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Introduction

Designing the French flag

(Ernst Mayr Lecture on 6th November 2001)

Believe it or not: "It is not birth, marriage, or death, but gastrulation, which is truly the most important time in your life." You may not easily agree with this statement made by Lewis Wolpert some 15 years ago, because you, like me and most others, may not have too vivid recollections of what happened between the 16th and 20th day of our early unborn lives. Nevertheless Wolpert's remark is well-turned. It is during gastrulation, during this dramatic sequence of invaginations, involutions and ingressions of migrating layers of cells, that your major body plan has been shaped; and it was the young Wolpert who has unveiled much of the mystery of how these spectacular rearrangements of embryonic tissues are orchestrated.

In fact, Lewis Wolpert started his career in developmental biology with one of his most stunning achievements. In the early 1960s, while doing his Ph.D. and post-doctoral work at King's College, University of London, he unravelled the mechanics and dynamics of the act of gastrulation. By using time-laps film recordings and theoretical modelling – a combination of techniques quite new in those days – he was able to show that the primary force of all the microscopic events occurring during this early stage of morphogenesis is cell motility. He was a successful visionary in emphasizing that interactions of rather simple changes in cell shape and cell contact could give rise to amazingly complex forms of embryonic development. In present-day biology we are quite used to the astonishing contrast between the simplicity of primary events and the depth of the resulting behaviour, but when Wolpert wrote his early papers it took a certain *chutzpah* to make such claims.

Surprisingly these claims were made by a young scientist who was trained in engineering rather than biology. Born in Johannesburg, South Africa, Lewis Wolpert took an early interest in mathematics and decided to study engineering. He was not too enthusiastic about the engineering courses he had to take at the University of Witwatersrand, but with a bit of luck he got through the final exam. In one of the examination papers he had to design a water tower and a bridge. The External Examiner showed that according to the candidate's calculations the water tower would break

and the bridge would collapse, but nevertheless he passed him by saying "I think you have got the general idea". Obviously, this polite remark was not enough yet for Lewis Wolpert to switch from engineering to, say, biology. Instead he went on to become Personal Assistant to the Director of the Building Research Institute in Pretoria. He designed mass housing for the African population, but also started a research programme on soil mechanics, particularly on "the movement of water in unsaturated soils". Such was the title of his first scientific paper published in 1952.

One year later, Wolpert left South Africa and hitchhiked up Africa for six months. On this trip he joined a German crocodile hunter down the Semliki Valley, spent with him three weeks on the beach of Mombasa, sailed on an Arab dhow to Mukallah in southern Yemen, travelled to Israel, where he worked for a year for the Water Department, and finally ended up in London. It was there, at Imperial College, that he got on his Road to Damascus, so to speak, and was converted from engineering to biology. While attending courses in soil mechanics, he received an enthusiastic letter from a friend in Edinburgh telling him about some fascinating research on the mechanical properties of biological membranes. Wolpert got immediately excited, left soil mechanics and turned to cell biology.

Fortunately enough, at that time the Nuffield Foundation was offering scholarships to young researchers who wanted to change from the physical to the biological sciences. (Nowadays the physical sciences would be very happy indeed, if an organization existed that worked the other way around.) Lewis Wolpert seized this opportunity and started his Ph.D. work on cell motility at King's College, London. Albeit a novice in this field, he was quick to acquire and use the experimental toolkit then available at the cutting edge of cell biology: on the one hand, he isolated fractions of cytoplasm in bulk and observed that they contracted when the energizer ATP was added; on the other hand he used pure fractions of membrane to prepare fluorescent antibodies, which he then applied to moving cells, and showed that the membranes were fluid. By now all this has become textbook knowledge.

This was a quick start. Only five years after he had received his Ph.D., Lewis Wolpert became Professor and Head of the Department of Biology as applied to Medicine at Middlesex Hospital, University of London. Being now at a medical school he felt it appropriate to exchange his former experimental animals – "lower" creatures such as sea urchins and hydra polyps – for "higher" vertebrates. He chose the developing limb of the chick as his new model system. It is as if he had become fascinated by the miraculous event that at a certain time there is an egg, and twenty-one days later you have a chick composed of some hundred different cell types, which are all differentiated in the right way at the right place, e.g. a muscle cell here and a bone cell there. Quite contrary to current thinking, Lewis Wolpert favoured the idea that the behaviour of a cell is determined by its position in the developing embryo. To focus this idea more clearly, he formulated the French flag patterning problem: what causes a line of totipotent cells, each of which could become either blue, white or red, to develop in such a way that it later will look like the French flag – one

third blue, one third white, and one third red? Wolpert's tentative answer was: it is positional information as provided, for instance, by the graded concentration of some morphogenetic substance that tells the cell what to do. For example, one could postulate that high, moderate and low concentrations of a molecular marker would programme cells in a line to become blue, white or red, respectively.

Wolpert's French flag patterning proposal had an enormous impact on the way of how developmental biologists started to think about pattern formation in morphogenesis. Its importance is not easily underplayed. In the meantime, thirty years later, molecular studies have identified Wolpert's positional signals. Genes of the *Hox* family specify positional values and thus give rise to the emergence of pattern. In all animals these genes provide each segment of the body with a unique identity, and do so over and over again, in space and time: along the front-to-rear axis of the body, along the axis of the limb of the chick or the wing of the fly. The same sequence of signals is used time and again, in the same embryo and in embryos of quite different organisms. Given this state of the art, the problem of pattern formation that had perplexed generations of biologists, may now be about to yield. To analyze the details is a question of time and work, but we now know that sooner or later we will get there – and it all started with Wolpert's French flag patterning proposal. In a beautiful textbook entitled "Principles of Development" Lewis Wolpert has drawn these findings and ideas together, succinctly and with verve.

Even a cursory glance at this book will reveal that Lewis Wolpert belongs to the rare brand of distinguished scientists who are also successful in the arts. The prominent biologist I have portrayed until now is one Lewis Wolpert. The other Lewis Wolpert is an equally committed scholar enquiring about the nature of science itself – about the rationale behind the defining feature of our age. His 1992 book "The Unnatural Nature of Science" is a spirited defence of the scientific endeavour. He argues that science does not correspond with the common sense view of the world, and that due to this peculiar nature of the scientific process science, unlike technology and religion, is a rare phenomenon in human cultural history. As Steve Jones, who recently updated Darwin's "Origin of Species", has once remarked, Wolpert's introduction to the philosophy of science has an enormous advantage: it is not written by a philosopher.

Science might be unnatural, but scientists are certainly not. To counteract the false image of scientists being a rather anonymous, homogeneous and personality-free gang of people, Wolpert conducted some thirty interviews with leading scientists, world-wide, on BBC Radio 3. These conversations later published in two books – "A Passion for Science" and "Passionate Minds" – make it abundantly clear that scientists are "driven", and that this "driven" quality is akin to religious experience, physical dependence, and sexual pleasure.

It is not astounding that Lewis Wolpert being a wanderer between different intellectual cultures has become a Fellow of both the Royal Society and the Royal Society of Literature. Last year he received the prestigious Royal Society Michael Faraday

Award for improving the Public Understanding of Science. Finally, for the last five years, he has been writing a more or less regular column for *The Independent* newspaper. There he covered a wide variety of scientific topics including, to my delight, an ant's-eye view of the world.

Last but not least there is another account Lewis Wolpert has written for the general public: "Malignant Sadness. The Anatomy of Depression". In this book, which is based on personal experience, he promotes the idea that depression results from a positive feedback loop between negative thinking and the biology of sadness. By making his own experience public Wolpert hopes to reduce the stigma that is still associated with this disease. "If you can describe your experience of a severe depression", he comments, "then you did not have one".

It is as if – and I am wording this rather carefully – a whiff of danger added excitement to Wolpert's style of life and intellectual activity, to the sparkle and fascination, by which he stands out from the crowded community of contemporary scientists.