Lewis Wolpert (19 October 1929 – 28 January 2021)

Lewis Wolpert was one of the giants of 20th Century Developmental Biology. His name is most often associated with “The French Flag model” and with his pronouncement that “it is not birth, marriage or death but gastrulation which is truly the most important time in your life”, but he has made contributions to many key problems. He stands out not so much for particular discoveries, but rather for his thinking and especially for how successfully and productively he was able to influence the ideas and experiments of others, his fierce commitment to Science as the best method of enquiry, and his candour about everything, including some of his most intimate problems.

Lewis was born in South Africa to orthodox Jewish parents. His father was born in Belfast and his mother’s family was from Lithuania. Lewis did not get on well with his parents and rebelled particularly because they wanted him to become “a nice Jewish boy”. Lewis liked making things, so he decided to study Civil Engineering in Johannesburg. After graduating, he got a job doing Soil Mechanics in Pretoria for a few years. Meanwhile he became interested in South African politics – one of his aunts was Helen Suzman, a courageous anti-apartheid Member of Parliament, and he befriended Charles Feinstein with whom they met Nelson Mandela. In 1952, Lewis and his friend Norman Morrison took off on a three-month-long hitch-hiking trip through Africa, heading North towards Arabia and the Mediterranean – Lewis carried a letter from Nelson Mandela recommending him to anyone they might encounter. After a few months of adventures, Lewis reached Italy and then Israel where he settled and worked for a while, but was not particularly happy there. So he decided to go to England to continue to work on Soil Mechanics, but not without first spending a little while in Paris for some fun times and learning French. In London, Lewis took a course on Soil Mechanics at Imperial College, but became increasingly uninterested in the subject. Advice from his friend Wilfred Stein to consider applying his engineering skills to study cell division, along with a paper by Michael Swann and Murdoch Mitchison, led him to enrol as a PhD student with James Danielli at King’s College London to study the mechanics to cell division and cell movement in biology. That was the turning point. The mid-1950s was a time of massive advances in Cell Biology, including the emergence of work by Michael Abercrombie at nearby University College London that first identified “contact inhibition” of locomotion and of cell division, and there were also a number of very active groups at King’s College and elsewhere so Lewis found this very exciting. After his PhD (1960) he obtained a lectureship at King’s College and set up a collaboration with Tyrve Gustafson in Sweden studying the cell mechanics of gastrulation in the sea urchin embryo. At the same time he performed some experiments on Hydra in collaboration with Gerry Webster (who also sadly died recently), trying to understand how it could regenerate a whole organism from a small fragment. These experiments opened his interest in the key questions of developmental biology.

In 1968, he was offered a Professorship and the headship of the awkwardly-named “Department of Biology as Applied to Medicine” at the Middlesex Hospital in London. Feeling that Hydra and sea urchins might be a little too remote from medicine, he became interested in development of the chick limb, attracted by some results from John Saunders in the USA. His mathematical and engineering skills prompted C.H. Waddington to invite him to a series of meetings of a small group of theoretical biologists working on a number of fields on Lake Como in Italy. Lewis’s first presentation to this group in 1968 introduced the “French Flag problem”, drawing the analogy of a field of cells to a flag, where the pattern is size-invariant: a small French Flag contains the same proportions of red, white and blue than a large one. Could biological systems be thought of in this way too? Lewis’s presentation also offered two alternative models, one called the “balancing model” where cells interact with their neighbours, and the other based on a gradient of a “morphogen” (Wolpert, 1968). The next year (1969) came what is probably his most influential paper (Wolpert, 1969), proposing
“positional information” that allows cells to assess their location within a tissue and behave accordingly. This elaborated on the second model: drawing on earlier concepts from Charles Manning Child and Alan Turing, he proposed that the tissue could have one or two opposing gradients of some property, perhaps diffusible substance(s), whose concentration would be interpreted by the cells to determine their location and thus their identity. Scaling is achieved because the slope of the gradient(s) is steeper in a smaller field than in a larger one, so fixed threshold values will position the boundaries between territories. At the Middlesex Hospital, he assembled a very productive team of experimentalists, many of whom themselves went on to make very important contributions to developmental biology. Among them were Cheryl Tickle, Julian Lewis, Denis Summerbell, Jim Smith, Nigel Holder and his long-term devoted technician Amata Hornbruch. Much of the work that came out from this group became very important. Experiments with Cheryl Tickle explored the relationship between signalling strength by the Zone of Polarising Activity (ZPA) and the resulting pattern of digits, as a test of the “French Flag” problem, which supported the idea of gradients of “morphogens” (Summerbell et al., 1973; Tickle et al., 1975). The idea also emerged of a “progress zone”, at the tip of the growing limb bud; the length of time spent by cells in this zone would determine their proximal (shoulder) versus distal (digits) position, providing a different way in which cells could acquire positional information (Wolpert et al., 1979). With Julian Lewis, also trained in mathematics, they proposed the principle of “Non-Equivalence” to explain results from a group in Toulouse (Philippe Sengel), relating to arms and legs might use similar positional information cues (Lewis and Wolpert, 1976). They also explored signalling by the “organizer”, Hensen’s node, which remarkably, can mimic the ZPA if transplanted into the anterior (radial) side of the limb bud of an older embryo (Hornbruch and Wolpert, 1986). These findings led to the idea that a small number of key positional signals might play different roles by being deployed at different times in different tissues, a concept that has turned out to be extraordinarily accurate (think of Hedgehog, BMP/Dpp, Nodal/Activin, Wnt, FGF and Notch). In other work, he proposed the first plausible model for the generation of left-right asymmetry based on asymmetric features within each cell in a tissue, relative to a fixed head-tail axis (Brown and Wolpert, 1990) which although not strictly correct, is not far from later findings by Hiroshi Hamada’s group that in mouse, this asymmetry is generated by cell-autonomous, directional beating of monocilia on the surface of cells in the node.

Lewis’s greatest skill was his ability to look at a biological problem and go straight for the jugular, asking the most interesting, pertinent and important question. The questions were always simple, almost naive, and would often generate enthusiasm and curiosity in those to whom he suggested them, and even more often bring a smile to their face. One question which he repeated many times (and has not yet been answered) is: “how come our limbs are the same length on both sides of the body? They grow for years, yet they end up being almost identical in size. What mechanisms could control this?”. His questions would serve to educate, to inspire and to direct others and that is the way he “did” Science. It was fitting that he was awarded the Faraday Medal for public understanding of Science by the Royal Society of London, and the Viktor Hamburger lifetime award for education by the Society for Developmental Biology (USA). Among many other awards, he was also given the Waddington Medal by the British Society for Developmental Biology and the Royal Medal by the Royal Society. After the Middlesex Hospital was closed down in the late 1990s, Lewis and Cheryl Tickle moved to the Department of Anatomy and Developmental Biology (now Cell and Developmental Biology) at UCL where he continued to think and write. For about 15 years, I had the pleasure of seeing him in action at our weekly lab meetings which he attended regularly, often asking simple but always incisive questions that were really appreciated by students and postdocs.
Lewis also wrote many books, including his widely used textbook on Developmental Biology (Wolpert, 1998), some to foster greater understanding of Science by the general public, on the Cell, on Religion and Belief, on Depression, on Gender, and much more. All with surprising honesty and candour. He suffered a major clinical depression at age 65 which arose during an otherwise happy period in his life, and Lewis never understood the cause. Whilst remaining very respectful of the beliefs of others, he considered Science to offer the best way to arrive at knowledge and understanding of the world around us, and did not believe in the existence of a God. Accordingly, he served as Vice-President and Patron of the British Humanist Association (now Humanists UK). He was particularly proud of having been elected both a Fellow of the Royal Society for his Science, and a Fellow of the Royal Academy of Literature for his prose.

During his life he married Elizabeth Brownstein (m. 1961, div. 1984), to Jill Neville (m. 1993, died 1997) and to Alison Hawkes (m. 2016). In the last few years he was increasingly frail and declined after a fall a few months ago, but just before he was about to be finally discharged he fell victim to Sars-CoV2 and died of complications of Covid-19 on 28 January 2021. He is survived by his wife Alison and four children, Miranda, Daniel, Matthew and Jessica. Lewis’s recollections of his own life through a wonderful series of short interviews available in YouTube (https://www.youtube.com/playlist?list=PLVV0r6CmEsFyjdGdW6_YWe0D1G9dW7Y-q) will give those who did not meet him a feel for his approach, honesty and warmth, and as a reminder and celebration of his life to those of us who had the privilege of interacting with him.
Acknowledgement: I am very grateful to Alison Hawkes for her helpful suggestions and for permission to use the photograph.

Claudio D. Stern, Department of Cell & Developmental Biology, University College London, U.K.

March 2021

REFERENCES: