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RETROSPECTIVE

Lewis Wolpert (1929–2021)

Pioneering developmental biologist

By **Cheryll Tickle** and **Jonathan Slack**

Lewis Wolpert, a towering figure in developmental biology, died on 28 January. He was 91. A charismatic advocate of his science, Lewis originated the concept of positional information to explain the formation of pattern in the development of an embryo. His work played a central role in building the field.

Lewis was born on 19 October 1929 in Johannesburg, South Africa. He studied civil engineering at the University of Witwatersrand and, after graduating in 1950 with his bachelor's of science, worked in Pretoria as a soil mechanic. He protested apartheid by attending demonstrations and distributing newspapers for Nelson Mandela. In 1953, he left South Africa for Israel and then moved to London, England, in 1954. There, he began with a postgraduate diploma in soil mechanics at Imperial College London and then did his Ph.D. at King's College London with biologist James Danielli, studying the mechanics of cell division in sea urchin embryos. At the marine station in Kristineberg, Sweden, Lewis met the embryologist Trygve Gustafson and became fascinated by sea urchin embryo development. Together, they showed how complicated changes in embryo shape could be explained by a small number of cellular properties. Lewis was appointed, in 1960, as a lecturer at King's College London and, in 1966, to a chair at the Middlesex Hospital Medical School, which later merged with University College London, where he remained until he retired in 2004.

In the early 1960s, Lewis worked on regeneration of hydra, a small freshwater animal. Both hydra and the sea urchin embryos can regulate their proportions—if a part is removed, then the whole pattern reforms itself at a smaller scale in the remaining tissue. Applying his engineering background, Lewis proposed a model in which position within the organism is specified by a linear gradient between two fixed boundary regions. He drew an analogy between the pattern of the body plan of an organism—e.g., an animal with a head, trunk, and tail—with the pattern of the French flag's blue, white, and red. He first presented the idea

in 1966 at a Theoretical Biology Symposium and published it in expanded form in 1969 in the *Journal of Theoretical Biology*. One of us (J.S.), enthralled by a lecture Lewis gave on this topic, later joined his research group. Lewis's ideas initially met with considerable hostility, but he was encouraged to stick with them by founders of the field of molecular biology, Sydney Brenner and Francis Crick.

Pattern formation is the process that controls the spatial organization of the embryo, leading to precisely ordered arrays of differentiated cells. Lewis proposed that this process occurs in two distinct steps. First,



cells are informed of their position in the embryo, for example, by a French flag-like mechanism. Second, they “interpret” this positional value according to their genetic constitution and developmental history, differentiating to form a specific cell or tissue type. The theory of positional information brought together various ideas of previous researchers in a new and predictive way. It was truly revolutionary in an era when developmental biologists were mostly focused on mechanisms of gene transcription. The theory is widely applicable and has illuminated many aspects of development, including specification of body plan in both vertebrate and invertebrate embryos.

After arriving at the Middlesex Hospital Medical School, Lewis took up the problem

of chick embryo limb development. He applied his concepts of positional information to this problem, and over many years, with several collaborators, including one of us (C.T.), laid the basis for today's detailed understanding of limb development. This knowledge has helped elucidate general principles about how organs form and provided insights into clinical conditions in which limb development is affected.

Both of us were lucky and privileged to be postdocs in Lewis's lab in the 1970s. The atmosphere was exhilarating, largely thanks to Lewis's infectious enthusiasm. We were working on deep biological problems that nobody else had recognized; his lab was “the” place to do science and the venue for some memorable parties. Lewis relished coming up with experiments to test his models, although he did not carry them out himself. (He was the first to admit that his practical skills were limited.) Seminars in his lab were very informal but always interesting. Because he was not particularly interested in details, Lewis allowed speakers to show only one slide of a gel. Our work became even more thrilling as, the experiments on the chick limb began to flesh out Lewis's concepts, providing evidence for a combination of graded signals and timing mechanisms specifying positional values. Lewis later proposed that positional information interacts with a repetitive prepattern to give limb digits their individual character.

In the 1990s, Lewis wrote the textbook *Principles of Development*, with the aim of presenting concepts and avoiding too much detail. He was excited by identification of developmentally important genes involved in limb development, studying Hox genes with biologist Denis Duboule. But his main interest was elaborating his models, for example, with theoretician Michel Kerszberg, querying whether diffusion was sufficiently robust to specify position.

Lewis's interests and influence extended far beyond developmental biology. He enjoyed biking and playing tennis. He was very active in promoting science to nonscientists in the United Kingdom through radio and television and wrote several popular science books. The best-known of these is *Malignant Sadness*, which is based on his own personal experience with depression. In *The Unnatural Nature of Science*, Lewis argued that science is completely different from art in that science is about the way in which the world works, whereas art is a personal creation. But we wonder whether developmental biologists would ever have thought about French flags if it had not been for him. ■

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