and, the same year, the television series *A Living Hell*. Most recently, in 2020, he appeared in the BBC radio series *The New Anatomy of Melancholy*, continuing to do much to dispel the stigma that attaches to depression.

Wolpert the man

Lewis Wolpert's scientific and academic achievements were many, but in writing this piece I discovered a great deal about the man. Anyone who met Wolpert would know him as self-deprecating and disarmingly open, with a sense of humour that was sometimes a little too quick for his own good. In collecting stories about him, however, I was unprepared for the many examples of Wolpert's kindness and generosity. Many concerned his willingness to speak – and listen – to students and young researchers, in a style that Kate Storey described to me as warmly irascible.

Peter Holland's story is typical. He told me of the time, as a PhD student, that he was introduced to Wolpert. The great man was in a huddle of other researchers, but Peter was marched up to Wolpert, who, now ignoring his colleagues, asked what Peter was working on. 'Hox genes' said Peter, which had only recently been discovered. 'Ah, you need to tell me more about that,' he said, pointing to two seats at the side of the poster room. They sat down together and (referring to a paper Wolpert had published with Julian Lewis) Peter explained, 'Well, Lewis, they are all to do with non-equivalence' (Lewis and Wolpert, 1976). With a widening smile, Wolpert put his arm round Holland and said, 'Peter, you know how to make an old man very happy.'

The most moving story I heard was from someone whose father was in the psychiatric ward of the Royal Free Hospital, where Wolpert himself had been treated for depression. During one particularly bleak visit, Wolpert's distinctive voice could be heard on the other side of the ward, reassuring a friend and recalling his own journey not that long ago. He remarked on the bed he had lain in, his fellow occupants, and on his own struggle, and he reassured his friend that it was possible to come through. A remarkable illustration of Wolpert's courage, honesty and selflessness. He'll be missed by many.

Acknowledgements
I am grateful to everyone who sent me stories about Lewis, and I'm only sorry I couldn't use them all. And, of course, I thank Lewis, for all he did for me and for making science such fun. I count myself lucky that I was able to tell him, as he neared the end of his life, how much he meant to me.

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